Review Article

Tuberculosis: Development of New Drugs and Treatment Regimens

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REVIEW ARTICLE

- The 2017 World Health Organization (WHO) guideline recommends a combination of TB treatment: 2 HRZE / 4HR (Daily)
- WHO 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 recommends 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, 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 the DR-TB treatment during the time of evaluationof 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 one of the components of the end TB strategy by the WHO.

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.[1]
- Globally, an estimated of 10 million TB cases is reported with 1.2 million mortality cases in 2019.[1]
  - Indonesia: the 2nd rank in the world with 845,000 TB cases
- The number of drug-resistant TB (DR-TB) cases increase every year.[1]
  - Indonesia: the 5th rank with 24,000 DR-TB cases in 2019
- New TB drugs and regimens are urgently needed to increase success treatment rates and reduce the duration of both drug-susceptible (DS) and drug-resistant (DR) TB (currently at least 6 and 9 months).[2]

1. WHO Global Tuberculosis Report 2020
2. Lancet Infect Dis. 2016; 16: e34-46.

Treatment of DS-TB by the WHO (2017)

2 HRZE / 4HR (Daily)

- Regimens containing fluoroquinolone as carried out 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.
- The use of FDC is recommended to be administered for DS-TB treatment.
- 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..

Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017, update.

Treatment of DS-TB by the ATS/IDSA (2016)

- The 2016 ATS/IDSA guidelines states differently to 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%.

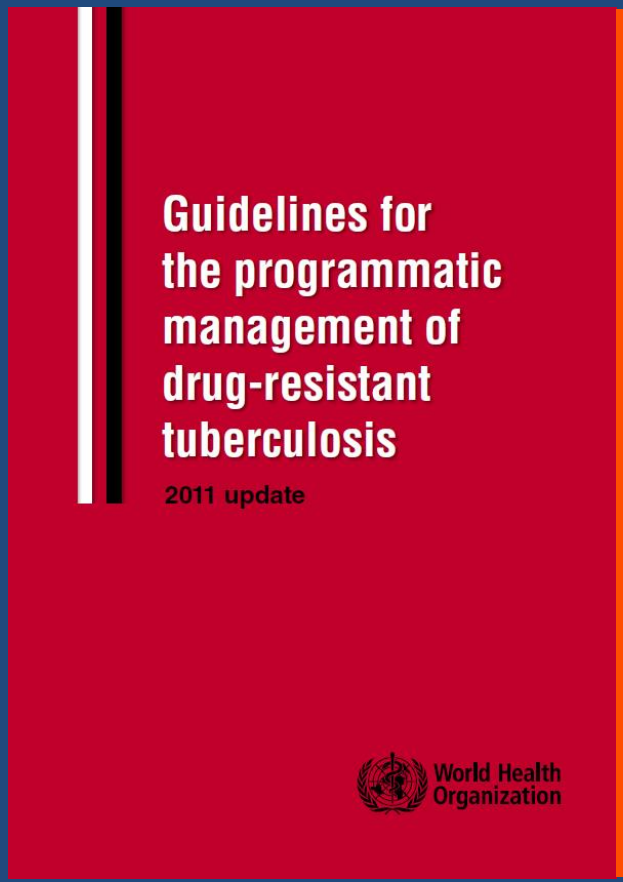
- Based on this consideration, the expert team's opinion was to extend the continuation phase with H and R for 3 months to reduce the possibility of relapse

ATS/IDSA. Clin Infect Dis. 2016; 63(7): e 147-95.

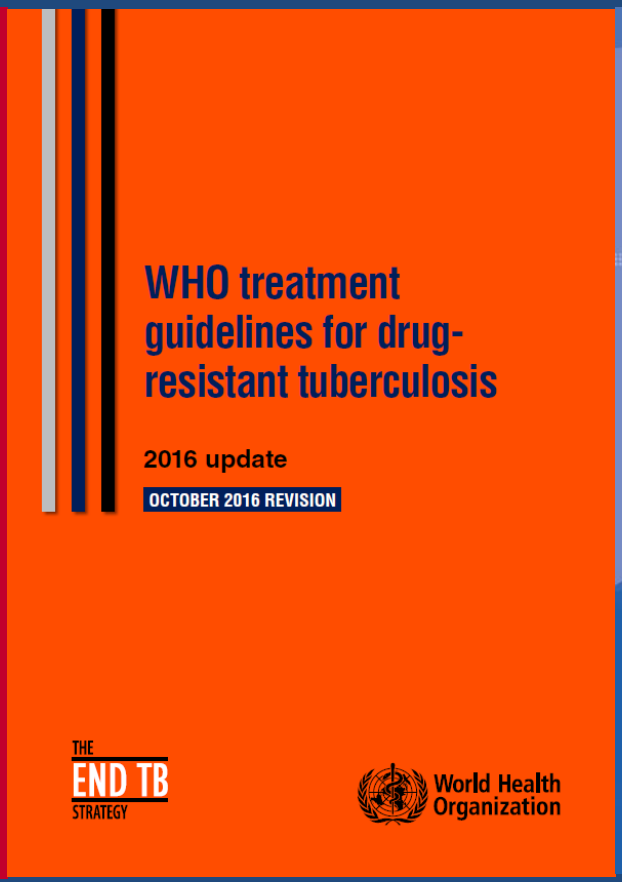
Treatment of DR-TB

- Both ATS (2019) and WHO (2020) guidelines recommends new drugs or repurposed oral agents with greater efficacy and do not recommend the use of injection drugs
- The current WHO guideline recommends 2 options of DR-TB treatment:
  - All oral shorter regimen
  - Longer/ individual regimen.

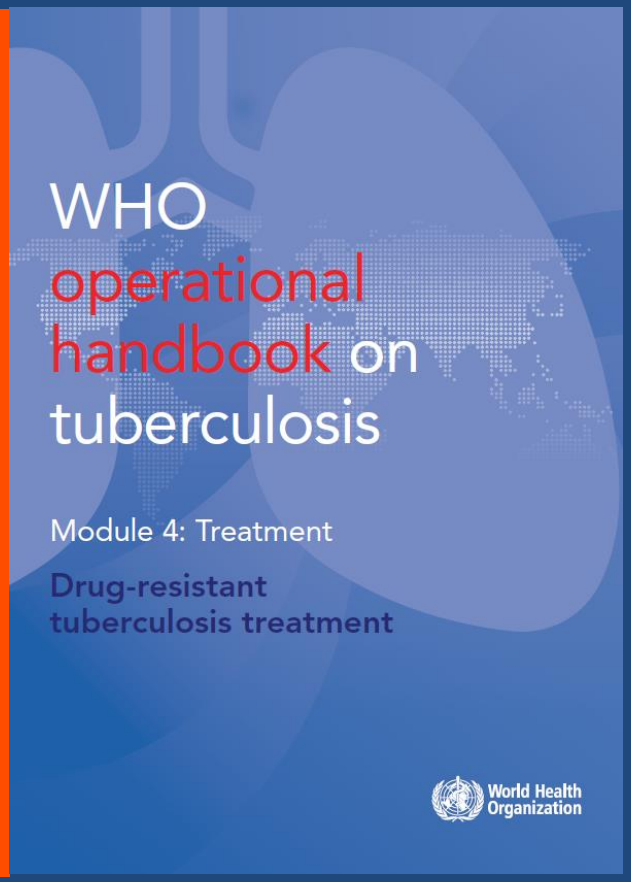
Updating DR TB Guidelines



2011



2016



2020

Pengelompokan obat TB (lini-1/lini-2) → dasar membuat rejimen TB RO

2011

Second-line parenteral agent (injectable anti-tuberculosis drugs)	kanamycin amikacin capreomycin
Fluoroquinolones	levofloxacin moxifloxacin gatifloxacin ofloxacin
Oral bacteriostatic second-line anti-tuberculosis drugs	ethionamide prothionamide cycloserine terizidone *p*-aminosalicylic acid
Group 5 drugs	clofazimine linezolid amoxicillin/clavulanate thioacetazone clarithromycin imipenem

2016

Group A. Fluoroquinolones[b]	Levofloxacin Moxifloxacin Gatifloxacin
Group B. Second-line injectable agents	Amikacin Capreomycin Kanamycin (Streptomycin)[c]
Group C. Other core second-line agents[b]	Ethionamide / prothionamide Cycloserine / terizidone Linezolid Clofazimine
Group D. Add-on agents (not part of the core MDR-TB regimen)	**D1** Pyrazinamide Ethambutol High-dose isoniazid
	D2 Bedaquiline Delamanid
	D3 *p*-aminosalicylic acid Imipenem–cilastatin[d] Meropenem[d] Amoxicillin-clavulanate[d] (Thioacetazone)[e]

2020

Group A: Include all three medicines	Levofloxacin *or* moxifloxacin
	Bedaquiline[b,c]
	Linezolid[d]
Group B: Add one or both medicines	Clofazimine
	Cycloserine *or* terizidone
Group C: Add to complete the regimen, and when medicines from Groups A and B cannot be used	Ethambutol
	Delamanid[c,e]
	Pyrazinamide[f]
	Imipenem-cilastatin *or* meropenem[g]
	Amikacin (*or* streptomycin)[h]
	Ethionamide *or* prothionamide[i]
	P-aminosalicylic acid[i]

Kanamycyn/capreomycin is not recommended anymore

All Oral Shorter Regimen

- The shorter regimen can be a preferred option for patients with confirmed MDR-TB, for whom resistance to fluoroquinolones has been ruled out, in the following criteria;
  - without resistance to a medicine in the shorter regimen (except isoniazid resistance);
  - without previous treatment with second-line medicines in the regimen for >1 month (unless susceptibility to these medicines is confirmed);
  - with no extensive TB disease and no severe extrapulmonary TB;
  - not pregnant; and
  - if a child, aged 6 years or more.
- Shorter regimens consist of

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

Grouping Anti-Tuberculosis Drugs and Composing Individual Regimen

Groups	Meidicine	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)	

Strategy to Design an Individual Regimen for MDR TB by ATS/IDSA (2019)

- Design a regimen **using 5 or more drugs**
- Drugs choicement is contingent on capacity to appropriately monitor for significant adverse effects, comorbidities, and preference/values
- In children with TB disease who are contacts with confirmed MDR-TB cases, the source case's isolate DST result should be used if an isolate is not obtained from the child.
- **Consult to clinical expert team** of TB **is recommended (ungraded good practice statement)**

Step 1:choose 1 fluoroquinolone	Levofloxacin Moxifloxacin
Step 2: Choose both of these prioritized drugs	Bedaquiline Linezolid
Step3: 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

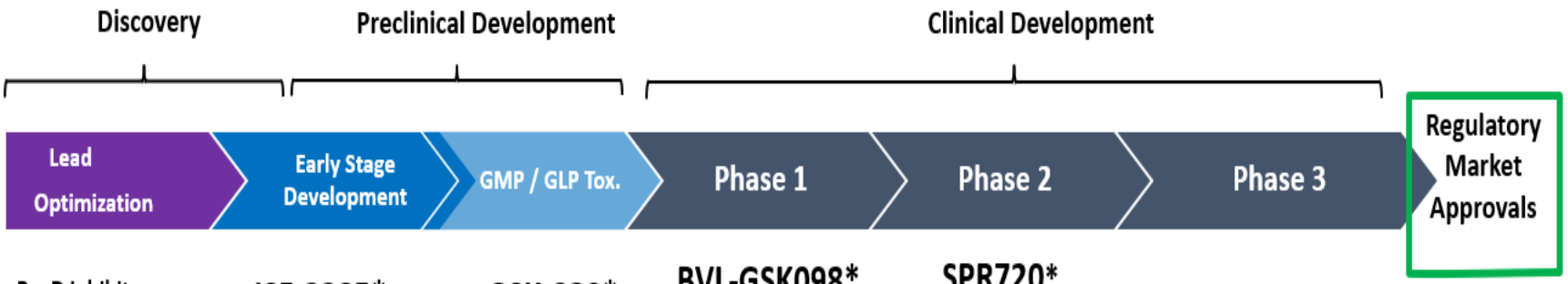
The New Compounds, Bedaquiline, Delamanid, Pretomanid, and Related Pipeline

- Regimens, consists of all new drugs, would be an important therapeutic advance, because they would reduce the needs for drug-susceptibility testing (DST).
- Two new drugs (bedaquiline and delamanid) have passed phase 3 trials and have been approved for MDR-TB treatment by WHO.
  - The new compounds of Q203, a novel ATP synthetase inhibitor (ClinicalTrials.gov NCT02530710), and TBA-354, a nitroimidazole (NCT02606214) have entered phase 1 trials. However, the study of TBA-354 had been suspended on January, 2016.
  - The US Food and Drug Administration (FDA) in December 2012 and the European Medicines Agency (EMA) in March 2014 has been approved the used of bedaquiline in pulmonary MDR-TB treatment for adult.
  - 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.
  - Pretomanid is a nitroimidazole and being studied for clinical trials on TB and DR-TB.
  - Sutezolid initially developed for evaluation of better potential in vivo activity and less toxicity in comparison with linezolid.

Repurposed Drugs

- Some repurposed drugs have been used for MDR-TB and XDR-TB treatment although are still being evaluated.
- Fluoroquinolones, kanamycin, amikacin, clofazimine, linezolid, carbapenem, amoxicillin/clavulanic acid are repurposed drugs.
  - Fluoroquinolone is widely available and used for treat several infectious diseases.
  - Clofazimine is an antileprosy drug, which showed sterilising activity and potential to reduce the treatment duration.
  - Faropenem and meropenem are being studied fo initial trials.
  - Studies of carbapenem (ertapenem, imipenem, meropenem) for MDR-TB and XDR-TB treatment reported good tolerance and safety results, but the activity of carbapenems is reduced because of the absence of active oral formulations and it needs to combine the amoxicillin and clavulanic acid (which keeps meropenem and carbapenems from β-lactamases).

2021 Global New TB Drug Pipeline [1]



PanD inhibitors
Indazole sulfonamides
Diarylthiazoles
DprE1 Inhibitors
Direct InhA Inhibitors
Mtb energy metabolism
Macrolides
Mycobacterial Gyrase Inhibitors
Arylsulfonamides
Inhibitors of MmpL3, Translocase-1, Clp, PKS13, F-ATP synthase
Oxazolidinones

JSF-3285*
MPL-446, 447*
CPZEN-45*
NTB-3119*
TB-47*
TZY-5-84
FNDR-20081*
Spectinamide – 1810*

GSK-839*
OTB-658
Sanfetrinem

BVL-GSK098*
GSK-286*
TBAJ-587
TBAJ-876
TBI-223
Macozinone* (PBTZ-169)
TBI-166

SPR720*
BTZ-043*
TBA-7371*
GSK-656* (070)
OPC-167832*
Delpazolid
Sutezolid
Telacebec* (Q203)
SQ-109*
Macozinone*

Bedaquiline*
Delamanid*
Pretomanid*

Rifapentine / Moxifloxacin (4-month regimen)

*New chemical class. Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical. Ongoing projects without a lead compound series identified: http://www.newtbdrugs.org/pipeline/discovery

Underline = updates since November 2020

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: March 2021

Latent Tuberculosis Infection

- Latent Tuberculosis Infection (LTBI) is a persistent immune response to the stimulation of *Mycobacterium tuberculosis* antigen without clinically manifested symptoms of active TB disease.
  - Person with LTBI do not have any symptoms and do not transmit TB, but if *Mycobacterium tuberculosis* in LTBI person become active, it will become TB disease.
- Prevention of active TB disease with LTBI treatment is also an important component in the end TB strategy by 2035.

LTBI Treatment

- The recommendation for LTBI treatment included 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, the updated guideline included 4R in high TB burden settings and 1 month of daily isoniazid and rifapentine (1HP).
- 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 (conditional recommendation).
  - Pyrazinamide should not be routinely used as the second drug if there are evidence of increased toxicity, adverse events, and discontinuations.

WHO. Global Tuberculosis Report 2019.
Am J Respir Crit Care Med. 2019; 200(10): 93-42.

Conclusion

- The treatment of DR TB has grown fast over the past few years.
- Managementof 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 the efforts to control TB to reach the end of TB 2035.
  - the development of new drugs for the treatment of LTBI is also very important.

Thank you