Personalized Tuberculosis Care for Drug-Resistant Tuberculosis

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...I am launching a new Precision Medicine Initiative... to give us all access to the personalized information we need to keep ourselves and our families healthier.

Barack Obama

Summary

Drug-resistant tuberculosis (DR-TB) includes mono-resistant forms of TB and multidrug-resistant tuberculosis (MDR-TB), defined by loss of susceptibility to Rifampicin and Isoniazid. MDR-TB is subdivided along a gradient of further loss of susceptibility, with extensively drug-resistant tuberculosis (XDR-TB) characterized by resistance to any fluoroquinolones and Linezolid or Bedaquiline. Even XDR-TB is far from homogeneous, and neither are patient groups affected by these different forms of DR-TB, with co-infections and comorbidities, differences in genetic background, disease severity, nutritional status, gender, and body composition. Drug exposure relative to minimal inhibitory concentrations for each regimen drug, including core- and companion drugs, determines the outcome. Inter- and intra-individual drug exposure are highly variable; therapeutic drug monitoring (TDM) by measuring drug exposure in multiple blood samples following drug administration is helpful in fine-tuning treatment. Apart from TB drugs, patients may benefit from host-directed

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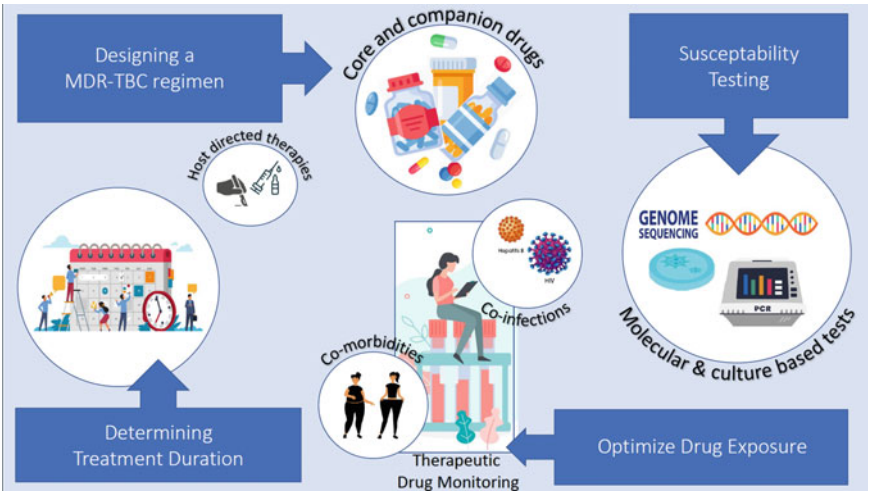
therapies, including therapeutic vaccinations and surgical interventions. TDM is still under development, but appropriate technologies have been developed to apply TDM even in low-resource settings.

Graphical Abstract



The basic components of diagnosing and treating multidrug-resistant tuberculosis (MDR-TB)

Keywords

Individualized treatment · Minimal inhibitory concentration · Multi-drug resistant · Pharmacodynamic modeling · Pharmacokinetic · Precision medicine · Therapeutic drug monitoring · Tuberculosis

1 Introduction

The standard treatment approach for drug-susceptible tuberculosis (DS-TB), as well as drug-resistant tuberculosis (DR-TB), has been extensively addressed. In this chapter, the focus is on the wide range of phenotypes that have one feature in common; drug resistance. Earlier clinical trials have clearly established the strength of standardized treatment, based on Rifampicin and Isoniazid for six months, with the addition of Pyrazinamide and Ethambutol for the first two months for DS-TB [1]. Loss of susceptibility of *Mycobacterium tuberculosis* (*M. tb*) against any of the companion drugs, and even Isoniazid alone, did not seem to alter the response to

treatment [2]. Only by adding Rifampicin, in combination with two months of Pyrazinamide, high cure rates were achieved with a treatment duration of six months [3]. It has long been thought that loss of susceptibility would be accompanied by fitness loss of the organism, which would, in turn, reduce transmission of these less susceptible strains. The focus of TB control was, therefore, on early detection of smear-positive (pulmonary) TB and improved treatment outcome by improving adherence to treatment, primarily by promoting witnessed drug ingestion [4]. Fitness loss has, however, largely been overestimated, and also compensatory fitness gain among DR-TB strains has been identified, which in turn explained how drug resistance could emerge and be transmitted [5, 6]. It has become clear that even Isoniazid mono-resistance is associated with less favourable outcome than TB caused by fully susceptible *M. tb* strains [5].

When Rifampicin resistance emerged unprecedentedly in the 1990s, with the first report from New York City [6, 7], awareness of a real global threat imposed by DR-TB emerged [8]. The problem with drug resistance is that for each pattern of susceptibility to anti-TB drugs, a unique phenotype is established: DR-TB is by definition heterogeneous in nature. Rifampicin-resistant TB (RR-TB) and TB resistant to both Isoniazid and Rifampicin, referred to as multidrug-resistant TB (MDR-TB), may seem homogeneous, but obviously, treatment outcome entirely depends on the completion of a regimen to which the causative microorganism is still susceptible. In general, the successful outcome has been reported at around 50% [9–11]. Clearly, with increasing numbers of drugs to which an isolate is no longer susceptible, the chances to establish an effective drug combination diminish [12]. This happens with XDR-TB, defined as TB caused by an *M. tb* resistant to not only Rifampicin and Isoniazid–making it MDR-TB–but also resistant to one of the fluoroquinolones, as well as–at least–one other group A drug (Bedaquiline or Linezolid). Group A drugs are ranked as the most potent second-line drugs in the treatment of DR-TB (Table 1).[1] XDR-TB carries an even worse prognosis, with the unsuccessful outcome resulting from toxicity of second-line drugs with inherent poor adherence [13] and a loss of core drugs with a high bactericidal and sterilizing capacity [12, 14, 15]. A successful treatment schedule consists of a combination of TB drugs during the intensive phase and a combination that follows during the continuation phase. During the intensive phase, bactericidal activity is primordial to bring the bacterial load down as quickly as possible. In the continuation phase, the selection of drugs is based on its potential to sterilize persister phenotype organisms to eradicate the residual bacterial load of *M. tb*, including difficult-to-reach sites like pulmonary cavities [16, 17] and meningeal [18] and cerebral lesions. Ideally, for each phenotype of MDR-TB, a randomized comparison would allow for evidence-based treatment, whereas individualized treatment is at best guided by expert opinion; see Fig. 1. The tremendous heterogeneity of drug susceptibility makes it extremely challenging, if not virtually impossible, to design randomized trials, to address all the different questions for each subset of patients with

[1] https://www.who.int/news/item/27-01-2021-who-announces-updated-definitions-of-extensively-drug-resistant-tuberculosis.

Table 1 Grouping of medicines recommended for use in longer MDR-TB regimens according to the WHO consolidated guidelines on drug-resistant tuberculosis treatment intended to guide the design of individualized, longer MDR-TB regimens

Group: step	Medicine	Abbreviation
Group A: include all three medicines	Levofloxacin or moxifloxacin	Lfx Mfx
	Bedaquiline	Bdq
	Linezolid	Lzd
Group B: add one or both medicines	Clofazimine	Cfz
	Cycloserine *OR* terizidone	Cs Trd
Group C: add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem–cilastatin or meropenem	Ipm–Cln Mpm
	Amikacin or streptomycin	Am (S)
	Ethionamide or prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

MDR-TB. With the high success rates of individualized treatment in some affluent parts of the world [11, 19–21] and a small margin of non-inferiority, such trials would require large sample sizes for each phenotype of drug resistance. Most drugs in current use are repurposed antimicrobials. There is a paucity of new anti-TB drugs; only two products–Delamanid and Bedaquiline–have reached the market in the last decades, and only a few drugs are expected to be registered in the next few years [22]. Only one treatment schedule with repurposed drugs has been tested in three different settings without a parallel control arm [23–25]. Only one randomized study was conducted with a standard care treatment arm as a comparator [26]. Only one study evaluating a treatment schedule including one repurposed and two novel agents was published, but this study lacked a parallel control group for comparison [27]. Therefore, during the last three decades, the evidence for MDR-TB treatment has been predominantly based on observational, retrospective data [11, 20]. The recommendations following these publications typically provide basic rules, without detailed treatment instructions to be followed [28, 29]. Here, we explain further why individualized treatment is inevitable and necessary for treating MDR-TB, in its different forms, in different patient populations [30–32]. Individualized treatment is widely accepted and appreciated, at least in settings where advanced technologies like molecular testing for mutations in *M. tb* isolates predicting susceptibility or resistance and dosing guidance based on measuring drug exposure are available.

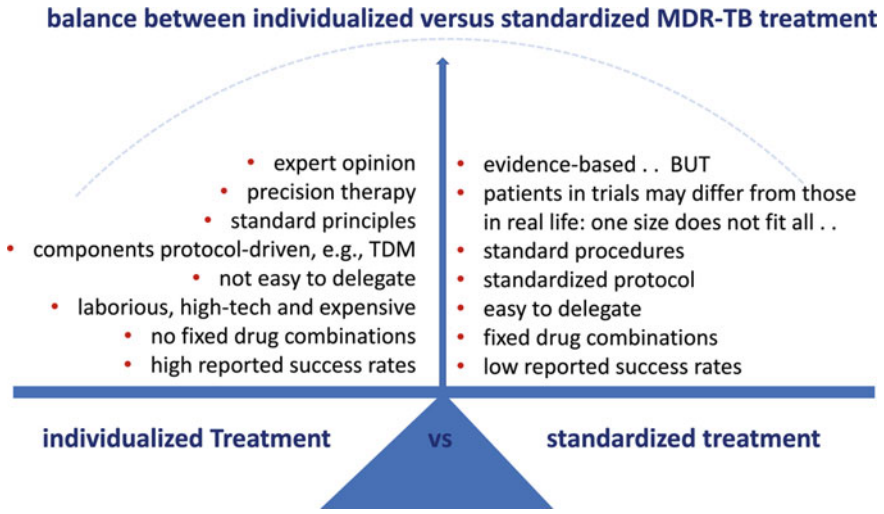


Fig. 1 A balanced discussion of standardized and individualized treatment for MDR-TB

In this chapter, we first discuss the general rules for the treatment of MDR-TB. Next, we focus on phenotypic and molecular tests to select drugs to be used as core drugs and additional drugs as companion agents, both during an intensive phase and during continuation treatment. Then, we discuss the evidence and the logic of therapeutic drug monitoring (TDM), i.e., the science of drug exposure measurement, followed by adjustments in drug dosing to optimize treatment, considering the target drug exposure–related to the minimal inhibitory drug concentration for a given drug, for a particular *M. tb* isolate [33]. Next, we discuss treatment of MDR-TB in patients with co-infections and comorbid conditions; we discuss host-directed therapies; the potential of immunotherapy, using therapeutic vaccinations; the role of surgery; and finally, we provide some general ideas to further advance the field, with a summary and conclusions.

2 Treating Multidrug-Resistant Tuberculosis: Basic Rules of Engagement and Designing a Regimen

The basic rules to design an appropriate regimen for MDR-TB are the following (Fig. 2):

- inclusion of highly potent drugs (core drugs) that
  - rapidly kill and reduce the bacterial burden; and
  - sterilize slowly replicating, persister organisms to prevent relapse;

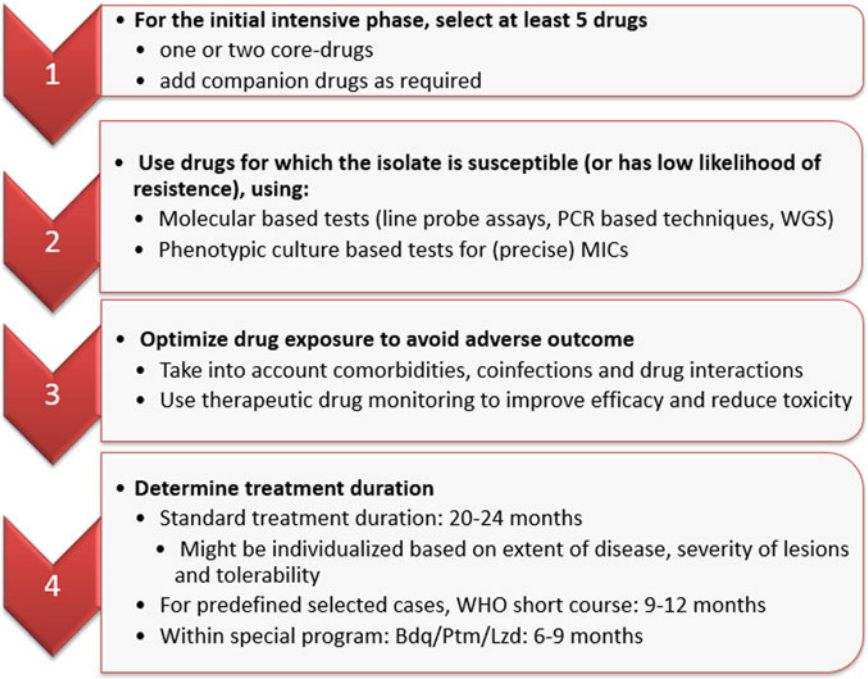


Fig. 2 Strategy on how to design a regimen for MDR-TB

- adding companion drugs to prevent sub-populations of resistant mutants from repopulating;
- drugs to be selected based on susceptibility testing;
- dosing should be adequate, and as drug exposure (i.e., pharmacokinetics) is highly variable, dosing should be guided by measuring drug exposure to improve effectiveness and to reduce the chance of toxicity; and
- treatment duration should be adequate to sterilize lesions, and no longer than necessary, to secure adherence and avoid unnecessary toxicity.

2.1 Individual Drugs

2.1.1 Core Drugs

Some of the TB drugs have high bactericidal activity, which is very important at the onset of treatment to quickly reduce the bacterial burden, and also sterilizing features that are extremely important to attack the sub-population of organisms with low metabolic activity and slow replication rate. This phenotype is referred to as the persister population [34]. Drugs with excellent sterilizing properties reduce the persister organisms and prevent relapse. Core TB drugs have excellent bactericidal

and sterilizing properties. Besides core drugs, several companion drugs are needed to suppress mutant organisms in the bacterial population. For these resistant mutants, it is important to prevent single drug treatment, as this inevitably results in treatment failure [35]. In MDR-TB, the critically important core drug Rifampicin is lost by definition; therefore, a treatment schedule for MDR-TB needs to have at least one, and preferably two, alternative core drugs (see Table 1, on how to build a regimen). Fluoroquinolones are critically important in managing MDR-TB [36]; loss of susceptibility results in a severely reduced chance of favorable outcome, at least with a combination of repurposed drugs [11, 37]. Although an entirely novel schedule with Bedaquiline, Pretomanid, and Linezolid provided promising results, resistance is luring even for XDR-TB [27]. For MDR-TB treatment, the second-line injectables (notably, the aminoglycosides Amikacin, Kanamycin, and the amino-peptide Capreomycin) have long been considered core agents [28]. However, it has been challenged by the analysis of a large observational database, where Kanamycin was associated with impaired outcomes [11]. Fourth-generation fluoroquinolones and the novel agent Bedaquiline may be considered core drugs [38], but also Linezolid is a highly effective bactericidal and sterilizing agent [39, 40].

Bedaquiline has indeed become a cornerstone of treatment for MDR-TB [41–45]. From different parts of the world, Bedaquiline resistance has, however, been reported [46, 47], sometimes in combination with the emergence of resistance to other TB drugs [48]. Bedaquiline is lipophilic, with a long secondary half-life; initial loading is necessary to establish adequate drug exposure in the early phase of treatment [37].

2.1.2 Companion Drugs

High-dose Isoniazid has potential value as a bactericidal agent to quickly reduce the bacterial load in the initial intensive phase of treatment. This may be especially helpful if MDR-TB strains are borderline susceptible for Isoniazid [49], e.g., in most *inh*A mutations, and also in many of the *kat*G mutations–except for mutations in codon 315 [41]. Clofazimine has been identified as an important companion drug with sterilizing capacity [42]. One study showed earlier sputum culture conversion than the control arm, while shorter treatment with clofazimine resulted in an equally successful outcome rate compared to standard treatment for MDR-TB [43]. Clofazimine is highly lipophilic; it binds to fat tissue and causes orange skin discoloration. In many areas in Asia, fair skin color is preferred, and the transient effect on skin color has a stigmatizing effect, with subsequently potentially impaired adherence. We have used this companion drug for a long time now and have not observed major problems in its use, even among patients from Asian descent.

2.2 Susceptibility Testing

The selection of agents in the (individualized) treatment regimen should preferentially be guided by the susceptibility of the organism and tolerability of the patient. Susceptibility testing using in vitro culture and susceptibility testing typically requires several weeks; ideally, not only susceptibility should be assessed,

defined as a minimal inhibitory concentration (MIC) below the breakpoint, but rather, a precise MIC, to enable optimal dosing, considering that the effect of any antimicrobial agent is predicted by drug exposure relative to the susceptibility of the organism [44]. Breakpoints are drug concentrations for which the vast majority of wild-type *M. tb* isolates is still susceptible. There are different breakpoints issued by different international organizations for Clinical Microbiology, the European community on antimicrobial susceptibility testing (EUCAST) being the most commonly followed by clinical microbiologists [45]. Breakpoints for anti-TB drugs issued by EUCAST have been criticized based on in vitro experiments using a so-called hollow fiber model for infections; these models imitate the fluctuating drug concentrations over time as they typically occur in patients following ingestion of anti-TB medication [50–52]. An inherent limitation with culture-based susceptibility testing results is the loss of detection of important drug-resistant subpopulations [53]. The bacterial population–especially in patients with advanced disease–is large; within this large bacterial load, naturally occurring mutants result in a subset of organisms resistant to at least one of the drugs in the treatment regimen [54]; this phenomenon has also been referred to as hetero-resistance [55].

2.3 Adequate Dosing

Some of the drugs in current use against *M. tb* are dosed in the low range of the therapeutic window. An important example is Rifampicin, where costs were an important concern when it was first introduced in the clinic in the early 1970s [2, 56], and its dosing was set at ten mg/kg body weight [57]. Later studies showed that Rifampicin was much more effective in eradicating and sterilizing lesions when administered at 30 mg/kg in a murine infection model [58], a dose that appeared to be well tolerated in humans with TB [59].

Low drug exposure results in the risk that by chance, 5% of the patient population exposed to standard dosing has inadequate drug exposure, allowing for naturally occurring mutant *M. tb* with a replication advantage under antimicrobial pressure that suppresses susceptible organisms, facilitating drug-resistant mutants to expand and repopulate lesions [60, 61]. Under persisting antimicrobial pressure, large numbers of drug-resistant organisms thrive and may, in turn, be transmitted in the population [62]. Adequate dosing to suppress borderline susceptible organisms is critically important to improve and optimize treatment outcomes [63]. Adequate dosing of multiple drugs is therefore primordial in designing a treatment schedule.

For most second-line drugs, drug exposure probably correlates better with the area under the concentration–time curve, $AUC_{0-24\ h}$, than the peak plasma concentration, or C_{max}. $AUC_{0-24\ h}$ is the computed drug exposure measured by drug blood concentrations following the first 24 h after drug ingestion; see Fig. 3. This pharmacokinetic (PK) parameter is divided by the susceptibility of the *M. tb* isolate–the MIC–reflecting the pharmacodynamic (PD) parameter, to arrive at the PK/PD equation: AUC/MIC, for each drug in any given treatment schedule. AUC/MIC targets have not been established for most second-line TB drugs; for

Linezolid, a target AUC/MIC >100 has been proposed [64]; for Moxifloxacin, a target of >53 based on the hollow fiber infection model was computed, and >100, based on animal studies.[2] Because of the potential of variability within the microbial population, the anticipated time delay before final MIC data become available, and the time required to fine-tune dosing based on PK measurements, the preferred design of the initial intensive treatment schedule comprises at least four to five drugs, including one or two core drugs [29, 35]. Drug resistance and susceptibility of *M. tb* are entirely genetically driven; mutations are relatively rare events, but the absolute number of mutants occurring after cell division is considerable in a large bacterial population. Mutants can be detected using molecular methods that, unlike phenotypic culture-based assays, can be made readily available. However, currently, still, amplification using culture is required to harvest sufficient quantities of bacterial DNA to run the tests. Currently, whole-genome analysis is gradually replacing older, PCR-based techniques [65]. Selecting drugs based on molecular assays could be done fairly rapidly, thereby avoiding exposure to unnecessarily toxic and ineffective agents and optimizing dosing based on PK measurement [66]. In summary, TDM has the potential to detect apparently low and apparently high drug exposures, which is a tremendous asset to improve effectiveness and reduce toxicity in patients with MDR-TB [33].

2.4 Treatment Duration

Treatment duration, both for the intensive initial phase as well for the continuation phase, might at some point also be individualized; this is perhaps the most difficult aspect of individualized treatment. The default duration of therapy for MDR-TB, 20–24 months, reflects the duration of therapy before the introduction of Rifampicin and Pyrazinamide, and by convention, the standard duration of MDR-TB treatment has been established at 20–24 months [29]. In practice, clinicians appear to make decisions on treatment duration based on the extent of disease and severity of lesions (e.g., large cavities, or severe forms of the extrapulmonary disease, e.g., meningeal, cerebral, or bone involvement) [16], as well as on tolerability and adverse effects of medication(s). Shorter duration–nine to eleven months and even six months–has been shown to yield successful outcomes in a number of studies. In a cohort study conducted in Bangladesh, a nine-month treatment schedule was tested, which included an initial phase of four to six months of Prothionamide, high-dose Isoniazid, Kanamycin, Moxifloxacin, Clofazimine, Pyrazinamide, and Ethambutol followed by five months of Moxifloxacin, Clofazimine, Pyrazinamide, and Ethambutol. Of the 206 study participants that received this treatment, 87.9% (95% confidence interval, 82.7–91.6) were cured without relapse [23].

The ‘Bangladesh’ regimen was later tested in several African countries, again with generally favorable outcomes [24, 25]. In a multi-center randomized clinical trial (STREAM), participants with MDR-TB in the experimental arm were treated

[2] Mathieu Bolhuis, unpublished data.

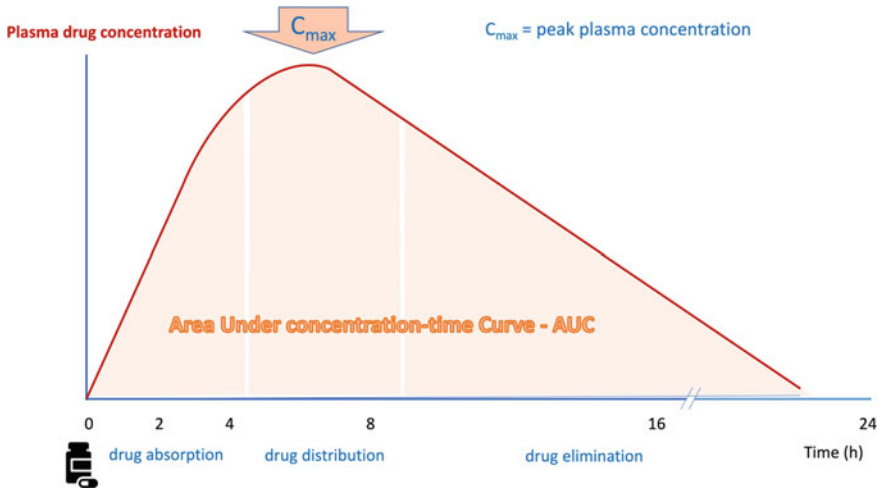


Fig. 3 Basics of pharmacokinetic (PK) analysis, based on drug concentrations measurement over time, following ingestion of a (TB) drug; the curve is the result of fitting, using specific PK software

for 40 weeks with high-dose Moxifloxacin, Clofazimine, Ethambutol, and Pyrazinamide supplemented by Kanamycin, Isoniazid, and Prothionamide in the first 16 weeks; at the pre-defined time point in week 132, 78.8% of study participants in the experimental arm had a favorable outcome, compared to 79.8% in the standard treatment arm; overall effectiveness, as well as adverse effects, were similar in both arms, but among participants receiving high-dose Moxifloxacin, dose adjustments were occasionally necessary if rate-corrected QT (QTc) intervals exceeded 500 ms [26]. Among the fluoroquinolones, exposure to Moxifloxacin relative to MIC is often too low; increased dosing of Moxifloxacin is more problematic than the increase in dosing for Levofloxacin [67], which for that reason might be the preferred fluoroquinolone. Gatifloxacin is probably even better [68], but unfortunately, this drug is currently not available on the market.

In their guidelines, the world health organization (WHO) has accepted a 'short-course' treatment for MDR-TB since 2017, provided that several different criteria were fulfilled, especially susceptibility to core drugs including fluoroquinolones and earlier also, the second-line injectables [69, 70]. Following the considerations mentioned above, a treatment duration between nine and twelve months appears justified, provided that:

- sufficient drug exposure (i.e., PK/PD), as well as drug penetration to all diseased sites, can be safely assumed;
- one or two core drugs with sufficient susceptibility are included in the treatment;
- adverse effects are acceptable; and
- adherence with therapy is optimal.

The major concern of all treatment schedules mentioned above is drug toxicity. Linezolid use is predominantly limited by its neurotoxicity and bone marrow suppression to a lesser extent. In our center, using PK/PD considerations with AUC/MIC targets and following patients with a process referred to as TDM, we have used Linezolid for prolonged periods without appreciable toxicity [71, 72], and we consider this agent as a core anti-TB drug [40].

The use of second-line injectable drugs is perhaps even more challenging. Daily painful intramuscular injections or risks associated with daily intravenous administration may be temporary inconveniences, but nephrotoxicity [73], ototoxicity, and vestibulotoxicity are perhaps even more worrying [74]. In a clinical collection of MDR-TB strains, MIC for Amikacin was one log-step lower than for Kanamycin [75], and therefore, among the injectables, Amikacin would be the preferred drug. In our center, we have meticulously followed patients with audiograms in the past and tailored dosing of aminoglycoside injectables using PK/PD directed dosing [76] with excellent clinical outcome, without any appreciable hearing loss [21, 77]. Still, under the new WHO guideline [70], injectables have only been used sporadically in our center. Figure 4a–c illustrate effective treatment using individualized treatment with TDM in extensive disease, with low toxicity despite prolonged use of Linezolid and Amikacin, and even without adjunctive (surgical) treatment.

If for some reason or other, no reasonable companion drug schedule can be constructed, other repurposed drugs might be considered. Ethionamide/Prothionamide is problematic because of (intestinal) adverse effects; Cycloserine may affect mood severely; and para-aminosalicylic acid is problematic by its large volume and intestinal adverse effects. Drugs to be considered in individualized schedules though currently not included in the list of WHO include Cotrimoxazole [78, 79] and carbapenems, e.g., Imipenem-Cilastatin, Meropenem [80], or Ertapenem [81, 82], preferably in combination with a beta-lactamase inhibitor.

Bedaquiline is definitively in the forefront now for all patients with MDR-TB, although even for this relatively novel agent, drug resistance is emerging [46]; the question of whether penetration into sanctuary sites like the cerebrospinal fluid is sufficient or not remains unresolved [83]. Delamanid is still considered an important companion drug, but its position may change over time [84]. Pretomanid has been included in the novel BPaL regimen [27, 85]; it has been added as a companion drug with low toxicity, fair bioavailability, and no major drug–drug interactions [86].

3 Pharmacokinetic/Pharmacodynamic Modeling: Therapeutic Drug Monitoring

As mentioned above, an important aspect of treatment individualization and precision treatment is monitoring drug exposure (PK) and adjusting dosing accordingly, using the principles of TDM [33]; see Fig. 3. The problem with the PK of drugs is complex but highly relevant [87]: there is a large inter-individual variation

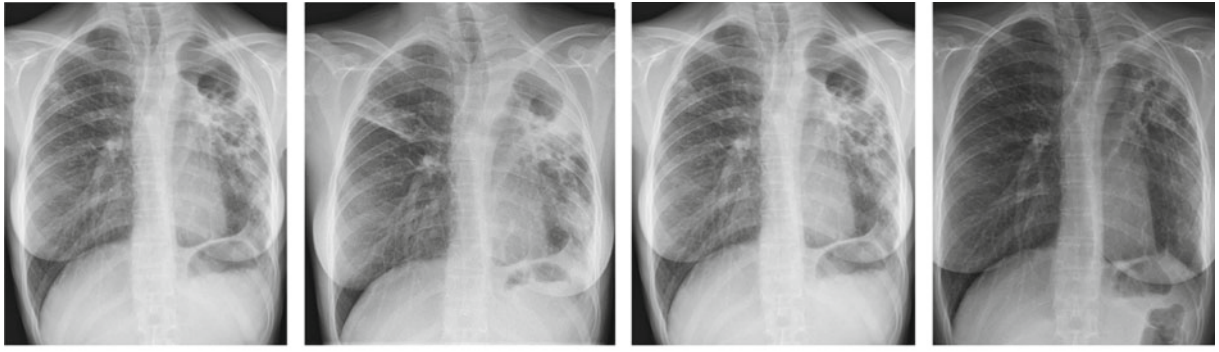


Fig. 4 A patient with severe multidrug-resistant cavitary pulmonary tuberculosis, successfully treated in 2015 with injectable Amikacin, combined with Linezolid, both dosed based on therapeutic drug monitoring; and Pyrazinamide, Prothionamide, Moxifloxacin, Clofazimine, and Cycloserine

in drug handling for many of the second-line TB drugs. For drugs like Linezolid and Moxifloxacin, which are eliminated by liver cytochrome enzymes, genetic polymorphisms vary across the human population; there are many drug–drug interactions. For drugs with renal elimination, the renal function determines the drug half-life. Nutritional status may vary, and drug absorption may be variable between individuals, but also within a patient who may gradually improve clinically gain weight with subsequent increase of the volume of distribution. Finally, concurrent food intake may have a considerable effect on drug absorption, both for the first-line drugs [88] and for various different second-line drugs. To sample venous blood over time and measure drug concentrations using high-tech equipment, like liquid chromatography combined with tandem mass spectrometry, followed by computation of $AUC_{0–24\ h}$ for each drug is challenging, even in affluent settings. MIC for each drug is initially assumed below the EUCAST breakpoint if, based on molecular testing, a wild-type gene is detected in the *M. tb* genome. If MIC is very low, drug dosing can subsequently be further reduced [44, 72]. In clinical practice, the largest asset is by detecting those individuals with toxic or subtherapeutic drug exposure, as they run the highest risk of adverse outcomes. These individuals may even be detected with appropriate TDM technology, using limited sampling combined with dried blood spots that can be sent by ordinary mail under ambient temperatures to a central-based lab facility, even in less affluent settings [89–91]. Patients' prioritization for TDM involves factors such as HIV co-infection, impaired renal clearance, hepatic dysfunction, diabetes mellitus, malnutrition, critical illness, TB meningitis, TB of the skeleton, drug–drug interactions, and poor response to TB treatment despite optimized adherence [33].

4 Host Factors: Coinfections and Comorbidities

Susceptibility to TB is driven by genetic susceptibility [92]. Likewise, pharmacogenetics is also important to explain inter-individual PK variability. To date, most studies have addressed first-line drugs, especially acetylator status variations for Isoniazid drug metabolism, driven by polymorphisms in genes coding for N-acetyltransferase [93, 94] and CYP polymorphisms driving PK and toxicity of Rifampicin [95, 96]. Few studies report on the impact of pharmacogenetics of second-line TB drugs [97]. PK variability is large, even in relatively homogeneous patient populations. However, many potential drug–drug interactions may influence exposure to second-line drugs in patients with chronic viral infections such as HIV and hepatitis B and C, in turn impacting on outcome of co-infected individuals [98]. Obesity is an emerging condition around the world, and it has become increasingly important among patients with TB and MDR-TB as well. For drugs with hydrophilic properties and low volumes of distribution, like aminoglycosides and Ethambutol, dosing should best be calculated on lean body mass [99, 100]. An important and emerging comorbid condition is diabetes mellitus [101, 102], which is notorious for changes in PK of first-line TB drugs [103]; few data on second-line

TB drugs have been published [104]. An association between diabetes and MDR-TB has also been reported [105]. In summary, we propose awareness of risks in drug exposure and therefore advise TDM and individualized therapy in patients with MDR-TB and comorbid conditions and co-infections.

5 Host-Directed Therapies

Statistics on the outcome of TB treatment have conventionally been dichotomized into favorable or successful and unfavorable or unsuccessful [106]. Although these outcome criteria have been extremely helpful to compare treatment schedules, these criteria largely obscure what happens after the successful completion of therapy. Fibrotic pulmonary sequelae may impair exercise capacity, and persistent cavitary lesions and bronchiectatic airways may become secondarily infected by *Pseudomonas* and *Aspergillus* spp. Patients may die prematurely from massive hemoptysis from aspergillomas and infected bronchiectasis long after they have been cured for their MDR-TB. Patients surviving TB meningitis may suffer from neurologic sequela, and patients with TB of the spinal column may experience spinal cord injury [107]. Indeed, many patients experience limitations in daily life, as they suffer sequela and impaired quality of life–and even reduced life expectancy after TB treatment completion [108].

Excessive and transient inflammation may be harmful and treated with anti-tumor necrosis factor-alpha agents, e.g., Infliximab, or anti-inflammatory agents such as corticosteroids [109]. In TB meningitis, the impact of concurrent treatment with Dexamethasone with optimized TB drug treatment though widely practiced has remained controversial [110]. In pulmonary TB, steroids have been discouraged, although severe paradoxical inflammation may respond favorably [111]. In MDR-TB, steroids are even riskier, especially in the early stages of treatment when paradoxical reactions are most common, and MICs for drugs chosen in the initial empirical treatment are less certain. Whether certain co-medications like macrolides might reduce fibrotic changes is currently under investigation in our center. Non-steroidal anti-inflammatory agents may have added benefits [112], but many clinicians hesitate to add these agents in standard care.

6 Therapeutic Vaccination

With the emergence of drug resistance, now even for the novel drug Bedaquiline [46], the daunting prospect of totally DR-TB is looming. With limited treatment options, the concept of enhancing host immune responses might be advantageous [113, 114]. Only a few vaccine products currently under investigation have reached phase III clinical development, and even fewer have been developed as therapeutic vaccine products [115]. Stimulating the immune system during active disease might

seem hazardous and even counter-intuitive because some of the host-directed therapies discussed above try to reduce exaggerated immune responses involved in paradoxical reactions, excessive and harmful inflammation in TB meningitis and central nervous system and spinal cord compression. The evidence from clinical studies with *M. vaccae* vaccination [116] and *Mycobacterium indicus pranii* [117] show no evident harm and some benefit in terms of earlier sputum culture conversion. One ongoing phase IIa trial is in progress, evaluating the immunogenicity and safety of RUTI, a novel anti-tuberculosis vaccine product expressing antigens of an inactivated *M. tb* strain cultured under stress conditions, thereby aiming at enhanced immune responses toward an antigenic repertoire associated with *M. tb* persisters [118, 119]. Clearly, targeting persister organisms–in essence, addressing the issue of sterilizing lesions–is critical to curing TB [34], and any attempt to address this is critically important to achieving a relapse-free cure for MDR-TB.

7 Surgery

For individual patients, individual teams may decide on the potential added value of surgical resection of tissues damaged beyond repair; such decisions are hardly evidence-based and typically depend on locally available skills and experience of surgical teams. Surgery is important in TB of the axial skeleton, and drainage of large pleural effusions and abscesses associated with TB of bone and lymph nodes is equally important. The role of resection surgery in pulmonary MDR-TB has predominantly been addressed in anecdotal case reports and series. A database of MDR-TB patients comprising over 6000 individual patient records was analyzed to detect any potential benefit of added surgery [120]. In this large database, partial but not total pneumonectomy was associated with improved outcomes. Observational data like these are potentially highly confounded by indication, and selection bias cannot be ruled out [121]. The position of surgery, therefore, remains adjunctive, as it may have added value in selected cases [122].

8 Conclusion

With the unprecedented emergence of drug resistance, individualized treatment for MDR-TB is inevitable and necessary. The down-side is obviously the limited scientific evidence; each individual group of resistance, and each identifiable group of patients with unique comorbid conditions, genetic background, nutritional status, the severity of disease, mix of pulmonary and extrapulmonary disease, and co-medications, would obscure any potential positive effect if groups of patients are too small and too heterogeneous to conduct a meaningful randomized trial with a relevant control regimen. Perhaps the only way to provide evidence for individual patients to entrust the proposed individualized treatment regimen would be to randomize individualized against standardized treatment for MDR-TB. The

evidence would otherwise need to come from the notion that in vitro and molecular testing of drug susceptibilities, combined with measured drug exposure, provides the best possible way for successful treatment outcomes. The evidence for the efficacy of individual drugs is only derived from large retrospective database analyses. Many questions remain unanswered, but the general principle that even the worst forms of MDR-TB are potentially curable should set the scene to aim high and attain high cure rates. New drugs are in the pipeline, like the Linezolid analog, Sutezolid [123], with lower MIC and potentially lower toxicity that might therefore be a suitable replacement for Linezolid [124]. Not only survival following treatment completion and cure, but also reduction of sequela and improved quality and quantity of life after completion of therapy are important. TDM is critically important, and it should be included in international guidelines for the management of MDR-TB. Providing adequate exposure to each of the drugs included in the regimen is critically important to improve the outcome of individual patients as well as to reduce the transmission of MDR-TB. During treatment, PK parameters may change over time, and in certain conditions like pregnancy, these changes may be dramatic, therefore requiring multiple interventions of TDM [125]. Molecular tests predicting susceptibility are gradually improving, but their weakness at this point in time is that they do not (yet) predict MIC reliably, and MIC for each drug in the regimen is critically important for those drugs that have a relatively narrow therapeutic window. The ambitious targets set by the UNION and the WHO to eradicate TB in the next two decades cannot be met without an increased effort to target MDR-TB; individualized treatment is essential to combat this daunting condition.

Core Messages

- MDR-TB is a daunting novel epidemic that frustrates efforts to defeat TB any time soon.
- MDR-TB management requires novel molecular diagnostic tools with fast lab turn-around times.
- MDR-TB treatment requires measures such as TDM to optimize efficacy and reduce toxicity.
- Host-directed therapies hold promise to further improve outcomes.

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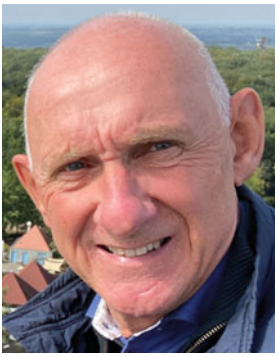

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