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# Classifying new anti-tuberculosis drugs: rationale and future perspectives

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SUMMARY

The classification of anti-tuberculosis (TB) drugs is important as it helps the clinician to build an appropriate anti-TB regimen for multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB cases that do not fulfil the criteria for the shorter MDR-TB regimen. The World Health Organization (WHO) has recently approved a revision of the classification of new anti-TB drugs based on current evidence on each drug. In the previous WHO guidelines, the choice of drugs was based on efficacy and toxicity in a step-down manner, from group 1 first-line drugs and groups 2–5 second-line drugs, to group 5 drugs with potentially limited efficacy or limited clinical evidence. In the revised WHO classification, exclusively aimed at managing drug-resistant cases, medicines are again listed in hierarchical order from group A to group D. In parallel, a possible future classification is independently proposed. The aim of this viewpoint article is to describe the evolution in WHO TB classification (taking into account an independently proposed new classification) and recent changes in WHO guidance, while commenting on the differences between them. The latest evidence on the ex-group 5 drugs is also discussed.


## 1. Introduction

The World Health Organization (WHO) has recently updated the classification of new anti-tuberculosis (TB) drugs based on a meta-analysis and expert panel recommendations.[1] During the period between the publication of the first WHO anti-TB drug classification and the revised version, an independent proposal for a new classification was made available in the literature.[2] Evidence for further reclassification is lacking and will only be forthcoming with data from new randomized controlled trials (RCTs) aimed at developing better (more effective and tolerated) regimens. However, even though a new classification is not required, discussion on possible future steps has begun,[2] with particular focus on some of the existing second-line anti-TB drugs.

The classification of anti-TB drugs is important as it helps the clinician to build an appropriate anti-TB regimen for multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB cases that do not fulfil the criteria for the shorter MDR-TB regimen.[3,4]

The aim of this viewpoint article is to describe the evolution in WHO TB classification (taking into account an independently proposed new classification) and recent changes in WHO guidance, while commenting on the differences between them. The latest evidence on the ex-group 5 drugs is also discussed.

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## 2. Classifications

In the previous WHO guidelines (2011), the choice of drugs was based on efficacy and toxicity in a step-down manner, from group 1 to group 5 (Table 1). Group 1 included first-line drugs and groups 2–5 included second-line drugs. Group 5 included the drugs with (at the time) potentially limited efficacy or limited clinical evidence.[3,4]

According to the new WHO drug classification (2016), patients with rifampicin-resistant or MDR-TB require a regimen with at least five effective TB medicines during the intensive phase: pyrazinamide and four core second-line TB drugs (see Table 1), one each from group A and group B, and at least two from group C. If the minimum number of effective TB medicines cannot be composed, an agent from group D2 and other agents from D3 should be added to bring the total to five. If pyrazinamide is compromised or cannot be used, the regimen can be reinforced with a drug from group C or D (preferably D2, and if not, from D3). Agents from group D1 are added if they are considered to add benefit (e.g., high-dose isoniazid in patients without high-level isoniazid resistance).[1] The total number of TB medicines included in the regimen needs to balance the expected benefit with the risk of harm and non-adherence.

Based on recent evidence on given compounds, some drugs are likely to increase or decrease in importance in the future.[2]

### 2.1. Group 1

In accordance with drug susceptibility testing (DST), all active group 1 drugs (Table 1) should be included in the regimen, taking into consideration that isoniazid, rifampicin/rifabutin, and pyrazinamide are core drugs and ethambutol is a companion drug. Streptomycin is no longer used routinely.

High-dose isoniazid can be added to an MDR/XDR-TB regimen when the *katG* mutation is not detected by line probe assay, but should not be counted as one of the four active drugs[1,3,4] (although recent evidence suggests the mutation confers intermediate resistance only). Pyrazinamide should always be used, as DST is unreliable; however, it should not be counted as one of the four active drugs.[1,3,4] Rifabutin should be considered if sensitivity is proven and a favourable mutation profile exists.[5] More specifically, if rifampicin resistance is detected with rifabutin susceptibility, rifabutin should be added to the regimen, but not counted as one of the four active drugs.[5]

As the new WHO classification is aimed at managing drug-resistant cases and not all cases, as in the previous classification, group 1 drugs lose priority. In the new WHO classification they belong, in fact, to group D1.

### 2.2. Group A

According to the new WHO classification,[1] group A now includes fluoroquinolones and group B includes injectable second-line drugs. Fluoroquinolones (particularly the later generation fluoroquinolones such as high-dose levofloxacin, gatifloxacin, or moxifloxacin) are core drugs, demonstrating bactericidal and sterilizing activity and a good safety profile;[2,3,6,7] their use predicts a favourable outcome in the treatment of MDR-TB.[7–11] They are the best agents for the treatment of MDR-TB.

### 2.3. Group B

The second-line injectable drugs have only bactericidal and no sterilizing activity. As their safety profile is clearly worse than that of fluoroquinolones, they remain a step below them on the ranking.[2,4,6]

**Table 1**
Summary of the existing classifications of anti-tuberculosis drugs (1 and 2) and possible future changes based on recent evidence (3)

| (1) WHO 2011 TB drugs classification | | (2) WHO 2016 TB drugs classification | | (3) Possible future evolutions | |
|---|---|---|---|---|---|
| *Group 1*<br>First-line oral anti-TB drugs | • Isoniazid<br>• Rifampicin<br>• Ethambutol<br>• Pyrazinamide | *Group A*<br>Fluoroquinolones | • Levofloxacin<br>• Moxifloxacin<br>• Gatifloxacin | *Group A*<br>Fluoroquinolones | • Levofloxacin<br>• Moxifloxacin<br>• Gatifloxacin |
| *Group 2*<br>Injectable anti-TB drugs (injectable or parenteral agents) | • Streptomycin<br>• Kanamycin<br>• Amikacin<br>• Capreomycin | *Group B*<br>Second-line injectable agents | • Amikacin<br>• Capreomycin<br>• Kanamycin<br>(Streptomycin) | *Group B*<br>Other core second-line agents | • Bedaquiline<br>• Delamanid<br>• Ethionamide/ prothionamide<br>• Cycloserine/ terizidone<br>• Linezolid<br>• Clofazimine |
| *Group 3*<br>Fluoroquinolones | • Levofloxacin<br>• Moxifloxacin<br>• Gatifloxacin<br>• Ofloxacin | *Group C*<br>Other core second-line agents | • Ethionamide/ prothionamide<br>• Cycloserine/ terizidone<br>• Linezolid<br>• Clofazimine | *Group C*<br>Second-line injectable agents | • Amikacin<br>• Capreomycin<br>• Kanamycin<br>• Meropenem/ clavulanate |
| *Group 4*<br>Oral bacteriostatic second-line anti-TB drugs | • Ethionamide/ prothionamide<br>• Cycloserine/terizidone<br>• *p*-Aminosalicylic acid | *Group D*<br>Add-on agents (not core MDR-TB regimen components) | D1 • Pyrazinamide<br>• Ethambutol<br>• High-dose isoniazid | *Group D*<br>Add-on agents (not core MDR-TB regimen components) | • Pyrazinamide<br>• Ethambutol<br>• High-dose isoniazid |
| *Group 5*<br>Anti-TB drugs with limited data on efficacy and long-term safety in the treatment of drug-resistant TB | • Linezolid<br>• Clofazimine<br>• Amoxicillin/ clavulanate<br>• Imipenem/cilastatin<br>• Meropenem<br>• High-dose isoniazid<br>• Thioacetazone<br>• Clarithromycin | | D2 • Bedaquiline<br>• Delamanid<br>D3 • *p*-Aminosalicylic acid<br>• Imipenem–cilastatin<br>• Meropenem<br>• Amoxicillin–clavulanate<br>• (Thioacetazone) | | • *p*-Aminosalicylic acid<br>• Amoxicillin–clavulanate<br>• Rifabutin |

WHO, World Health Organization; MDR-TB, multidrug-resistant tuberculosis.