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Individualizing management of extensively drug-resistant tuberculosis: diagnostics, treatment, and biomarkers

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ABSTRACT

Introduction: Success rates for treatment of extensively drug resistant tuberculosis (XDR-TB) are low due to limited treatment options, delayed diagnosis and inadequate health care infrastructure.

Areas covered: This review analyses existing programmes of prevention, diagnosis and treatment of XDR-TB. Improved diagnostic procedures and rapid molecular tests help to select appropriate drugs and dosages. Drugs dosages can be further tailored to the specific conditions of the patient based on quantitative susceptibility testing of the *M. tuberculosis* isolate and use of therapeutic drug monitoring. Pharmacovigilance is important for preserving activity of the novel drugs bedaquiline and delamanid. Furthermore, biomarkers of treatment response must be developed and validated to guide therapeutic decisions.

Expert commentary: Given the currently poor treatment outcomes and the association of XDR-TB with HIV in endemic regions, a more patient oriented approach regarding diagnostics, drug selection and tailoring and treatment evaluation will improve treatment outcome. The different areas of expertise should be covered by a multidisciplinary team and may involve the transition of patients from hospitalized to home or community-based treatment.

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1. Background

Tuberculosis (TB), caused by *Mycobacterium tuberculosis* (*MTB*), is now the leading cause of death from an infectious disease worldwide. Around 1.5 million of the 9.6 million people who developed TB died from this disease in 2014 [1]. Emergence and spread of multidrug-resistant (MDR) *MTB* strains affect about half a million people worldwide annually. MDR-TB is defined as resistance to isoniazid and rifampicin. The incidence differs by geographic region and ranges from 3.3% in newly diagnosed cases to 20% in previously treated patients [1]. Even more worrisome is the average incidence of MDR-TB in retreatment cases in Belarus of 69% [1]. Approximately 34% of newly diagnosed TB patients have MDR-TB [1], which reflects the importance of transmission of MDR-Tb strains. Extensively drug-resistant TB (XDR-TB) is defined by MDR-TB with additional resistance to a fluoroquinolone and a second-line injectable drug (amikacin, kanamycin, or capreomycin). Especially, the

spread of MDR/XDR-TB strains of the Beijing genotype is of a great concern [2]. Treatment success of MDR-TB is generally around 50%, lower (20%) and higher success rates (80%) have been reported depending upon comorbidities and available diagnostics and available drugs within these cohorts [1,3]. Treatment becomes truly difficult in cases where the fluoroquinolones or injectables cannot be used and the oral bacteriostatic drugs were the only treatment options left. Success rates for XDR-TB treatment are therefore generally quite low; those with treatment failure remain at risk of transmitting infection, and those able to be microbiologically cured can suffer considerable morbidity including chronic lung disease and permanent treatment-related adverse events[4]. Two novel drugs, bedaquiline and delamanid have recently been approved for use within some treatment programs, while other antimicrobial agents licensed for other infections are often used in combination or as a last resort [5–7]. This reviews aims to give a concise

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overview on the new developments in prevention, diagnosis, and treatment of XDR-TB.

2. XDR-TB care as part of TB program; current situation

The dimension and order of magnitude of the emerging XDR-TB was for the first time realized only when the so-called 'Tugela Ferry outbreak' was reported in 2006 and stimulated concerted global action. In this first report, 52/53 XDR-TB inpatients succumbed to their infection within a median of 16 days and 44/44 patients tested were HIV coinfecting [8].

Important for a positive treatment outcome in MDR/XDR-TB is that those patients diagnosed are appropriately 'channeled' toward optimal care: a study from South Africa on MDR/XDR-TB patients demonstrated that tracing patients following establishment of a diagnosis is of the utmost importance. The most frequent reason for non-referral of diagnosed patients for specialist care was loss to follow-up [9].

Outcome determinants in XDR-TB patients are, not limited to HIV coinfection or the specific therapeutic regimens applied, but include also overall the access to drugs [10], the utilization of care which can often be hampered by stigma [11], and the level of care available. High levels of care for drug-resistant TB or among HIV coinfecting patients do not necessarily need to be hospitalized [12]. Demands for treatment programs include quality-assured drugs, regimens being based on an adequate number, and the selection of effective drugs given for an appropriate duration [13].

Whilst the role of individual drugs is not ascertained [13], it has been suggested that in areas of high prevalence where drug-susceptibility testing may be incomplete, that the use of drugs which are not widely used in this particular setting is an essential contributor to success [14]. Although increasing resistance from MDR to XDR-TB and has been associated with stepwise increase in poor outcome, and weighted relative risks for each drug have been ascribed [15,16].

In some well-resourced settings with low drug-resistant TB endemicity, rather than novel drugs, meticulous therapeutic drug monitoring (TDM) [17] and adverse event assessment alongside repeated resistance assessments are major determinants associated with positive treatment outcomes [3].

Standard therapy for drug-sensitive TB follows established guidelines; however, to date, globally harmonized treatment standards for MDR-TB and XDR-TB in particular do not exist. The global surveillance data on TB drug resistance has significantly improved in detail and hence accuracy over the past couple of years, as a consequence of higher coverage for drug susceptibility testing [1]. Limited resources are an obvious reason for not getting close to optimal diagnosis and treatment of particular higher degrees of MDR/XDR-TB in most settings. WHO has issued guidelines for programmatic management of TB alongside with a comprehensive handbook that details all treatment aspects of MDR/XDR-TB [18,19]. Treatment should be either on an in- or outpatient basis (a recent systematic review and meta-analysis of hospital- versus ambulatory-based management of multidrug-resistant TB did not yield statistically significant differences for all the

outcomes considered) [20]. Nevertheless specialist guidance and within the framework of a national program to warrant optimal treatment regimen design, infection control, as well as contact tracing standards are essential elements.

With regard to treatment access, support and as a result favorable outcomes, WHO suggested as one of the main reasons for inadequate access to diagnosis and treatment of DR-TB, that the programmatic management of DR-TB (PMDT) is often too centralized; with hospital-based models of care being considered a barrier to PMDT expansion due to their dependency on hospitals or referral centers. Wider use of ambulatory care is considered as the way forward [1].

An example for standardized, elaborated treatment guidelines in a high burden country are the South-African guidelines [21]. An example for a highly individualized approach in an affluent, low-endemic setting is the Netherlands [3]. However, for clearly understandable reasons, given the complexity of the issue and the difficulty of obtaining unambiguous results within a reasonable time frame, guidelines for the management of DR-TB are still largely based on expert opinion. These remains, limited observational data on drug regimens based on drugs for which there is often only limited evidence of efficacy to date [22].

3. Special cases; XDR-TB/HIV

The coinfection of human immunodeficiency virus (HIV) and XDR-TB complicates disease management and treatment outcomes significantly and is mainly concentrated in sub-Saharan Africa [12]. In South Africa where HIV diagnostic testing and capacity for drug-susceptibility testing of *MTB* isolates is robust, 40–80% of patients with XDR-TB are HIV infected [23,24]. In the Russian Federation and Eastern Europe, XDR-TB and HIV are often associated with injection drug use [25]. In a Latvian cohort of 5,200 TB patients, the risk of developing drug-resistant TB was double in HIV infection compared to those without HIV [26]. Delay in XDR-TB diagnosis contributes to poor treatment outcomes among HIV-infected patients. Higher rates of extrapulmonary disease and smear-negative TB in the HIV-infected patients limit diagnosis from sputum. Effort in culturing the isolate is imperative, and aspiration of lymph node and pleural fluid, as well as mycobacterial blood and urine culture, have been of additive yield in diagnosing XDR-TB in some HIV-infected cohorts [27].

Once TB is diagnosed in HIV-infected patients, international consensus now favors antiretroviral (ART) naïve patients to start ART within 2 weeks of starting treatment on TB if $CD4 < 50 \text{ cells/mm}^3$ or if there is significantly advanced disease [28]. Second-line TB drug and ART interactions or additive toxicities must also be monitored closely. For example, neuropsychiatric effects of efavirenz and cycloserine/terizidone have been recorded, but also ototoxicity, nephrotoxicity, and electrolyte abnormalities of capreomycin and tenofovir, hematological abnormalities related to earlier generation nucleoside reverse transcriptase inhibitors such as zidovudine and linezolid, gastrointestinal side effects associated with many ART drugs, thionamides and para-aminosalicylic acid, and ototoxicity from injectable agents has been frequent among

studied cohorts of with HIV coinfection [29–31]. The integrase inhibitor class of ART offers less interaction with second-line TB medications but is not routinely available in many highly TB endemic settings. There is accumulating evidence for the safety and efficacy of bedaquiline in HIV-infected patients with XDR-TB. In the South African early access program for bedaquiline, the majority were HIV infected and of those remaining on bedaquiline with 6 months of follow-up, 48 (76%) had either culture converted or remained culture negative, a significant improvement from historical norms [32]. Formal trials of delamanid have to date enrolled very few patients with HIV and none on ART [33]. The phase III trial of the completely oral regimen of bedaquiline, pretomanid, and linezolid does include HIV-infected patients but with CD4 count and ART regimen-based exclusions limiting the number of those participants who belong to the most important target group (Clinical Trials Gov NCT02333799).

4. Prevention of XDR-TB during MDR-TB treatment

XDR-TB can be primarily transmitted from person to person or secondary to the development through high bacillary load, inadequate treatment (poor compliance, iatrogenic, drug stock outs, programmatic weakness), low body mass index, or previous failures [34–38]. Prevention of the development of drug-resistant TB is essential given the recent worldwide increase in incidence. An example of important steps to prevent XDR-TB come from Tugela Ferry in the KwaZulu-Natal province of South Africa following sustained nosocomial and community transmission of XDR-TB. Since the initial report of XDR-TB in that community in 2006, considerable effort toward infection control, intensified community-based TB and HIV case finding and methods to decrease nosocomial transmission have curbed the local epidemic [23,39]. Nevertheless, mortality remains associated with modifiable risk factors such as lack of receipt of ART, suggesting further programmatic interventions could improve treatment outcome [23,40]. Prevention can be strengthened through the programmatic expansion of treatment access and infection control strategies and enhancement of basic healthcare infrastructure, which are the cornerstones of a TB control program. Early awareness and diagnosis of drug-resistant TB is essential to limit spread. Recognition of risk factors for drug resistance would provide useful clues; history of erratic past treatment, close contact with drug-resistant TB, drug addiction, alcoholism, and migration from an area endemic for drug resistance [41]. New drugs may also help to ameliorate the development of drug resistance by more rapid sputum conversion and perhaps shortening the duration of treatment of TB [42]; however, adding single active drugs to a failing regimen may lead to further resistance. Furthermore, amplification of drug resistance may occur while on apparently adequate treatment, given problems with malabsorption, altered drug metabolism or drug interactions with concomitant antiretroviral therapy (ART), also play a role [43,44].

5. Diagnosis of XDR-TB; DST/LPA

Since the introduction of molecular assays for the detection of resistance, MDR-TB can generally be diagnosed readily within hours [45] and this is the first step in early diagnosis of XDR-TB. The GeneXpert MTB/RIF (Cepheid, Sunnyvale, USA) can efficiently detect rifampicin resistance in most MDR-TB cases, although in the first version of the test, especially in geographic areas with a low prevalence of MDR-TB, false-positive tests are a problem [46]. This is associated with the detection of a mutation not associated with rifampicin resistance. In the new version of the GeneXpert cartridge (the 'Ultra'), this problem should have been solved. In addition, the sensitivity in the detection of *MTB* in ZN-negative sputa approaches that of culture.

In comparison to the GeneXpert, the advantage of line probe assays (LPA) in the detection of MDR-TB is that the detected resistance mutations in most cases can be characterized. LPA allow a range of mutations in amplified DNA to be screened by hybridization to a macro-DNA array [47]. Although these tests are technically more demanding and require more expertise of the laboratory staff involved, this offers a high degree of confidence in the diagnosis of MDR-TB [48]. Nevertheless, it remains important to establish the positive and negative predictive value of LPA in each geographic region where they are implemented [49]. Clinicians should not be confronted only with the specific details of the results of such tests, but with probabilities that *MTB* is resistant, or MDR. Especially in the molecular detection of resistance against fluoroquinolones and amino glycosides, detection of a mutation in particular genomic targets of *MTB* does not always imply resistance [49]; the predictive value of each mutation differs significantly, and expertise in translating laboratory findings into predictive values for clinicians is of the utmost importance. For more information on genes and mutations, we refer to more dedicated in-depth reviews [47].

The next step in the molecular detection of MDR- and XDR-TB is whole-genome sequencing (WGS). Where in the current molecular assays the most important genomic targets in *MTB* are investigated for the presence of resistance mutations, in the future around 25 genes that have ever been associated with resistance against antituberculous drugs can be simultaneously examined for alterations in comparison to the native sequence [50]. However, for many infrequently encountered mutations, the predictive value needs to still be established, especially for drugs not regularly used in treatment of resistant TB.

The standard phenotypic drug susceptibility testing usually involves testing of the inhibition of growth of *MTB* at the critical concentration of the drugs. Nowadays, the MGIT960 is the gold standard. However, treatment of MDR/XDR-TB should be individualized and based on a combination of true minimum inhibitory concentration (MIC) of drugs when testing the *MTB* isolate *in vitro* and the plasma levels that can be achieved in the respective patient [17,51,52]. This may become in reach of more laboratories when cheaper MIC methods will be standardized, like the 96-well Sensititre approach [53].

6. Treatment of XDR-TB

Treatment of XDR-TB is a significant challenge given the limited data on treatment regimens and outcome. A meta-analysis showed that the likelihood of cure seems to be lower than in MDR-TB cases, between 18% and 67% [54]. These authors also reported that the use of later-generation fluoroquinolones increased positive-treatment outcome by 40%, though the susceptibility of the later-generation fluoroquinolones is not routinely tested in all settings [54]. An analysis by Falzon et al. showed that treatment success was highest when the treatment regimen contained 6 drugs in the intensive phase and at least four in the continuation phase [55]. In another meta-analysis resistance to all injectables showed significantly worse outcome compared to just resistance to a single drug of this class; also the odds of treatment failure and death were higher in all patients with XDR-TB and an additional resistance [15,16,56].

The WHO recommends that the treatment regimen for XDR-TB should contain pyrazinamide or ethambutol in case *MTB* is susceptible. As shown by Jacobsen et al., a higher generation fluoroquinolone of group A should be used, e.g. moxifloxacin, levofloxacin, or gatifloxacin [19]. Also a second-line injectable agent of group B should be used. The use of all group C drugs that were not used in a previous regimen should be applied. In the new drug classification of the WHO (see Table 1), linezolid and clofazimine are promoted from drugs with unclear efficacy to core drugs for MDR TB treatment [19].

A recent study by Lee et al. showed 27 out of 38 patients treated with linezolid still had negative sputum culture results 1 year after ending treatment [57]. Side effects appear to be dose related, but the dose of linezolid can be decreased without losing efficacy by using TDM [57–61].

Clofazimine added to the treatment of MDR/XDR-TB showed good results; however, only 66% of the patients with XDR-TB in this meta-analysis experienced favorable outcome [62]. Preliminary data suggest that clofazimine improves killing of persisting *MTB* and might therefore be useful to prevent amplification and thus improve outcome.

Bedaquiline and delamanid are two newly approved anti-TB drugs and are classified as group D2 drugs. Bedaquiline has

only been studied with culture conversion as primary outcome parameter. Studies showed faster and more frequent culture conversion in patients with MDR/XDR-TB compared to placebo or using bedaquiline in treatment regimens [63–65]. A study with delamanid for only 2 months showed earlier sputum culture conversion as well [66]. Recently, the first report using both drugs at the same time was published and this was well tolerated.

Other drugs are categorized in group D3 or are more experimental. The combination of meropenem-clavulanate for XDR-TB was recently studied by Tiberi et al. showing the same culture conversion rates for patients with XDR-TB compared to MDR-TB, whereas only 6 patients out of 96 showed adverse events [67,68]. Recently, the first studies using ertapenem in MDR/XDR-TB patients were published. One study showed favorable results in 3 out of 5 patients. The other two died shortly after start of treatment [34]. Van Rijn et al. showed a favorable pharmacokinetic/pharmacodynamics (PK/PD) profile for this drug in MDR-TB patients. These obtained results and the easier possibility of administering this once per day dosed carbapenem at home makes it a promising drug for the future [69].

Older drugs that have recently been restudied for TB are co-trimoxazole and thioridazine. Alsaad et al. studied PK/PD data of co-trimoxazole in 10 patients [70]. It was well tolerated, though the free area under the concentration time curve/MIC ratio of more than 25 was reached in only one patient. Thioridazine, an old antipsychotic, showed promising results in an Argentinian study in 2012 with cure in 10 out of 12 patients. This drug also might contribute to earlier sputum conversion [71], due to its inhibitory effect on efflux pumps and, hence, an accumulation of drug in the intracellular environment, resulting in cell death.

Recently, an 8 step approach for designing a XDR-TB regimen containing at least 5 active drugs used an online decision tool to help physicians [72]

TDM and PK/PD science seems a valuable asset to optimize drug exposure of individual drugs in relation to drug susceptibility and patients' tolerance to the drug [73]. Supportive evidence from *in vitro* studies have shown a clear relation between drug exposure and efficacy of treatment [74,75]. Moreover, acquired drug resistance could be reproduced in these models. Clinical data to support TDM originates from nonrandomized studies making it difficult to assess its true value. However, its potential use for optimizing treatment in individual patients is more and more appreciated in TB referral clinics. Availability of simple tools to perform TDM may facilitate implementation in a programmatic setting.

7. Potential role of host-derived biomarkers in treatment guidance

As mortality rates are very high (around 30–80%) for XDR-TB, there is an urgent need for measuring the response to its treatment [54]. Optimizing treatment of XDR-TB cases is complex as response is dependent on the infecting strain, host metabolism, quality of the drugs, and compliance as well as other factors. Most testing as currently used looks at one of the factors. By using nonspecific host markers as surrogate markers to quantify clinical response could help determine the

Table 1. The new WHO table for rifampicin resistant and MDR TB [19].

A. Fluoroquinolones #		Levofloxacin Moxifloxacin Gatifloxacin
B. Second-line injectable agents #		Amikacin Capreomycin Kanamycin
C. Other core second-line agents		Ethionamide/Protionamide Cycloserine/Terizidone Linezolid Clofazimine
Add on agents	D1	Pyrazinamide Ethambutol
	D2	High-dose isoniazid Bedaquiline Delamanid
	D3	P-aminosalicylic acid Imipenem-cilastatin Meropenem Amoxicillin-clavulanate

For XDR-TB: use any drug from group A /B for which susceptibility is proven.

response to treatment as a result of the interaction of all these factors. Detailed studies focused on disclosure of patient biomarker with prognostic profiles to demonstrate the disease or treatment success, but remained elusive [76,77]. None the less, the kinetics of nonspecific disease-associated biomarkers are increasingly recognized as having potential for the monitoring of treatment success and could play a role in guiding the therapy of complex (M[X]DR-TB) cases [78,79].

Host-derived markers are universally present in healthy and disease individuals and the levels present in healthy individuals are in almost all cases already established. This is in contrast to pathogen-derived markers (such as pathogen DNA) which are only present in diseased individuals and in a proportion of patients may be at barely detectable levels. Therefore, although highly specific pathogen-derived biomarkers remain challenging to detect in all patients this combined with the lack of highly specific antibodies associated with TB infection is the main challenge for TB diagnostics. We suggest that the kinetics of relatively less specific host biomarkers in response to treatment may have advantages over monitoring pathogen-derived biomarkers for many patients [80–82].

Multiple studies have demonstrated that there is a measurable and consistent response related to TB disease severity and or the effect of therapy [83–88]. Early evidence suggests that these responses will be informative before culture or microscopic conversion is currently detected [78,79,89,90]. Thus, as measuring the response of host biomarker kinetics has the potential to be both simple and rapid [91], measuring biomarkers deserve attention. Moreover, biomarkers can also be applicable to atypical cases (non-pulmonary and infections in children).

Treatment of TB and particularly XDR-TB is complex and long. In order to achieve universally good outcomes, even with new regimens, personalization of treatment will likely remain necessary for at least a proportion of patients. Optimizing treatment in an individual approach has several different aims: at one extreme some patients may be effectively cured long before the end of the standard treatment duration and may be exposed to toxic drugs for an unnecessarily long period. A second group of patients respond to treatment but is not fully cured and is at risk of relapse after the standard duration of treatment. Finally, for a variable proportion of patients, host factors, drug levels achieved, or bacterial resistance undermine the regimen and treatment fails. Each of these issues can be addressed by bacterial phenotyping as well as monitoring of drug levels as discussed elsewhere in this review. Whatever is measured, the ultimate aim, to optimize treatment and treatment duration, is an accurate ‘test of cure.’

As a fully standardized treatment that is optimal for all patients is currently not available in order to minimize under, or over, treatment an easily measurable biomarker signature closely associated with successful cure is desirable. This remains an area of intensive work [77,92,93]. Related to this aim, it is worth noting that ‘successfully treated’ TB patients are one of the primary groups at risk of developing active TB again, with a risk of around 2000 per 100 000 person years [94]. Disease-associated host biomarkers, useful for treatment monitoring based on transcriptomic [95], metabolic [96], or

immunological markers [97] could thus also have a role in screening high-risk groups including patients post treatment or latently infected individuals to monitor increased chance of break down to active disease.

The kinetics of the most promising biomarkers are now being validated in independent studies and initial data suggest that at least some the associations identified are reproducible [78,79,90,97]. Differences in host marker responses between sensitive and MDR-TB patients have been observed. However, more detailed analysis as well as larger studies are needed to accurately determine the sensitivity and specificity of these responses and their link with particular drugs and drug resistance profiles. Biomarkers that respond to effective therapy would not only be valuable to individually optimize therapy of MDR-TB and XDR-TB patients but also facilitate the development of new treatments approaches [98]. Pre-validated biomarkers with reproducible kinetics in independent studies must then be tested, in standardized formats, for specificity and sensitivity and ultimately clinical impact in larger cohorts. The collection and measurement of samples suitable for this type of analysis should be considered when planning larger treatment trials in order to advance treatment monitoring from microscopy and culture toward rapid near-patient measurements. To date, only few studies have been able to contribute to the understanding of biomarkers during TB treatment of which the most promising is the whole-blood bactericidal activity is uniquely suited to assess the combined effects of host-directed chemotherapy and antimicrobial chemotherapy [5].

8. Design of XDR-TB care; a patient-centered approach within a programmatic framework

Programmatic management of XDR-TB comprises four main elements: case finding, treatment regimens, monitoring the response to treatment, and selecting models of care [18]. Case finding of XDR-TB is generally a two-step approach: diagnosing MDR-TB, followed by identifying resistance to FQ or injectables (XDR if resistance to both drug classes is detected, pre-XDR if resistance to one class is found). Ideally, using molecular assays provide rapid results. Rapid diagnosis of (pre-)XDR is becoming important especially now that the 9-month ‘Bangladesh’ regimen is showing promise [99,100] and results from a clinical trial are expected soon [101]. WHO recently endorsed this short-course regimen for MDR-TB [19]. While this much shorter treatment has clear benefits over the standard 20–24-month second-line regimen but is likely ineffective when (pre-)XDR-TB is treated. Patients are thus ideally triaged for shortened or standard treatment using specific molecular assays (LPA) but to date these have incomplete sensitivity for both drug classes [102]. In addition for injectables (kanamycin, amikacin, capreomycin), there is partial cross-resistance with specific mutations being associated with different levels of resistance to each of these drugs [5]. While standardization of non-(pre-)XDR MDR-TB treatment is increasingly possible, the limited choice of effective drugs and their unfavorable toxicity profile leave treatment regimens for XDR-TB to be highly individualized. These will likely include new drugs such as bedaquiline and delamanid. Programmatic

introduction of new TB drugs has several requirements including assuring access; supply of chain management and training, but also pharmacovigilance to detect toxicities not identified in the relatively small phase II trials on which their conditional approval was based [103]. Treatment response monitoring is important not only for patient management but also for evaluating the treatment program through regular cohort analysis (e.g. quarterly interim analysis) [18]. It should be based on sputum culture, with cure defined as a patient who has completed treatment with no evidence of failure and three or more consecutive negative cultures taken at least 30 days apart after the intensive phase [104]. The definition of treatment failure includes the need for a permanent regimen change with at least two active anti-TB drugs for efficacy, to halt resistance progression, and also to allow for redundancy for potential adverse drug reactions. The latter has been challenged [105]. The lengthy treatment with often severe toxicities call for social and psychological support for this often vulnerable patient group [106]. Providing patient-centered care, i.e. care that is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions, is all the more important to support patients and enhance treatment adherence and completion [107]. In most XDR endemic settings, substantial effort has to be made to achieve cure in substantial proportion of the patients to prevent being discharged to the community. A patient-centered care model should involve individualized locations of care (community versus hospital, etc.), regimens (TDM/MIC), multidisciplinary (psychological, social and nutritional support), and novel aspects of adherence. In situations of palliative care, safe infection control practices are of utmost importance for transitioning a patient into the community [24,54].

9. Conclusion

Although treatment of XDR-TB is challenging, the introduction of intensified care that is based on individual case consideration is the solution (Figure 1). Moreover, development of drug resistance while receiving treatment for MDR-TB should receive more attention. The intensified care of XDR-TB patients starts with rapid diagnostics with molecular techniques followed by sensitivity testing in combination with assessment of drug exposure to advance the selection of the most appropriate treatment regimen. Daily observed therapy in

combination with early assessment of adverse events should prevent adherence problems and cases lost to follow-up. If novel drugs are incorporated in such an approach, treatment success will likely increase to levels that are reached for those with MDR-TB.

10. Expert commentary

As laid out above, the global threat of XDR-TB is real, with many challenges that need to be overcome before significant treatment success can be achieved. Currently, treatment outcome results are still poor and may be worse still given the relative lack of monitoring treatment. Van Altena et al. reported good treatment results in MDR-TB patients with individualized treatment using a mix of strategies [3]. The backbone is the specialized TB centers that can deliver all these strategies and should therefore play a major role in the treatment of XDR-TB. Both when the patients are hospitalized or with a supervising role in case of ambulatory care.

The choice of drugs for the therapy of XDR-TB should be based on drug susceptibility testing results. In high-burden settings, where resources are often limited, molecular resistance assays are used instead as they have a high throughput and superior performance characteristics to conventional culture and drug-susceptibility testing [108]. However, individualized treatment is based on true minimum inhibitory concentration (MIC) of drugs when testing the *MTB* isolate [17,51,52]. In addition to easy-to-implement MIC testing [109], a central reference laboratory is crucial for optimal treatment outcome in XDR-TB.

Individualizing treatment is based on pharmacokinetic results of the drugs measured in a patient in relation to the MIC of the isolate of that patient. Full curves can be easily achieved when patients are admitted. In an ambulatory or low-resource setting, limited sampling strategies can be done using dry blood spots [110–112]. These filter paper cards can be sent to central laboratories where the blood drug concentrations can be analyzed by punching the blood spot followed by subsequent extraction and analysis using mass spectrometry [17].

Surgery as part of the treatment for XDR-TB is also an individualized intervention. Selection criteria for surgical resection for MDR-TB were described by Iseman et al. and are still in use [113]. Surgery is an option in patients when treatment failure or relapse is very likely or when localized disease

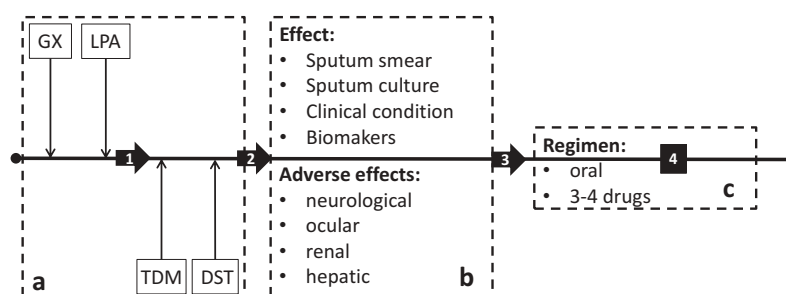


Figure 1. Overview of XDR-TB treatment. A: initiation phase, B: intensive phase, C: continuation phase, 1: treatment regimen based on GX and LPA, 2: treatment regimen tailored to DST and TDM, 3: treatment regimen for continuation treatment, 4: duration of treatment, GX: GeneXpert, LPA: Line probe assay, TDM: therapeutic drug monitoring, DST: drug susceptibility testing.

enables resection. In case of persistent smear or culture, positivity surgery is performed to reduce the bacterial burden even when accompanied with minimal bilateral nodes or infiltrates [114]. An additional benefit of surgery is that the knowledge of the penetration of the second-line anti-TB drugs into the affected tissue can be increased [115,116]. However, facilities to perform surgery on DR-TB patients remain critically limited.

11. Five-year view

TB treatment is long and for M/XDR-TB even longer. Drugs with sterilizing capacity are urgently needed to shorten treatment. However, even with the current available drugs, one can select patients that may benefit from a shorter treatment. Patients without extensive disease and cavities responding very well to treatment may qualify for a shorter treatment. Biomarkers predictive of treatment response will be helpful to support such a decision. Results of new studies hopefully provide the required evidence to include differentiation in treatment duration in WHO treatment guidelines.

As persistent smear or culture positivity is a serious problem, other treatment options, in adjunct to new drugs or surgery, should be looked at as well. The WHO has already mentioned that when toxicity of an injectable agent is a limiting factor but when considered effective, inhaling such an agent using a nebulizer can be considered [19]. Little is known about the early bactericidal activity of inhalation of anti-TB drugs. The first report studying the effect of inhalation of colistin on transmission of TB, however, unfortunately not an EBA study, was presented at the Union conference in Vancouver in 2013 [117,118]. Theoretically, inhalation of a drug can produce high concentrations at the site of infection. Even in case of less susceptible bacteria, the inhaled drugs can be used to reduce the bacterial load due to favorable PK/PD parameters. As the first dried powder inhalation products entered the market in 2010 for anti-pseudomonas treatment, we expect more in the next 5 years.

A novel approach to try to improve TB treatment outcome is to use therapeutic vaccines [119]. These vaccines modulate the immune system to help it target persisting and dormant TB bacilli thereby improving the sterilizing capacity of the human immune system [120]. To date, several phase II and III studies have been performed focusing on safety, immunogenicity, and improved treatment outcome. However, more data is needed before therapeutic vaccines can become mainstream treatment in TB treatment. The next 5 years will show if therapeutic TB vaccines are as promising as expected.

Clinical evaluation and validation of the value of WGS is urgently needed. It could potentially replace current available diagnostic tests like LPA and DST. To claim this role, it should become cheaper and more widely available. It should not only be available at central level but also at intermediate level. Moreover, results should be easily interpreted and represent similar results as from LPA and DST. Compared to DST, it saves a lot of time and is very helpful to tailor treatment including dose to the individual patient. Before it can be implemented in routine care, prospective studies providing supportive evidence are required [121]. As WGS is currently a hot topic, in

5 years it is expected that it may set it first step in implementation studies for guiding treatment of drug resistant TB [122].

Key issues

- XDR-TB is defined by MDR-TB with additional resistance to, a fluoroquinolone and a second-line injectable drug (amikacin, kanamycin or capreomycin).
- Success rates for treatment of extensively drug resistant tuberculosis (XDR-TB) are low due to limited treatment options, delayed diagnosis and inadequate health care infrastructure.
- The co-infection of human immunodeficiency virus (HIV) and XDR-TB complicates disease management and treatment outcomes significantly.
- Prevention of the development of XDR-TB is essential in MDR-TB treatment
- The introduction of molecular assays for the detection of resistance will help in early diagnosis of XDR-TB
- A step approach for designing a XDR-TB regimen containing at least 5 active drugs followed by a tailoring to the dose base on drug susceptibility and patients tolerance to the drug may help to optimize treatment in individual patients.
- Biomarkers to provide information on treatment response suitable to guide treatment duration are urgently needed.
- A more patient oriented approach by a multidisciplinary team regarding diagnostics, drug selection and tailoring and treatment evaluation will improve treatment outcome.
- Therapeutic vaccines to help the human immune system to target persisting and dormant TB bacilli may improve sterilizing capacity of current treatment.
- Clinical evaluation and validation of the value of whole genome sequencing is urgently needed.

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