REVIEW ARTICLE

Tuberculosis: Development of New Drugs and Treatment Regimens

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ABSTRACT

Tuberculosis (TB) still becomes a public health crisis. Drug-resistant TB (DR-TB) becomes a concern as the increasing DR-TB cases in countries with high TB burden. The 2017 World Health Organization (WHO) guideline recommended a combination of TB treatment consisting of 2 months of intensive phase with isoniazid (H), rifampisin (R), pyrazinamid (Z), and ethambutol (E), followed by 4 months of continuation phase with HR daily. WHO has updated DR-TB treatment guidelines several times. In 2016, WHO recommended shorter regimen and individual regimen based on certain conditions. The most updated 2020 WHO guideline recommended the short regimen consisting of all oral drugs as well as changes in the grouping of medicines used in DR-TB regimens in longer/individual regimens. Bedaquiline, delamanid, pretomanid, and sutezolid are new drugs which have been studied for their uses as anti-TB drugs (ATD). Bedaquilin and delamanid, which have passed phase 3 trials, have been approved and recommended by WHO for DR-TB treatment. Repurposed drugs have been used for DR-TB treatment during the time of evaluation of drugs list and regimens for DR-TB treatment. Fluoroquinolones, clofazimine, linezolid, carbapenem, amoxicillin/clavulanic acid are repurposed drugs. TB and DR-TB management will be updated at any time, based on the latest findings in studies, to evaluate and improve the effectiveness of current treatments. Prevention of active TB disease by the treatment of latent TB infection (LTBI) is also a critical component of the end TB strategy by WHO. Therefore, the development of new drugs for the LTBI treatment is also needed

INTRODUCTION

Tuberculosis (TB) continues to be a public health crisis worldwide. Globally, an estimated of 10 million TB cases is reported with 1.2 million mortality cases in 2019.[1] The number of drug-resistant TB (DR-TB) cases increase every year. Combination of rifampisin (R), isoniazid (H), pirazynamide (Z), ethambutol (E) with or without streptomycin (S) is a standardized first line regimen in drug-sensitive TB (DS-TB). Multi-Drug Resistant TB (MDR-TB) is defined as TB caused by strains of *Mycobacterium tuberculosis* which are resistant to at least R and H, two of the most potent first line anti-TB drugs.[2] Indonesia is one of 30 countrieswith high TB burden in the world and is in the 2nd rank in the world with 845,000 TB cases, while DR-TB cases is in the 5th rank with 24,000 cases in 2019.[1] TB treatments aim to cure patients, prevent complications and death, avoid recurrence, reduce the potential for transmission to susceptible people, and limit the emergence and spread of drug-resistant strains.

Current treatment for DS-TB, which consists of isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z) for 6 months (2HREZ/4HR), shows high cure rates at around 90 - 95%.[3] Anti-TB drugs also cause side effects from mild to severe. Problems with compliance, sub-optimal drug levels, and tolerability can lead to resistance. Shorter and more tolerated regimens are desperately needed to increase adherence and reduce loss to follow-up both DS-TB and DR-TB cases.[4] Effectiveness of TB treatment depends on combinations of several bactericidal drugs and sterilizing activity in an adequate duration, to keep antimicrobial efficacy while preventing drug-resistant mutants and achieve permanent cure.[5]

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New TB drugs and regimens are urgently needed to improve cure rates and shorten the treatment of both drug-susceptible (DS) and drug-resistant (DR) TB (currently at least 6 to 9 months respectively). Regimens that consist of entirely new drugs will be an important therapeutic advance, because they will reduce the need of drug-susceptibility testing (DST).[6] The current development of shorter and simpler treatments with a combination of new drugs and existing drugs requires detailed information about the safety and toxicity of each drugs; potential drug interactions; potential drug resistance when used for treatment; and its use in certain patients such as HIV, pregnant women, and children.[7]

The current research is underway to develop a shorter, more effective, safer, and more tolerated combination of treatments.[3] Treatment of DR-TB is challenging as it needs combinations of several second line anti-TB drugs with a longer duration, high cost, and more adverse effects, and high rate of loss to follow-up cases. WHO has updated the guideline of DR-TB several times in 2006, 2011, 2016, and currently in 2020. The 2016 guideline of DR-TB recommended shorter regimen and individual regimen under specific conditions.[8] In 2020, WHO recommended shorter regimen consisted of fully oral regimens and changes in grouping DR-TB drugs in making longer/individual DR- TB regimens. Fully oral regimens become the preferred option for most patients. Three medicines – fluoroquinolones (levofloxacin or moxifloxacin),bedaquiline, and linezolid – are strongly recommended in a longer regimen, completed by other medicines which are relatively safe.[9] The success of the treatmentis positively associated with the use of linezolid(adjusted risk difference 0.15, 95% CI 0.11-0.18),
levofloxacin (0.15, 0.13-0.18), carbapenems (0.14, 0.06-0.21), moxifloxacin (0.11, 0.08-0.14), bedaquiline (0.10, 0.05-0.14), and clofazimine (0.06, 0.01-0.10). There is a significant association between reduced mortality andthe use of linezolid (–0.20, –0.23 to –0.16), levofloxacin (–0.06, –0.09 to –0.04), moxifloxacin (–0.07, –0.10 to –0.04), or bedaquiline (–0.14, –0.19 to –0.10).[10]

Treatment of Drug Sensitive Tuberculosis

Treatment regimen for DS-TB consists of a 2-month intensive phase with daily HRZE, followed by a 4-month continuation phase with HR.[3,11] WHO updated the DS-TB guideline in 2017 as follows:

- In DS pulmonary TB patients, regimens containing fluoroquinolone as performed in four studies; 4MfxHRZ, 4MfxRZE, 2MfxRZE / 2 (Mfx + RFP), 2MfxRZE / 4 (Mfx + RFP), 2GfxHRZ / 2GfxHR, 2 (GfxHRZ) / 2 (GfxHR), 2 (MfxHRZ) / 2 (MfxHR) are not recommended. (E: ethambutol, Gfx: Gatifloxacin, H: isoniazid, Mfx: moxifloxacin, R: rifampicin, RFP: rifapentine, Z: pyrazinamide). The regimen contains rifampicin (2HRZE / 4HR) remains the recommended regimen.
- The use of FDC is recommended to be administered for DS-TB treatment.
- In all DS pulmonary TB patients, the use of three-time weekly dosage is not recommended in both the intensive and continuation phases.
- In DS pulmonary TB patients with HIV infection and receiving ARV (antiretroviral) therapy during TB treatment, a standard 6-month treatment is recommended, compared with an extension of the duration of treatment 8 months or more.

In patients who need re-treatment, category 2 WHO regimens should no longer be given, the choice of regimen is considered based on DST.

The 2016 ATS/IDSA guidelines stated differently than the 2017 WHO guidelines in terms of duration of treatment in the continuation phase. Sputum culture examination results at the end of intensive phase (2 months) are related to the possibility of recurrence after the completion of TB treatment. Patients with cavity on chest X-ray at the initial treatment and positive cultures after 2 months of treatment are risk factors of relapse by 20%, compared with pulmonary TB patients without these risk factors by 2%. Based on this consideration, the expert team's opinion was to extend the continuation phase with H and R for 3 months to reduce the possibility of relapse.[12] High doses of rifampicin andrifapentine have been studied to shorten TB treatment. In the PanACEA MAMS-TB-01 trial, rifampicin 35 mg/kg per day which added to standard doses of isoniazid, pyrazinamide, and ethambutol yielded an improved hazard ratio for stable culture conversion in liquid medium over 12 weeks (hazard ratio 1.75, 95% CI 1.21–2.55). However, the effect on culture status at 8 weeks using solid medium (10% positive *vs* 15% incontrols) was predicted to cause a relapse rate of 13% ifonly administered for 4 months. In studies of rifapentine
1.200 mg once a day proposed for a phase 3 trial

(NCT02410772) also resulted in 10% of patients with positive cultures using solid medium at 8 weeks in a phase 2 trial. Regimens resulting in 13% relapse cases are not likely to be accepted by TB control programmes.[6]

Treatment of Drug Resistant Tuberculosis

WHO has updated classification of anti-DR TB drugs several times. The previous WHO guideline classified anti DR-TB drugs into 5 main groups based on its effectiveness and safety. This classification was recommended in 2006 and was updated in 2008, 2011, 2016, 2018, and 2020.

The current WHO guideline recommended 2 options of DR-TB treatment which are shorter and longer/individual regimen. Based on the available evidence, the shorter regimen can be a preferred option for patients with confirmed MDR/RR-TB (with at least confirmed resistance to rifampicin), for whom resistance to fluoroquinolones has been ruled out, in the following situations; without resistance or suspectedineffectiveness of a medicine in the shorter regimen (except isoniazid resistance); without exposure to previous treatment with second-line medicines in theregimen for more than 1 month (unless susceptibility to these medicines is confirmed); with no extensive TBdisease and with no severe extrapulmonary TB; not pregnant; and if a child, aged 6 years or more.[9,13] Shorter regimens consist of:[9]

6 Bdq with 4–6 Lfx/Mfx-Cfz-Z-E-H high dose-Eto/ 5 Lfx/Mfx-Cfz-Z-E

(Bdq = Bedaquilline; Lfx = Levofloxacin; Mfx = Moxifloxacin; Cfz = Clofazimin; Z = Pirazinamid; H = Isoniasid; E = Etambutol; H = Isoniazid; Eto = Etionamid)

A study in Cameroon showed high effectiveness of the shorter regimen, among 150/236 treated patients with eligible STR, 134 (89%) successfully completed the treatment, 10 patients died, 5 patients were loss to follow-up, 1 patient failed the treatment, and no relapse cases. The main adverse effect was hearing impairment on 46/106 (43%) patients.[14] Standardized 12-month treatment for MDR-TB was highly effective and well tolerated in patients not previously exposed to second-line drugs in Nigeria, and the main adverse effects were vomiting (26.2%) and hearing impairment (20%) but no treatment had to be stopped and no relapse cases.[15]

Currently, the used of Mfx in STR are still debatable due to the presence of prolonged QT as an adverse effect. A study shows that Mfx is more likely to cause QTc prolongation than the other fluoroquinolones (FQs), although FQ is likely to be the most effectivedrug against MDR-TB. The risk of QTc prolongation with the FQs is higher when there are electrolyte imbalances and when other QTc prolonging medicationsare used.[16]

Grouping Anti-Tuberculosis Drugs and Composing Individual Regimen

WHO has changed the grouping of drugs to make an individualized regimen based on the efficacy hierarchy of each drug. This change was made based on scientific evidence obtained from quality research results. Bedaquiline did not appear to be one of the maindrugs of choice in making a combination of DR-TBtreatment at the beginning of the 2008 DR-TB guidelines, but was changed in the 2020 guidelines as bedaquiline becomes the main drug of choice. Kanamycin and capreomycin, which were originally used as the main drugs in making DR-TB treatmentregimens, are no longer recommended as one of the DR-TB drugs in DR-TB regimens. Table 1 below is a grouping of TB drugs according to their hierarchy and the steps to make regimens.

Injection drugs are no longer a priority in making individualized MDR-TB regimens. Kanamycin and capreomycin are no longer recommended, thus an entirely oral regimen is the preferred choice by patients. Three drugs such as fluoroquinolone (levofloxacin or moxifloxacin), bedaquilin, and linezolid are strongly recommended for use in individualized regimens. In MDR/RR-TB patients on longer regimens, a total treatment duration of 18–20 months is suggested formost patients; the duration may be modified according to the patient's response to therapy. In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patientson longer regimens, the performance of sputum culturein addition to sputum smear microscopy is recommended to monitor treatment response. It is desirable for sputum culture to be repeated at monthly intervals.[9] The guideline in Indonesia recommended 5 drugs in the intensive phase and 4 drugs in the continuation phase.

Table 1. Grouping of medicines recommended for use in longer MDR-TB regimens[9]

Groups	Medicine	Steps
A	Levofloxacin (Lfx) OR Moxifloxacin (Mfx)	Include all three medicines
	Bedaquiline (Bdq)	
	Linezolid (Lzd)	
B	Clofazimine (Cfz)	Add one or both medicines
	Cycloserine (Cs) OR Terizidone (Trd)	
C	Ethambutol (E)	Add to complete the regimen and when medicines from Groups A and B can not be used
	Delamanid (Dlm)	
	Pyrazinamide (Z)	
	Imipenem-Cilastatin (Ipm-Cln) OR Meropenem (Mpm)	
	Amikacin (Am) OR Streptomycin (S)	
	Ethionamide (Eto) OR Prothionamide (Pto)	
	p-aminosalicylic acid (PAS)	

Table 2. Clinical strategy to build an individualized treatment regimen for MDR TB[17]

- Build a regimen **using 5 or more drugs**
- Choice of drugs is contingent on capacity to appropriately monitor for significant adverse effects, patient comorbidities, and preference/values (choices therefore subject to program and patient safety limitations)
- In children with TB disease who are contacts of infectious MDR-TB source cases, the source case's isolate DST result should be used if an isolate is not obtained from the child.
- TB **expert medical consultation is recommended (ungraded good practice statement)**

Step 1: Choose 1 fluoroquinolone	Levofloxacin Moxifloxacin
Step 2: Choose both of these prioritized drugs	Bedaquiline Linezolid
Step 3: Choose both of these prioritized drugs	Clofazimine Cycloserine/ terizidone
Step 4: If a regimen cannot be assembled with five effective oral drugs, and the isolate is susceptible, use one of these injectable agents	Amikasin Streptomycin
Step 5: If needed or if oral agents preferred over injectable agents in Step 4, use the following drugs	Delamanid Pyrazinamide Ethambutol
Step 6: If limited options and cannot assemble a regimen of five effective drugs, consider use of the following drugs	Ethionamide atau prothionamide Imipenem-cilastatin/ clavulanate or meropenem/ clavulanate *p*-Aminosalicylic acid High-dose isoniazid
The following drugs are no longer recommended for inclusion in MDR-TB regimens	Capreomycin dan kanamycin Amoxicillin/clavulanate (when used without a carbapenem) Azithromycin and clarithromycin

Both ATS (2019) and WHO (2020) guidelines recommended new drugs or repurposed oral agents with greater efficacy and do not recommend the use of injection drugs.[9,17] Clinical step to make an individualized regimen recommended by ATS in determining certain drugs is presented in Table 2 below.

Fluoroquinolones (levofloxacin or moxifloxacin), bedaquilin, and linezolid are recommended as the main drugs in individualized regimens. Delamanid is a drug currently used to complete treatment regimens and when drugs in groups A and B can not be used (Table 1). The use of bedaquiline is acceptable for children aged atleast 6 years old and delamanid is for 3 years old children. Further study for bedaquiline is needed to determine optimal pharmacokinetic in children, cost effectiveness, and optimization of the duration in both adults and children, while delamanid is needed to be studied for its role in MDR TB regimens in children (pharmacokinetics/pharmacodynamics), patients with HIV, pregnant women, drug resistance mechanisms, and the optimization of the duration both in adults and children. Knowledge about the safety of bedaquiline and

Table 3. Summary of recommendations on drugs for use in a treatment regimen for patients with multidrug-resistant tuberculosis, including strength of recommendation, certainty in the evidence, and relative effects on death and treatment success. OR = Adjusted Odds Ratio; CI = Confidence Interval[17]

Drug/Drug Class	Recommendation		Certainty in the evidence	Relative (95% CI) Death	Relative (95% CI) Success
	FOR	AGAINST			
Bedaquiline	Strong		Very Low	**0.4** (0.3-0.5)	**2.0** (1.4-2.9)
Fluoroquionone: Moxifloxacin	Strong		Very Low	**0.5** (0.4-0.6)	**3.8** (2.8-5.2)
Fluoroquionone: Levofloxacin	Strong		Very Low	**0.6** (0.5-0.7)	**4.2** (3.3-5.4)
Linezolid	Conditional		Very Low	**0.3** (0.2-0.3)	**3.4** (2.6-4.5)
Clofazimine	Conditional		Very Low	**0.8** (0.6-1.0)	**1.5** (1.1-2.1)
Cycloserine	Conditional		Very Low	**0.6** (0.5-0.6)	**1.5** (1.4-1.7)
Injection: Amikacin	Conditional		Very Low	**1.0** (0.8-1.2)	**2.0** (1.5-2.6)
Injection: Streptomycin	Conditional		Very Low	**0.8** (0.6-1.1)	**1.5** (1.1-2.1)
Ethambutol	Conditional		Very Low	**1.0** (0.9-1.2)	**0.9** (0.7-1.1)
Pyrazinamide	Conditional		Very Low	**0.7** (0.6-0.8)	**0.7** (0.5-0.9)
Injection: Carbapenem with clavulanic acid	Conditional		Very Low	**1.0** (0.5-1.7)	**4.0** (1.7-9.1)
Delamanid	Concur with WHO conditional recommendation				
Ethionamid Prothionamide		Conditional	Very Low	**0.9** (0.8-1.0)	**0.8** (0.7-0.9)
Injection: Kanamycin		Conditional	Very Low	**1.1** (0.9-1.2)	**0.5** (0.4-0.6)
p-Aminosalicylic Acid		Conditional	Very Low	**1.2** (1.1-1.4)	**0.8** (0.7-1.0)
Injection: Capreomycin		Conditional	Very Low	**1.4** (1.1-1.7)	**0.8** (0.6-1.1)
Macrolide: Azithromycin Clarithromycin		Strong	Very Low	**1.6** (1.2-2.0)	**0.6** (0.5-0.8)
Amoxicillin-clavulanat		Stong	Very Low	**1.7** (1.3-2.1)	**0.6** (0.5-0.8)

delamanid in pregnant and nursing women is very rare, thus it is recommended to use individualized regimens by using drugs with a guaranteed safety profile. The results of treatment during pregnancy and supervision after childbirth are also needed to be documented to provide information on MDR-TB treatment recommendations in future pregnancy.[9]

American Thoracic Society (ATS) have grouped the drugs list used for DR-TB, including a list of not recommended drugs. Table 3 below is a recommendation of MDR TB drugs.[17]

The guideline of DR-TB recommended by ATS (2019) and WHO (2020) have some differences as follows:[9,17]

- WHO recommendations are applied for MDR and RR-TB. Guideline of ATS/CDC/ERS/IDSA does not recommend DR-TB treatment guideline for rifampin-resistant patients, thus it needs to be proved with the presence of isoniazid resistance.
- The minimum numbers of drugs likely to beeffective at the start of treatment are 5 in the ATS/CDC/ERS/IDSA guidelines and 4 in the WHO guidelines.
- Linezolid and bedaquiline are strongly recommended by WHO. ATS/CDC/ERS/IDSA agrees with the WHO recommendation that delamanid can be used for MDR-TB treatment.

- Composing a standardized individual regimens between WHO and ATS/CDC/ERS/IDSA is different.
- WHO maintains the recommendation on the standardized 9-11 month shorter regimen under specific conditions, whereas ATS/CDC/ERS/IDSA cannot make a recommendation for or against the shorter regimen compared with individualized regimens.
- For patients with isoniazid-resistant TB, WHO does not recommend providing a shorter duration of pyrazinamide use under situations as recommended by ATS/CDC/ERS/IDSA guideline.

Although WHO recommends evaluation of drug resistance, their guideline accepts that globally empirical regimens will continue to be used. ATS/CDC/ERS/IDSA guideline requires microbiological data to create a regimen suitable for the individual patient's strain of tuberculosis.[17]

Recommendations regarding the composition, duration, and monitoring of individualized regimens of MDR-TB are applicable generally for children, adults, people with HIV-AIDS, and for patients with RR/MDR-TB who are resistant to fluoroquinolones or other drugs, and people under specific conditions. Currently, bedaquilin can be given to children aged ≥6 years old and delamanid can be given starting from the age of 3 years old children. The regimen is substantially different in terms of composition and recommended duration, which can be investigated further in an operational research.

The New Compounds, Bedaquiline, Delamanid, Pretomanid, and Related Pipeline

Regimens which consist of entirely new drugswill be an important therapeutic advance because they will reduce the needs for DST. Two new drugs (bedaquilineand and delamanid) have passed phase 3 trials and have been approved for MDR-TB treatment by WHO.

Two new compounds have entered phase 1 trials: Q203, a novel ATP synthetase inhibitor (ClinicalTrials.gov NCT02530710), and TBA-354, a nitroimidazole (NCT02606214). However, as of January 2016, the only study of TBA-354 had been suspended. So far, studies of SQ109—an asymmetrical diamine—have not shown antituberculosis activity in sputum, alone or in combination with rifampicin over 14 days, either in rifampicin-containing regimens over 3 months.[6]

Bedaquiline is the first novel drug that has been conditionally approved for treating adult pulmonary MDR-TB by US Food and Drug Administration (FDA) in December 2012 and by European Medicines Agency (EMA) in March 2014. The clinical evidence for using bedaquiline mainly came from one phase II clinical trial performed in two stages, which showed that adding bedaquiline to a standard MDR-TB treatment regimen significantly decreased the time to sputum culture conversion and significantly increased the proportion of patients with culture conversion from 9% to 48% at 8 weeks.[18]

Delamanid is a derivative of metronidazole and a nitroimidazopyran and was approved by EMA in November 2013 for conditional use in the treatment of MDR-TB. The clinical evidence for delamanid use is based on short-term phase II clinical trial data, involving 481 MDR-TB patients, which showed a higher proportion of sputum culture conversion. An open-label extension of this phase II trial showed that delamaniduse for more than 6 months, in comparison with use for less than 2 months, significantly increased the proportion with favourable outcomes (cure or treatment completion) from 55% to 74.5% and significantly reduced mortality from 8.3% to 1.0%. Delamanid significantly prolongs QT interval, thus it is important toincrease vigilance when combining delamanid with bedaquiline, clofazimine, and fluoroquinolones(especially moxifloxacin).[18]

Pretomanid is a nitroimidazole developed by TB Alliance and is being considered as a component in TB and MDR-TB regimens. This agent is being studied for clinical trials on TB and DR-TB.[3] A phase II randomized controlled trial of Early Bactericidal Activity (EBA) (NC-003) involving patients with smear-positive pulmonary TB suggested that EBA of pretomanid was highly dependent on its synergy with pyrazinamide, and a triad of pretomanid, moxifloxacin, and pyrazinamide gave the highest EBA, thereby suggesting its potential for further clinical trials.[18]

Sutezolid is a linezolid analogue initially developed for evaluation of better potential in vivo activity and less toxicity in comparison with linezolid. With a substantially lower Minimum Inhibitory

Concentration (MIC) against *Mycobacterium tuberculosis* and reduction of MIC in acidic pH,sutezolid has demonstrated a higher bactericidal activity than linezolid, as well as perhaps a potential sterilising activity. The whole blood bactericidal activity of sutezolid 600 mg twice daily is higher than linezolid 300 mg once daily. Although EBA of sutezolid is significantly lower than that of the standard regimen, a whole blood bactericidal activity assay has demonstratedits synergistic activity with pyrazinamide. Sutezolid does not appear to cause QT interval prolongation or bone marrow suppression, although there are stillconcerns regarding potential neurotoxicity andhepatotoxicity.[18]

No hematological toxic effects were reported in phase 1 trials for sutezolid 600 mg twice a day for 28 days, which was thought to reduce the inhibition of mitochondrial protein synthesis. Sutezolid dose of 600 mg twice a day and 1,200 mg once a day were well tolerated and showed sputum EBA in patients with TB.[7]

Repurposed Drugs

The repurposed drugs have been used for MDR-TB and XDR-TB treatment while being evaluated ofnew DR-TB drugs and regimens. Fluoroquinolones, kanamycin, amikacin, clofazimine, linezolid, carbapenem, and amoxicillin/clavulanic acid are repurposed drugs. The 3rd and 4th generation of fluoroquinolones (levofloxacin, moxifloxacin, and gatifloxacin) are often used for the treatment of H monoresistant TB and MDR-TB, which are the most important components in second-line drugs.[19,20] As fluoroquinolone is widely available and is used for treating several infectious diseases, it is important to consider the potential for resistance in patients who are not diagnosed with TB and treated with fluoroquinolone.[21] The antileprosy drug, clofazimine, has shown sterilising activity and treatment-shortening potential. A new rimino- phenazine, TBI-166, has entered phase 1 trials and will hopefully not produce skin discolouration, a common adverse effect of clofazimine.[3]

Linezolid has been reported as a failing regimen on 39 XDR-TB patients with sputum culture conversion on solid media was 35% after 2 months and 87% after 6 months. 82% patients experienced linezolid toxicities, resulting in 3 patients permanently discontinued from linezolid. Based on these results, research on linezolid was conducted to identify the optimal dose to minimize toxicity without reducing their efficacy.[22] Linezolid was effective in achieving culture conversion, but 82% of patients experienced adverse effects such as myelosuppression, peripheral neuropathy, and optic neuropathy. Patients who received 300 mg per day experienced fewer adverse effects than 600 mg per day, but it can cause resistance.[3]

Carbapenem may play a role in MDR-TB regimen based on in vitro activity and case reports. Initial trials of faropenem and meropenem are ongoing. Sulfonamides have also been proposed as anti-TB drugs based on the sensitivity in vitro, but no prospective trialshave been conducted. Several prophylactic cotrimoxazole studies in HIV patients in Africa have reported no effect on TB.[6] Meta-analyzes and systematicreviews of carbapenem use (ertapenem, imipenem, meropenem) for MDR-TB and XDR-TB treatment showed good tolerance and safety records, but the absence of active oral formulations and the need forcombination of amoxicillin and clavulanic acid (which keeps meropenem and carbapenems from β-lactamases) reduced the activity of carbapenems.[3] Recent reviews mentioned 6 drugs with antimicrobial activity against *Mycobacterium tuberculosis* (phenothiazine, metronidazole, doxyxycline, disulfiram, tigecycline, and co-trimoxazole) which appeared to be promising and areproposed to be anti-TB drugs based on in vitrosensitivity tests, but there are no prospective trials performed.[21]

Latent Tuberculosis Treatment

Latent tuberculosis infection (LTBI) is apersistent immune response to the stimulation of *Mycobacterium tuberculosis* antigen without clinically manifested symptoms of active TB disease.[21] A person with LTBI does not have any symptoms and does not transmit TB, but if *Mycobacterium tuberculosis* in LTBI person becomes active, it will become TB disease. Prevention of active TB disease with LTBI treatment is also an important component in the end of TB strategyby 2035.

WHO recommended LTBI treatment including a weekly dose of rifapentine and isoniazid for 3 months (3HP), a daily dose of rifampicin plus isoniazid for 3 months (3RH), a daily dose of rifampicin for 4 months

(4R), and a daily dose of isoniazid for 6 months (6H) or longer. In July 2019, WHO updated the 2018 guidelines based on the new evidence of the use of 2 other TB preventive treatment regimens: 4R in high TB burden settings and 1 month of daily isoniazid and rifapentine (1HP). Updated recommendations will be published in the first quarter of 2020.[21] Rifapentine is given once in a week with combination of isoniazid for LTBI.[12] ATS recommends LTBI treatment for people in contacts with patients with MDR-TB using a later generation of fluoroquinolone or single therapy using 2nd line drug for 6 to 12 months of treatment, based on the drug susceptibility of the source-case *Mycobacterium tuberculosis* isolate, followed with observation alone (conditional recommendation, very low certainty in the evidence). If there are evidence of increased toxicity, adverse events, and discontinuations, pyrazinamide should not be routinely used as the second drug.[17]

Clinicians and patients have long desired shorter, more tolerable, and safer alternatives for treatment of LTBI rather than standardized daily isoniazid for 9 months or more. In 2011, the phase 3 TB TC Study 26 (NCT00164450), undertaken in 7,731 participants, showed non-inferiority of weekly rifapentine and isoniazid (given for 3 months), when compared with 9 months of daily isoniazid. Rifapentine is still unavailable in most countries worldwide. So far, no data are available from phase 3 trials to eradicate latent infection due to drug-resistant *Mycobacterium tuberculosis*, though two trials are underway assessing 6 months of daily levofloxacin versus placebo, and a large trial will soon begin assessing 6 months of daily delamanid versus 9 months of daily isoniazid, in adults and children. Drug-resistant LTBI is a high priority for the control of the growing DR-TB threat. Table 4 below summarized the trials that are being and will be conducted to examine chemoprophylaxis for individuals exposed to TB and DR-TB, which are being prepared or will be performed as soon as possible.[3]

Table 4. Ongoing and planned trials for the treatment of latent tuberculosis infection[3]

	Phase	Study population	Study groups	Notes
Drug-susceptible infection				
A5279 (NCT01404312)	3	3,000, HIV + adults (aged ≥18 years)	1 month isoniazid (300 mg) and rifapentine (600 mg) daily *vs* 9 months isoniazid (300 mg)daily	Opened May, 2012, results March, 2018; pharmacokinetic substudy of rifapentine and efavirenz completed; ACTG
CORTIS, CORTIS-HR (NCT02735590)	3	3,200, HIV– adults (aged ≥18 years) and 860 HIV+ adults (aged ≥18 years), stratified by risk of active TB is bytranscriptomics	12 doses isoniazid (maximum 900 mg) and rifapentine (900 mg) weekly *vs* no intervention	Opened July, 2016, results September, 2018; University of Cape Town Lung Institute
WHIP3TB (NCT02980016)	3	4,000, HIV– and HIV+ adults (aged≥18 years)	12 doses isoniazid (maximum 900 mg) and rifapentine (900 mg) weekly in year 1, or 12 doses isoniazid (900 mg) and rifapentine (900 mg) weekly in years 1 and 2 *vs* 6 months isoniazid (300 mg) daily in year 1	Opened November, 2016, results September, 2019; South Africa; Aurum Institute
IMPAACT 2001 (NCT02651259)	½	82, HIV– and HIV+ pregnant or lactating women (aged ≥18 years)	Pharmacokinetics, safety: 12 doses isoniazid (maximum 900 mg) and rifapentine (900 mg) weekly	Opened February, 2017; results December, 2018; IMPAACT
TBTC Study 35	2	80, HIV– and HIV+ children (aged <12 years)	Pharmacokinetics, safety: 12 doses weekly rifapentine (2535 mg/kg) plus isoniazid (10 15 mg/kg) in children aged <2, 2–5, and 6–12 years	Opens March, 2018, results 2021; South Africa; CDC TBTC, Sanofi

Drug-resistant infection				
V-QUIN MDR (ACTRN1261600021542 6)	3	2,006, HIV– and HIV+ adults and children (aged ≥15 years)	6 months levofloxacin (250, 500, or 750 mg) *vs* placebo (blinded, cluster randomized)	Opened, 2016, results, 2019; Vietnam, Australia; NHMRC
TB-CHAMP (ISRCTN92634082)	3	1,556, HIV– andHIV+ children (aged ≤5 years)	6 months levofloxacin (15–20 mg/kg daily) *vs* placebo (blinded, cluster randomized)	Opened late 2017, results, 2021; South Africa; BMRC
ACTG A5300B/IMPAACT I2003B PHOENIx	3	3,452, HIV– and HIV+ adults and children (aged ≥6 years)	6 months delamanid (maximum 200 mg once daily) *vs* 9 months isoniazid (300 mg daily)	Opens mid-2018; ACTG, IMPAACT

CDCTBTC = Centers for Disease and Prevention Tuberculosis Trials Consortium. IMPAACT = International Maternal Pediatric Adolescent AIDS Clinical Trials Network. NHMRC = Australia National Health and Medical Research Council. BMRC = British Medical Research Council. ACTG = AIDS Clinical Trials Group.

CONCLUSION

The treatment of DR TB has grown fast over the past few years. A new, shorter MDR-TB regimens and an increase in the availability of new or repurposed drugs is needed. Management of TB and DR-TB will be updated any time according to the latest findings to evaluate and improve the effectiveness of current treatments. The treatment of latent TB is one of theefforts to control TB to reach the end of TB 2035. Therefore, the development of new drugs for the treatment of LTBI is also very important.

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