Management of multidrug-resistant tuberculosis in human immunodeficiency virus patients

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Abstract. Tuberculosis (TB) is a chronic infectious disease mainly caused by Mycobacterium tuberculosis (MTB). 10.4 million new TB cases will appear in 2015 worldwide. There were an estimated 1.4 million TB deaths in 2015, and an additional 0.4 million deaths resulting from TB disease among people living with human immunodeficiency virus (HIV). Multidrug-resistant and extensively drug-resistant tuberculosis (MDR and XDR-TB) are major public health concerns worldwide. 480,000 new cases of MDR-TB will appear in 2015 and an additional 100,000 people with rifampicin-resistant TB (RR-TB) who were also newly eligible for MDR-TB treatment. Their association with HIV infection has contributed to the slowing down of TB incidence decline over the last two decades, therefore representing one important barrier to reach TB elimination. Patients infected with MDR-TB require more expensive treatment regimens than drug-susceptible TB, with poor treatment. Patients with multidrug-resistant tuberculosis do not receive rifampicin; drug interactions risk is markedly reduced. However, overlapping toxicities may limit options for co-treatment of HIV and multidrug-resistant tuberculosis.

1. Introduction
Tuberculosis (TB) is a chronic infectious disease mainly caused by Mycobacterium tuberculosis (MTB). Occasionally caused by other organisms of the Mycobacterium tuberculosis complex, M. bovis, M. africanum, M. canetti, and rarely, M. microti[1].

Human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), multidrug-resistant tuberculosis (MDR-TB), and extensively drug-resistant tuberculosis (XDR-TB) are jeopardizing the TB control program worldwide. In 2015, there were an estimated 10.4 million new TB cases worldwide, of which there were 5.9 million (56%) among men, there were 3.5 million (34%) among women and there were 1.0 million (10%) among children. People living with HIV are 1.2 million (11%) of all new TB cases[2].

Six countries accounted for 60% of the new cases: India, Indonesia, China, Nigeria, Pakistan, and South Africa. Worldwide, the rate of decline in TB incidence remained at only 1.5% from 2014 to 2015. In 2015, there were an estimated 480,000 new cases MDR-TB and an additional 100,000 people with rifampicin-resistant TB (RR-TB) who were also newly eligible for MDR-TB treatment. There were an estimated 1.4 million TB deaths in 2015, and an additional 0.4 million deaths resulting from TB disease among people living with HIV. TB is one of the top 10 causes of mortality in 2015 worldwide[2].
A meta-analysis from 24 studies in 2014 demonstrated that there is a significant positive association between HIV/AIDS and primary MDR-TB with the summary OR of 2.28 (95% CI, 1.52–3.04), this evidence showed there is a strong association between MDR-TB and HIV[3].

2. Definition
By the World Health Organization’s definitions for tuberculosis control, tuberculosis-resistance had categories based on drug susceptibility testing (DST) of clinical isolates as:

- Mono-resistance: resistance to one first-line anti-TB drug only
- Polydrug-resistance: resistance to more than one first-line anti-TB drug (other than both isoniazid and rifampicin)
- Multidrug-resistance: resistance to at least both isoniazid and rifampicin
- Extensivedrug-resistance: resistance to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin, and amikacin), in addition to multidrug-resistance
- Rifampicin-resistance: resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, whether mono-resistance, multidrug-resistance, polydrug-resistance or extensivedrug-resistance.

Primary or initial-resistance(resistance among new cases), is defined as patients with TB resistant to one or more anti-TB drugs, but who had never been previously treated for TB or had treatment less than one month. ‘Secondary-resistance’ (resistance among previously treated cases) is defined as patients diagnosed with TB who started anti-TB treatment and subsequently acquired resistance to one or more of the drugs used[4].

Patients infected with MDR-TB require more expensive treatment regimens than drug-susceptible TB, with poor treatment success. There should be suspicion of drug-resistance, including MDR-TB, in persons with a history of prior treatment or in treatment failure cases[5].

3. Relationship Between MDR-TB and HIV
HIV positive people with pulmonary TB may have the classic symptoms of TB, but many people with both TB and HIV infection have asig of TB or even less specific ones. HIV positive people with TB have so-called “sub-clinical” TB, which often not recognized as TB and subsequently, there are delays in both TB diagnosis and TB treatment. HIV infected people are also more likely than people who are not infected with HIV to have extrapulmonary TB. Forty to eighty percent of HIV infected people with TB often came with extrapulmonary TB condition, it is compared with 10-20% of people without HIV [6].

HIV co-infection might also directly contribute to the accumulation of resistance in MTB. First, as resistance mutations entail a fitness cost to the bacterium (at least initially), some resistant strains might be more successful in HIV positive hosts with weakened immunity leading to a reduced selective pressure on the bacillus. Second, some antiretroviral drugs used to treat HIV might have a mutagenic effect on mycobacterial genomes[7].

4. Treatment
MTB co-infection in patients pre-infected with HIV and with full-blown AIDS is an emergingpandemic threat[8]. Due to increased recognition of the morbidity and mortality associated with this co-infection, the World Health Organization (WHO) recommends aggressive approaches for MTB screening during initial visits related to HIV screening and treatment[9].

The optimal number of drugs, combination of drugs, and duration of therapy has not been established yet. Based on expert opinion, the 2003 ATS/IDSA/CDC guidelines recommended 18-24 months depending on the extent of disease and resistance pattern. Earlier editions of the survival guide recommended minimum treatment durations for MDR-TB is 18-24 months beyond culture conversion, again based on expert opinion[10].
Table 1. Treatment regimens for the management of patients with MDR/XDR-TB\cite{11}.

| Pattern of drug resistance | Suggested regimen | Minimum duration of treatment | Comments |
|----------------------------|-------------------|------------------------------|----------|
| INH and RIF                | PZA, EMB, newer-generation fluoroquinolone (MFX or high-dose LFX), and injectable agent during the intensive phase (for at least six months beyond culture conversion), and one additional oral agent (LZD, ETA, CS or PAS). | 18 months beyond culture conversion | In patients with an extensive or cavitary disease, consider a longer duration for the injectable agent, as well as an additional oral drug. Consider adding more than one oral drug if there has been the prior use of PZA or EMB. |
| INH, RIF, and EMB or PZA   | EMB or PZA (if available), a newer-generation fluoroquinolone (MFX or high-dose LFX), injectable agent during the intensive phase (for at least six months beyond culture conversion), and two additional oral agents (LZD, ETA, CS, or PAS). | 18 months beyond culture conversion | In patients with an extensive or cavitary disease, consider a longer duration for the injectable agent, as well as an additional oral drug. |
| INH, RIF, EMB, PZA         | Injectable agent during the intensive phase (for at least six months beyond culture conversion), and a newer-generation fluoroquinolone (MFX or high-dose LFX), and 3-4 oral agents (LZD, ETA, CS, PAS or additional second- or third-line agents if needed). | 18 months beyond culture conversion | In patients with an extensive or cavitary disease, consider a longer duration for the injectable agent. |
| INH, RIF, EMB, PZA, fluoroquinolone (Pre-XDR) | 4-5 second- or third-line drugs (include LZD, BDQ, or DLM) and an injectable agent. | 24 months beyond culture conversion | Duration of injectables should be at least 12 months if tolerated. Consider high-dose MFX. Consider surgery. TDM may be useful. |
| INH, RIF, EMB, PZA, injectables (Pre-XDR) | MFX (or high-dose LFX) plus at least 4-5 second- or third-line oral drugs. Include LZD, BDQ, or DLM. Include an injectable drug if there is one available to which the isolate is susceptible. | 24 months beyond culture conversion | Consider surgery. TDM may be useful. |
| INH, RIF, fluoroquinolone, injectable (XDR) | 5-6 second- and third-line agents, LZD, BDQ, or DLM; high-dose MFX can be added (unless documented resistance). Use PZA and EMB if TB remains susceptible. Include an injectable drug if there is one available to which the isolate is susceptible. | 24 months beyond culture conversion | Consider high-dose INH treatment if low-level resistance is documented. Consider surgery. TDM may be useful. |
WHO recommendations based on the results of a systematic review and individual patient meta-analysis that included 32 studies and over 9000 patients (excluding the XDR-TB patients) reported in 2012:\(^{[11]}\):

- WHO recommends that patients with MDR-TB treat with at least four likely effective drugs as well as PZA during the intensive phase, defined as the first time give the injectable agent.
- Drugs likely to be effective are those that have not been taken previously by the patient and to which \textit{in vitro} drug susceptibility is documented.
- Regimens should include an injectable, a higher-generation fluoroquinolone, ETA, and either CS or PAS and PZA.
- In patients with highly-resistant organisms, consider using group five drugs, and should be in consultation with someone who has experience using these drugs to treat MDR-TB.

WHO recommendations for duration of therapy:

- Intensive phase should be at least eight months.
- The total duration of therapy should be at least 20 months in those who previously not receive any treatment for MDR-TB and at least 24 months in those previously treated for MDR-TB.

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**Figure 1.** Building a treatment regimen for MDR-TB.

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### STEP 1

| First Line Drugs          | Fluoroquinolones       | Injectable agents |
|---------------------------|------------------------|-------------------|
| Pyrazinamide              | Levofoxacin            | Amikacin          |
| Ethambutol                | Moxifloxac            | Capreomycin       |

**Use Any Available**

**One of these**

**One of these**

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### STEP 2

Add second-line drugs until you have 4–6 drugs (optimally at least 5) to which the isolate is susceptible (and preferably which have not been used to treat the patient previously)

| Oral second-line drugs |
|------------------------|
| Cycloserine            |
| Ethionamide            |
| PAS                    |
| Linezolid              |

**Pick one or more of these**

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### STEP 3

If there are not 4–6 drugs available in the above categories, consider third-line drugs in consultation with an MDR-TB expert

| Third-line drugs         | Consider use of these |
|--------------------------|-----------------------|
| Bedaquiline              | Meropenem/Clavulanate |
| Delamanid                | Amoxicillin/Clavulanate |
| Clofazimine              | Clarithromycin        |
| Imipenem                 | High-dose INH         |
5. MDR-TB drugs with antiretrovirals (ARVs) interaction

MDR-TB is a growing public health threat and may be particularly lethal among patients infected with HIV. Although knowledge of the metabolic pathways of some second-line drugs is incomplete because many of these drugs were developed and licensed decades ago, it is believed that most of these drugs do not have significant drug interactions with ARVs. The second-line aminoglycoside antituberculosis drugs are primarily excreted by renal as unchanged compounds and are unlikely to have metabolic drug interactions with ARVs. Fluoroquinolones are also unlikely to have significant drug interactions with ARVs[12]. Since patients with MDR-TB do not receive rifampin, the risk of clinically-significant drug interactions is markedly reduced. However, overlapping toxicities such as nephrotoxicity, QT prolongation on the electrocardiogram, psychiatric side effects, and gastrointestinal intolerance may limit options for co-treatment of HIV and MDR-TB[12].

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