Treatment for multi-drug resistant tuberculosis (MDR-TB) in Uganda

Dr. Kizito Omona gives an overview of the treatment for multi-drug resistant tuberculosis (MDR-TB) in Uganda.

Introduction

Tuberculosis (TB) disease is a disease in humans caused by mycobacteria tuberculosis complex which comprises eight distinct but closely related organisms – M. bovis, M. caprae, M. africanum, M. microti, M. pinnipedii, M. mungi, M. orygis and M. canetti1. The most common and important agent of human disease is M. tuberculosis. The disease is spread from person to person through air. It affects the lungs and other parts of the body such as the brain, kidneys or spine. TB is treatable and curable. However, if not properly treated, persons with TB can die or suffer co-morbid conditions that grossly impair their economic productivity. The bacteria that causes TB can become more resistant to treatment when not properly managed, leading to drug-resistant TB (DR-TB). Resistance leads to; [(1)] Multidrug-resistant TB (MDR-TB) or [(2)] extensively drug resistant TB (XDR-TB). MDR-TB is caused by TB bacteria that are resistant to at least isoniazid and rifampin, which are the two most potent TB drugs while extensively drug resistant TB (XDR-TB) is a rare type of MDR-TB that is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of the three injectable second-line drugs (amikacin, kanamycin, or capreomycin)[2,3].

Definitions of key terms in Drug Resistant TB (DR-TB) Treatment

These definitions were adopted from World health Organization and Ugandan Ministry of Health [1(p202),4];

1. **Bacteriologically confirmed**: when a biological specimen is positive by smear microscopy, culture or a rapid diagnostic test for TB recommended by WHO.
2. **Clinically diagnosed:** when a person who does not fulfil the criteria for bacteriological confirmation has been diagnosed with TB disease by a medical practitioner who has decided to give the person a full course of TB treatment.
3. **Drug-resistant TB (DR-TB):** TB disease caused by a strain of Mycobacterium tuberculosis complex that is resistant to any TB medicines.
4. **Drug susceptibility testing (DST):** in vitro testing using either molecular or genotypic techniques to detect resistance-conferring mutations, or phenotypic methods to determine susceptibility to a medicine.
5. **Extensive (or advanced) pulmonary TB disease**: the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged below 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest radiography.
6. **Multidrug-resistant TB (MDR-TB):** TB disease caused by a strain of M. tuberculosis complex that is resistant to rifampicin and isoniazid.
7. **Extensively drug-resistant TB (XDR-TB):** TB disease caused by a strain of M. tuberculosis complex that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (levofloxacin or moxifloxacin) and to at least one other "Group A" drug (bedaquiline or linezolid).
8. **Rifampicin-resistant TB (RR-TB):** TB disease caused by a strain of M. tuberculosis complex that is resistant to rifampicin. These strains may be susceptible or resistant to isoniazid (i.e. MDR-TB), or resistant to other first-line or second-line TB medicines.
9. **MDR/RR-TB:** This refers to either multidrug-resistant TB (MDR-TB) or rifampicin-resistant TB (RR-TB).

Background and Trends of Drug Resistant TB (DR-TB) in Uganda

In a recent survey by WHO (2023), it was found that Uganda has a TB prevalence of 253 cases per 100,000 population. This puts the country among the world's 30 high-burden countries, with about 3,500 new cases every year and a total incidence of 91,000 cases. Two out of every 100 TB-infected people in Uganda have drug-resistant TB (DR-TB) and require second-line drugs to improve their outcomes and approximately 15% of TB cases in Uganda are children aged below 14 years. DR-TB typically develops in TB patients who have abused their TB treatment drugs or who do not complete their treatment as prescribed. These new strains of DR-TB bacteria could also spread and infect new patients who also develop resistance to treatment. DR-TB is also quite expensive to treat at the rate of about $1,200 per patient in Uganda[5]. In another study, it was found that in Uganda, 12% of previously treated TB cases and 1.6% of new cases had MDR-TB and required specialized treatment and care[6]. In 2023 alone, the treatment success rate in the community based directly observed therapy (DOT) group was at 12% higher than that in the health facility DOT[7], all pointing to the community burden of the disease. The morbidity level of MDR-TB is quite high with different eperiences[2,8,] rendering the affected person economically unproductive. See the trend of the disease over the years between 2010 and 2020 in the Figures 1 and Figure 2. From Figure 1, it can be seen that the number of people contracting TB are much higher

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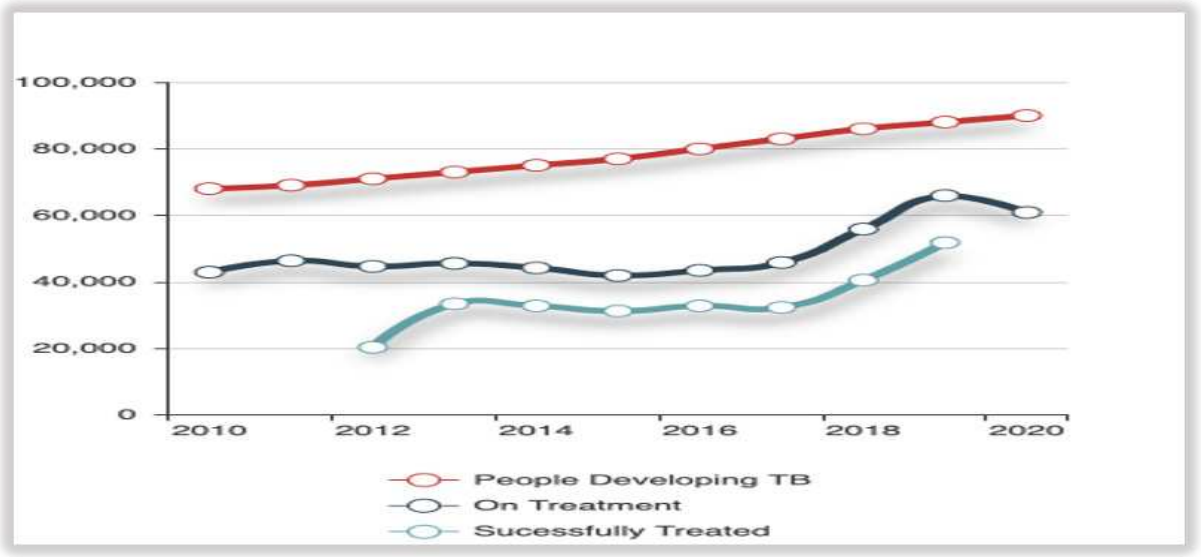


Figure 1: Trend of TB in Uganda Between 2010 and 2020 (Source: WHO)

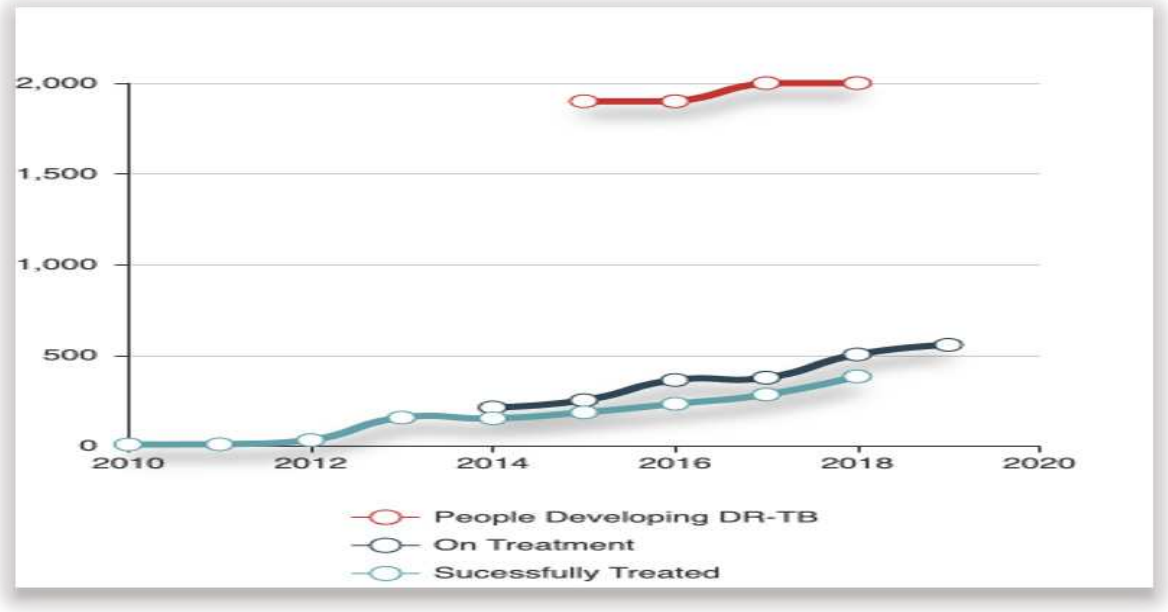


Figure 2: Trend of Drug Resistant TB (DR-TB) in Uganda Between 2010 and 2020 (Source: WHO)

than the number of those on treatment or those who are successfully treated. A similar explanation is shown in Figure 2 where the number of people developing DR-TB is even much higher than those who are on treatment or those who are successfully treated.

In order to address the country's TB burden, Ugandan Ministry of Health (MoH) developed a robust TB and Leprosy Strategic Plan 2020/21-2024/25). The plan emphasizes patient care among other interventions and also suggests a strategy which highlights the implementation status of the country's TB response in relation to the strategic direction, global evidence, and high-level advocacy[5].

Regimen options in the treatment of DR-TB

In 2022, WHO recommended three regimen options as shown in Table 1. The key factors that define treatment regimen choice include drug-resistance profile, prior exposure to TB medicines and patient history, drug-resistance profile of close contacts, the patient's age, extent of pulmonary TB disease and localization of extrapulmonary TB lesions.

1. **Option 1: 6-month BPaLM/BPaL Regimen**
   This regimen is indicated in patients with MDR/RR-TB where fluoroquinolone susceptibility is presumed or documented. It is also called '6-month all-oral treatment regimen' and comprises of the following drugs; bedaquiline, pretomanid, linezolid and moxifloxacin. It is possible to omit moxifloxacin

and continue with the BPaL regimen for MDR/RR-TB patients with confirmed fluoroquinolone resistance.

This recommendation applies to: (a) People with MDR/RR-TB or with MDR/RR-TB and resistance to fluoroquinolones (pre-XDR-TB). (b) People with confirmed pulmonary TB and all forms of extrapulmonary TB except for TB involving CNS, osteoarticular and disseminated (miliary) TB. (c) Adults and adolescents aged 14 years and older. (d) All people regardless of HIV status. (e) Patients with less than 1-month previous exposure to bedaquiline, linezolid, pretomanid or delamanid. When exposure is greater than 1 month, these patients may still receive these regimens if resistance to the specific medicines with such exposure has been ruled out.

Note that this recommendation does not apply to pregnant and breastfeeding women owing to limited evidence on the safety of pretomanid.

2. **Option 2: 9-month all-oral regimen (4–6 Bdq(6 m)-Lfx/Mfx-Cfz-Z-E-Hh-Eto or Lzd(2 m) / 5 Lfx/ MfxCfz-Z-E)**

This option is indicated in patients with MDR/ RR-TB and in whom resistance to fluoroquinolones has been excluded. It is also called the '9-month all-oral regimen' and comprises of bedaquiline (used for 6 months), in combination with levofloxacin/ moxifloxacin, ethionamide, ethambutol, isoniazid (high dose), pyrazinamide and clofazimine (for 4 months, with the possibility of extending to 6 months if the patient remains sputum smear positive at the end of 4 months); followed by treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide (for 5 months). Ethionamide can be replaced by 2 months of linezolid.

3. **Option 3: Longer individualized regimens**

It is indicated for patients with MDR/RR-TB who are not eligible for or had no favourable treatment outcome using the above 6-month or 9-month regimens, have TB disease caused by M. tuberculosis strains with extensive drug resistance (such as extensively drug-resistant TB [XDR-TB]) or have intolerance to key components of the above-mentioned regimens. These regimens have a duration of at least 18 months and are individually designed based on a hierarchical grouping of second-line TB medicines, the drug-resistance profile and the patient's medical history.

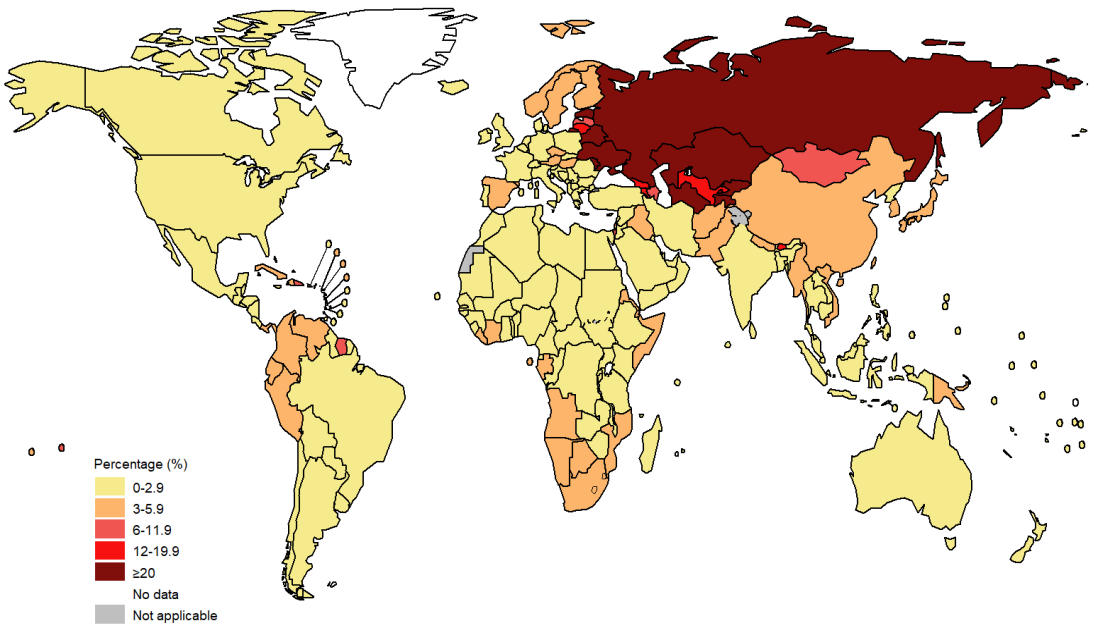
The 9-month all-oral regimen (with either ethionamide or linezolid) may be offered to the following patients with MDR/RR-TB (where resistance to at least rifampicin has been confirmed and resistance to fluoroquinolones has been ruled out): (a) those with no documented resistance or suspected ineffectiveness of bedaquiline, clofazimine, or ethionamide or linezolid (whichever is considered for inclusion in the regimen); (b) those with no exposure to previous treatment with bedaquiline, fluoroquinolones, clofazimine, or ethionamide or linezolid (whichever is considered for inclusion in the regimen) for more than 1 month. When prior drug exposure is greater than 1 month, patients may still receive this regimen if resistance to the specific medicine with such exposure has been ruled out; (c)those with no extensive or severe TB disease and no severe extrapulmonary TB; (d) all people living with or without HIV; (e)women who are pregnant or breastfeeding: these patients may be considered eligible for the linezolid-containing 9-month regimen, but they should not receive the 9-month regimen containing ethionamide; and (f) children and adults without bacteriological confirmation of TB or resistance patterns but who require MDR/RR-TB treatment based on clinical signs and symptoms of TB (including radiological findings) and history of contact with someone with confirmed MDR/RR-TB. These patients may be eligible for this regimen based on the drug resistance profile of the isolate obtained from the most likely index case.

Table 1:Regimen options and factors to consider for selection of treatment regimens for patients with MDR/ RR-TB (Source: WHO, 2022)

Regimens	MDR/RR-TB fluoroquinolone susceptible	Pre-XDR-TB	XDR-TB	Extensive pulmonary TB	Extrapulmonary TB	Age <14 years
1. 6-month BPaLM/ BPaL	Yes (BPaL)	Yes (BPaLM)	No	Yes	Yes – except TB involving CNS, miliary TB and osteoarticular TB	No
2. 9-month all-oral	Yes	No	No	No	Yes – except TB meningitis, miliary TB, osteoarticular TB and pericardial TB	Yes
3. Longer individualized 18-month	Yes[a]/No	Yes[a]/No	Yes	Yes	Yes	Yes
Additional factors to consider if several regimens are possible	(i) Drug intolerance or adverse events					
	(ii) Treatment history, previous exposure to regimen component drugs or likelihood of drug effectiveness					
	(iii) Patient or family preference					
	(iv) Access to and cost of regimen component drugs					

BPaL: bedaquiline, pretomanid and linezolid; **BPaLM:** bedaquiline, pretomanid, linezolid and moxifloxacin; **CNS:** central nervous system; MDR/RR-TB: multidrug- or rifampicin-resistant TB; **TB:** tuberculosis; **XDR-TB:** extensively drug-resistant TB.

[a] When 6-month BPaLM/BPaL and 9-month regimens could not be used.



Percentage of new TB cases with MDR/RR-TB, 2021, *courtesy of WHO.*

Key considerations in DR-TB treatment

There are three key considerations that must not be missed by service providers;

1. Access to drug susceptibility testing (DST)

The current guidelines for treatment of DR-TB stress the need for access to reliable, quality-assured drug susceptibility testing (DST), to be provided by national TB programmes (NTPs) and associated laboratories. This informs the use of the WHO-recommended regimens. Rapid molecular testing is making it increasingly feasible for NTPs to detect MDR/RR-TB and other types of resistance quickly, and to use the results to guide treatment decisions9,10.

2. Safety monitoring and management, provision of patient support and management of comorbidities

All treatment offered to people with MDR/RR-TB should align with WHO-recommended standards, including patient-centred care and support, informed consent, principles of good clinical practice, active TB drug safety monitoring and management (aDSM), and regular patient monitoring to assess regimen effectiveness. Therefore, health care providers must offer careful clinical and bacteriological follow-up to assess the TB treatment response, with general laboratory support to monitor and manage adverse events and comorbidities.

3. Regimen options in the treatment of DR-TB

In patients with MDR/RR-TB, there are several regimens that can be used based on current WHO policy (2022).

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