EXPERT REVIEWS

Common errors in multidrug-resistant tuberculosis management

Expert Rev. Respir. Med. Early online, 1–9 (2013)

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Multidrug-resistant tuberculosis (MDR-TB), defined as being resistant to at least rifampicin and isoniazid, has an increasing burden and threats TB control. Diagnosis is limited and usually delayed while treatment is long lasting, toxic and poorly effective. MDR-TB management in scarce-resource settings is demanding however it is feasible and extremely necessary. In these settings, cure rates do not usually exceed 60–70% and MDR-TB management is novel for many TB programs. In this challenging scenario, both clinical and programmatic errors are likely to occur. The majority of these errors may be prevented or alleviated with appropriate and timely training in addition to uninterrupted procurement of high-quality drugs, updated national guidelines and laws and an overall improvement in management capacities. While new tools for diagnosis and shorter and less toxic treatment are not available in developing countries, MDR-TB management will remain complex in scarce resource settings. Focusing special attention on the common errors in diagnosis, regimen design and especially treatment delivery may benefit patients and programs with current outdated tools. The present article is a compilation of typical errors repeatedly observed by the authors in a wide range of countries during technical assistant missions and trainings.

Keywords: clinical management • errors • extensively-drug resistance • multidrug resistance • tuberculosis • XDR

Multidrug-resistant tuberculosis (MDR-TB) is defined as TB that is resistant to at least isoniazid and rifampicin. The WHO prevalence estimate for notified MDR-TB patients is 630,000 [1]. Hence, the total number of patients is thought to be much higher and the trend is probably increasing. The increasing prevalence of TB resistance is currently a major concern for global TB control [2]. Once resistance exists, treatment of patients is necessary from a humanitarian point of view but also as a way to reduce primary transmission. It may already be too late to avoid resistance transmission, since currently half of the total MDR-TB patients are thought to have arisen from initial TB cases [3], a problem that is extraordinarily relevant in high MDR-TB prevalent countries.

Other measures such as infection control and antiretroviral therapy are essential to control MDR-TB in high HIV incidence settings [4]. Resistance has again put TB on the international agenda with an increase in research and development. However, for decades the management of resistant TB cases was only delivered in referral centers in high-income countries by a small number of specialized clinicians [5]. In developing countries, these patients were classified as chronic or incurable. In the recent past, waiting for death was the only thing to do in many developing countries in these cases. Conversely, no research progress in TB has been made for decades [6]. There are few clinical trials ongoing and a consensus on the way to treat these patients has only been made in the last decade. Therefore, the scientific evidence is scarce and the number of controversies high [7]. Apart from scientific evidence, there is an urgent necessity for point-of-care tests, new drugs and simple and low-toxicity regimens. Complex and costly solutions used in high-income countries for MDR-TB are the only available solution. Indeed, extrapolation is difficult and MDR-TB patients in developing countries present success rates of approximately 60% [8–10] which is even lower for extensively resistant TB (XDR-TB) [11]. Considering that

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 10.1586/17476348.2014.856758 © 2013 Informa UK Ltd ISSN 1747-6348

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the success rate in the WHO-Euro region is only 56%, maybe current solutions are not even appropriate for middle-income countries [1].

The rising visibility of the problem, success in advocacy and funds available for drugs has created an unprecedented improvement and also an increase in MDR-TB management [12]. Unfortunately, it is thought that only 0.5% of the overall MDR-TB patients receive adequate treatment [5]. The use of second-line drugs (more toxic and less effective) [4] is certainly something new in developing countries even for physicians with vast TB experience [6]. Learning by doing is a situation often found in countries starting to treat MDR-TB patients. Apart from drugs and physicians, an MDR-TB program requires a health system that is able to monitor side effects and the daily intake of drugs for 18–24 months. In many low-income countries, only one standardized regimen is available for the MDR-TB patients and represents the first and last chance for cure. With the currently outdated tools, low trained staff and weak healthcare systems, a cure for MDR-TB is not straightforward. In this challenging scenario, clinical or programmatic errors are prone to happen at several levels. The substandard use of second-line drugs not only contributes to low cure rates but also to drug resistance amplification in the community, reducing future cure possibilities [13]. Placing attention on essential knowledge for TB care [14] and previously frequently found errors in MDR-TB management might be helpful to avoid them in other settings.

The aim of this perspective article is to describe and warn against a number of typical mistakes found in MDR-TB clinical and programmatic management which the authors have repeatedly observed in over 20 countries from Latin America, Africa, Middle East, Asia and Europe during technical assistance missions between January 2000 and December 2012. The ultimate goal is to provide guidance for the prevention of avoidable errors even in the most resource-constrained settings. Instances of common mistakes in MDR-TB management were tallied. Nevertheless, this article only includes those observed in at least five different MDR-TB settings.

Common errors found can be described in terms of the clinical or programmatic level. Nonetheless, both are inherently related and consequences of mismanagement in one level affect the other. Therefore, a discussion divided into errors at diagnosis, regimen design and treatment delivery was preferred (Table 1).

Errors in diagnosis

Drug resistance detection is inaccessible to the vast majority of patients in need [5]. As we have witnessed, even in countries that have new rapid tests in referral centers, access to MDR-TB diagnosis is difficult. There are several reasons including centralized use, weaknesses of health systems, lack of coordination, inefficient communication and other different logistic issues (expired cartridges, consumables stock-outs and others).

As a consequence, many patients start MDR-TB regimens while waiting for the results [15]. This is sometimes the optimal decision because delaying treatment for 4–8 months (or even longer) [16] to make a clinical decision may put the patient's life at an even higher risk. Reference laboratories are usually a far distance from the patient's home and are busy. Clinicians are forced by necessity to make empiric decisions that might be lifesaving in circumstances such as severe clinical conditions or TB/HIV. However, it can sometimes occur that after 6–8 months of waiting, with the patient on MDR-TB treatment, a full susceptible test arrives. There are a number of explanations that may justify full drug susceptibility despite failing an initial treatment [13,17]. The most frequent causes are late negatives and dead bacilli: patients with bilateral and extensive disease need longer than 6 months of treatment to clear the airway from bacilli [18]. In addition, when adherence is suboptimal patients may fail treatment (just because they are not taking medication) and can present susceptible strains. For these reasons, WHO category II treatment, which is a bad treatment for MDR-TB, is able to cure a moderate proportion of failures to category I who are not rifampicin resistant. In contrast to those already with MDR-TB resistance, category II treatment may increase resistance patterns. Starting MDR-TB regimens without confirmation might be justified if national surveys alert on high levels of primary MDR-TB among new cases or failure of other treatments. Nevertheless, rifampicin and isoniazid resistance confirmation and species differentiation is always advisable [7,19,20]. In any case, the use of second-line drugs to treat susceptible TB is still a life-saving measure but implies consuming precious resources. Accelerating the connection between reference laboratories and clinicians through telephone or email is basic to avoid deaths on the back log or second-line drug misuse.

A great number of changes in TB diagnosis is ahead and will hopefully limit the number of errors in current gold standard resistant test (proportion method) interpretation. As an example, South Africa has already used more than half a million Genexpert® cartridges while India introduced GenoType® MTBDRplus [101]. Nonetheless, the most widely used test for resistance detection in developing countries is still the proportion methods. The proportion method, which was described more than four decades ago [21], present great limitations such as lengthy delays and reduced reliability. Reliability to rifampicin, isoniazid, quinolones and injectables is high but is limited for many of the other anti-TB drugs [20,22–25]. To date, the major predictor of anti-TB drug resistance is still considered the use of drugs in monotherapy for more than 1 month [7,19,20,26,27]. Unexpectedly, many national guidelines stipulate that MDR-TB treatment is to be adjusted after susceptibility test results including susceptibility to group 4 and 5 drugs which are nowadays neither reliable nor recommended by WHO [4]. The authors have observed multiple mistakes leading to resistance amplification when using susceptibility tests for designing individualized regimens. For example, if a result was resistant to cycloserine, the drug was not used despite having never been used by the patient or in the country. Knowing that susceptibility testing is not reliable for group 4 and 5 drugs and especially poor for cycloserine, the

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Table 1. Common errors in multidrug-resistant tuberculosis management and potential ways solve them.

Error	Problem/reasoning	What to do
Errors in diagnosis		
Overdiagnose of MDR-TB based on clinical facts	Chronic cases and failures to category II treatment are the main risk groups for MDR-TB	Before starting MDR-TB treatment, perform a good clinical history including adherence and drugs used in the past
	Frequently, complicated cases and failures to category I in low MDR-TB prevalence settings are labeled as MDR-TB, and SLDs treatment is started without resistance confirmation	Whenever possible, perform smear, culture, DST and species identification to rule out all differential diagnosis possibilities
		In severe clinical conditions and HIV infection staring SLDs treatment on a high-risk MDR-TB patient while waiting the results might be life-saving
Complete credibility to DST	Regular DST is most reliable for R and H and acceptable for FQ and injectables	DST interpretation should be done according to patient history of drugs taken in the past, searching for real or covered monotherapies.
	It is currently not recommended for group 4 and 5 drugs	New genotypic DST are an advance in terms of speed and probably reliability at least for rifampicin resistance
		Perform DST when assuming treatment failure to first-line or second-line regimens. In countries with high initial MDR-TB rates consider DST to all initial cases
Errors in regimen designing		
Adding a single drug a failing regimen	To create resistance, two conditions are necessary: High bacillary load (e.g., cavitary lesions, bilateral disease), and monotherapy. At ambient pressure, natural mutant resistant bacilli are selected among the bacillary load. Often, over a non-curative treatment, a single drug is added resulting in a masked monotherapy	Start treatment with at least 3–4 effective drugs (always including a new-generation quinolone and an injectable plus other effective 2 companion drugs)
		Avoid sequential introduction of drugs
Stock out and further improvisation	SLDs shortages are frequent. Sometimes clinicians are forced to change treatments based on drug availability. Treatment shifts and improvisations are not always adequate and in many instances lead to amplification of the resistance pattern	Careful planning and drug provision may be done by pharmacologists or specialists
		Consider the risk behind fakes or low-quality drugs. Use high-quality drugs
		Avoid treatment improvisations as possible. The drug selection should follow a rational order
Errors in treatment delivery		
Lack adequate management of SLDs side effects	Lack of ancillary drugs or training in side effects recognition especially during the intensive phase	Ancillary drugs should be available and free
		Intensive use of ancillary drugs
		Provide treatment with light meals
		Drug ramping
Suboptimal dosage	Due to side effects, sometimes dosage is reduced especially for group 4 drugs. When dosages are subtherapeutic become ineffective, leading to masked monotherapy	Maintain all drugs at recommended dosage unless there are life-threatening side effects
		Take into account drug–drug interaction especially in TB/HIV coinfected patients

DST: Drug susceptibility test; FQ: Fluoroquinolones; H: Isoniazid; MDR-TB: Multidrug-resistant tuberculosis; R: Rifampicin; SLDs: Second-line drugs.

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doi: 10.1586/17476348.2014.856758
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Table 1. Common errors in multidrug-resistant tuberculosis management and potential ways solve them (cont.).

Error	Problem/reasoning	What to do
Errors in treatment delivery (cont.)		
Early injectable withdrawal	When the injectable is withdrawn too early, the bacillary load could remain high which is one of the premises to resistance amplification. Without injectable and with high bacillary burden treatment turns less effective and eventually resulting in further resistances and failure	Maintain injectables for 4–8 months and always at least until culture conversion (two negative cultures with a minimum separation of 1 month)
		In conditions like hearing loss or pregnancy capreomycin use is preferred
		If shots are painful, intravenous infusion could be used
		In case of toxicity injectables 3-times per week instead of daily may offer similar effectiveness
No DOT	DOT, adherence and side effect management tend to be acceptable during hospitalization. Conversely, all can be suboptimal during the ambulatory phase, leading to default	Train the staff managing the continuation phase and provide ancillary treatment and socio-economic support during continuation phase
		Strengthen the communication between hospital and healthcare centers

DST: Drug susceptibility test; FQ: Fluoroquinolones; H: Isoniazid; MDR-TB: Multidrug-resistant tuberculosis; R: Rifampicin; SLDs: Second-line drugs.

aforementioned example might be considered an error. Other findings like rifampicin resistance but isoniazid susceptibility on a high MDR-TB risk patient can be misleading. In such a case, the probability of MDR-TB is high. Reliability of the susceptibility test to isoniazid is very high, perhaps close to 90%, but not 100% [20]. Hence, considering isoniazid as an essential drug and providing a rifampicin monoresistant treatment, would risk quinolones susceptibility and limit cure chances. Providing an MDR-TB regimen adding isoniazid is probably a better option for these patients [28].

In other settings, several susceptibility tests are performed to the same patient throughout the treatment, showing discordant results driving unnecessary therapy switches. Susceptibility testing might be performed only after assuming the failure to the regimen given [28], similarly to what is done in HIV contexts.

A recent error found in the use of Genexpert especially in the private sector is using the test for all presumptive TB patients without phenotypic susceptibility confirmation. The positive predictive value for initial TB cases in countries with less than 5% MDR-TB prevalence (most high burden TB countries) is approximately 32.4% [29]. Hence, rounding 1 in 3 positive resistant tests when applied to a non-high-risk resistance group will be a false positive, contributing again to over diagnosis of MDR-TB. Newer versions of the real time PCR test will probably not solve this problem, but will increase its sensitivity and specificity. The understanding of mutations conferring resistance to TB is still exiguous. Calls for advances in gene-based technology are not only motivated to shorten delays but also to increase resistance reliability and increase treatment options [23,24,102].

Errors in regimen design

With the advent of standard treatments for MDR-TB, the likelihood of errors had decreased. Conversely, the accessibility to treatment is still reduced even for those already diagnosed. Backlogs for treatment are frequent especially in low-income countries where treatment is only available in one center, where hospitalization is required or when there is limited drug access. People frequently die on the backlog while for those alive the indirect and emotional costs could be so high, discouraging them to start. Physicians can suffer medical dilemmas: sometimes they do not have enough knowledge or the tools but need to face the necessity for drug resistance treatment. If the national TB program cannot offer a solution, patients search care in the private sector. With clinicians lacking specific TB skills, the classical error of '*adding a single drug to a falling regimen*' tends to happen. In TB or HIV, adding a single drug drives resistance amplification [30,31]. Thanks to an increase in MDR-TB visibility and training, this error is less frequent than it used to be. Nonetheless, variants of this error were found for compassionate reasons using bi-therapies or weak combinations. Often the same initial unsuccessful treatment is prescribed with only one or two newly available drugs (e.g., ofloxacin + ethionamide). Resistance may emerge within months. When the rest of the treatment arrives in the country (e.g., kanamycin + cycloserine), these drugs are added to the previous regimen to which the bacilli population is already resistant. After all these sequential monotherapies or weak combinations, patients end up developing resistance to all drugs given.

Until a few years ago, ciprofloxacin and amikacin were the only second-line drugs available in many developing countries.

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These practices might be among the causes of the current XDR-TB epidemic [4]. MDR-TB treatment should be based on *at least four effective drugs* which are new drugs according to clinical history or susceptibility test [4]. All drugs should be given *at the same time*. Sequential addition of drugs will often result in opportunities for resistance amplification. The start of treatment should be avoided whenever possible if 3 or 4 effective drugs are not available. A later generation quinolone (preferentially high dose) and an injectable should be the core of the regimen complemented by two other effective companion drugs [28,32,33]. Hence four effective drugs in the initial phase and at least three on the continuation should be given.

Second-line drug availability is a frequently neglected matter that leads to regimen errors. The availability depends in large part on the health authority's motivation, the organization of procurement, customs and import regulation. Drugs of poor quality are frequently used in some countries and this may be one of the causes of MDR-TB [34]. In addition, drug stock-outs are unfortunately frequent even for first-line drugs in developing countries [35]. Once stock-outs occur, clinicians must manage the best they can to offer a solution, sometimes leading to inappropriate regimens and switches [7]. Even well-organized MDR-TB programs often have to struggle to procure second-line drugs. Expiration dates are reduced and shipment delays high. Reliable information systems are critically needed for meticulous forecasting. The supply chain is highly complex, new for most programs and sometimes overlooked. Innovative strategies, such as the creation of regional drugs banks or formal inter-country procurement and distribution networks, would help.

Overall, there is a great need for less toxic and shorter regimens for MDR-TB. Experiences with 9-month MDR-TB regimens are encouraging. Regimens such as this with high efficacy, being cheaper and shorter, would probably reduce not only costs but also delivery errors, increasing adherence and the final effectiveness and treatment accessibility [36]. On the other hand, this regimen uses seven drugs on the initial phase and the pill burden is high. Apart from reducing length, simplification is still needed.

Errors in treatment delivery

Treatment delivery in low-income countries usually relies on already overburdened and low trained physicians or nurses. According to our observations, errors in treatment delivery seem to be increasing and might be a key factor for the high default, failure and death rates among MDR-TB patients. Not only the treatment length but side effects are another major cause of default [36]. With current medication, side effects are always to be expected when treating MDR-TB. Fortunately, most are easily treatable and rarely life-threatening [4]. Prescribing ancillary treatment (mostly proton pump inhibitors or anti-H2), providing drugs with light meals, and drug ramping are suitable approaches [37]. In many MDR-TB sites visited, ancillary drugs simply do not exist or patients cannot afford them. In these situations, the approach to reduce side effects by reducing drug dosage (especially for group 4 drugs, see Table 2) tends to happen. Side effects are reduced but treatment efficacy is reduced too. Decreasing dosage even by just one-third, dramatically reduces these drugs effectiveness [4]. Subtherapeutic dosage of companion drugs ends up creating masked monotherapies of quinolones in the continuation phase.

Table 2. Rational classification of anti-tuberculosis drugs.

Group number	Drug name
Group 1: First-line oral agents	Isoniazid; rifampicin; ethambutol; pyrazinamide
Group 2: Fluoroquinolones	Levofloxacin; moxifloxacin; gatifloxacin; ofloxacin
Group 3: Injectable agents	Capreomycin; kanamycin; amikacin; streptomycin†
Group 4: Oral bacteriostatic second-line agents	Ethionamide/protionamide; cycloserine/terizidone; *p*-aminosalicylic acid
Group 5: Reinforcement drugs	Clofazimine; amoxicillin/clavulanate; linezolid; imipenem/cilastatin; thioacetazone; clarithromycin; high-dose isoniazid
New agents	Bedaquiline, delamanid

†Due to high primary resistance prevalence to streptomycin, this drug is not recommended for the treatment of multidrug-resistant tuberculosis patient and should not be used.
Data taken from [4,6,7].

Irreversible hearing loss is a real and frequent limitation when using injectables for a long period. Additionally, intramuscular injections in malnourished patients can be very painful. Renal insufficiency and electrolyte abnormalities can be dangerous for the HIV patients being treated with capreomycin and tenofovir [38]. Drug–drug interactions in the coinfected MDR-TB patient require major awareness and coordination between specialists. In any case, a very early injectable withdrawal without culture conversion reduces cure chances [28]. Early withdrawn may lead to quinolone and other drugs resistance amplification during the continuation phase. We have also seen the opposite, patients with smear negativization on the first 1–3 months that were maintained with long-lasting use of injectable ended up deaf or with renal insufficiency. To avoid toxicity and reduce cost, injectables can be used three-times per week instead of daily [4]. However, whether effectiveness is fully comparable remains controversial [39,40]. Capreomycin is less ototoxic and teratogenic, and can be used in patients with personal or family history of hearing loss [4]. Nonetheless, its high price is a real limitation in low-income countries. To avoid painful shots, intravenous application through peripheral catheter is safely and effectively used in many programs [41]. The current recommended length of injectable varies from 4 to 8 months [4,42,43]. More studies are needed to ascertain

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the earliest moment to stop the injectable. Generally, clinicians have to make a pragmatic decision whether to prioritize side effects or MDR-TB treatment efficacy: if the patient is not correctly treated for TB they will most likely die from TB.

Another issue deserving more attention is adherence, especially during the continuation phase. We recurrently observed poor or no DOT for MDR-TB cases. Another variation of this error was having DOT on the continuation phase but keeping drug delivery split as it was in the hospital (e.g., drugs every 8–12 h) ending up with DOT only for a fraction of the regimen. In some settings, MDR-TB cases were referred to untrained units with just a short referral letter and a bag of pills. Health center staff were afraid of patients or unable to manage their side effects. Careful communication between hospitals, peripheral centers and social workers are strong prerequisites for a successful MDR-TB program. Side-effect management and training for the staff delivering the continuation phase is rarely included in budgets. There is no sense in starting an expensive and toxic MDR-TB treatment if the continuation phase cannot be assured.

In addition, infection control conditions in peripheral centers tend to be poor. We have repeatedly seen presumptive or already diagnosed MDR-TB patients waiting next to children with asthma in overcrowded poorly ventilated waiting rooms. No progress is seen if we treat one resistant patient and we infect many in our own health facilities. All these treatment efforts will vanish if basic administrative measures in hospitals, prisons and other congregate settings are not adopted. A strong impulse in prevention is needed especially in settings where HIV or DM are prevalent.

Prevention of MDR-TB creation

After the description of these common errors, a key question is how to be a step ahead and create better policies or practices to avoid resistance amplification. A supportive solution at the clinical level might be increasing the initial phase by 1 month in those already positive at the end of the continuation phase or even including ethambutol for the whole continuation phase of the aforementioned cases. WHO currently recommends ethambutol for the whole treatment duration in countries with high levels of isoniazid mono-resistance [17]. Nevertheless, the lack of trials and evidence are great barriers to include these potential preventive practices into country guidelines.

This perspective article reviews the necessity to improve training and knowledge in order to reduce errors. However, this is clearly not enough to cope with the MDR-TB problem. Many programs use outdated guidelines, present insufficient or intermittent procurement of drugs or use drugs of insufficient quality. The inability to offer free diagnosis or free treatment is other major barrier to access to care. Even basic administrative infection control measures (one of the most cost-effective preventive interventions) are not seriously considered. In general, weaknesses of the TB programs and lack of health authority support are contributing to a poor and delayed response to this growing problem. As mentioned by Frieden, a decade ago 'a poorly functioning program can create MDR-TB faster than any program can cure, even if unlimited resources are available' [44]. Likewise, as seen in successful experiences in underfunded MDR-TB settings, the clue to success relies on the human factor and the improvement of their management capacities [41].

Conclusion

MDR-TB management in developing countries is challenging. The likelihood of presenting clinical and programmatic errors is high. Nonetheless, treatment is feasible and necessary. MDR-TB management is something new for most TB programs and highly demanding in terms of economic and human resources. Until MDR-TB is more easily and quickly diagnosed and regimens are simplified much further, similar errors will continue to be observed in the field during technical assistances. The starting point of many errors is a lack of training. To avoid preventable deaths, drug resistance amplification and primary resistance spread, comprehensive understanding of TB disease is needed. Several mistakes are linked to misconceptions in diagnosis, regimen design and especially treatment delivery. Rising awareness on the common errors observed may benefit patients and programs in scarce resource settings.

Expert commentary

We are certainly living in a remarkable moment in TB history. Genetic tests for TB and resistance diagnosis are probably the biggest advance in TB diagnosis since Koch's sputum smear microscope observation. We are still far from a highly sensitive point of care test for TB but no doubt we are in a better situation than 10 years ago. Many of the mentioned errors in susceptibility test interpretation will decline with the use of genetic tests while we gain capacity and speed in treatment delivery. Due to the cost of Genexpert and the high logistical needs of GenoType MTBDRplus, their introduction in many developing countries will be slow and maybe only introduced in reference centers. Laboratories, rapid testing and information systems need modernization in order to provide timely results and avoid unnecessary delays that cause morbidity and mortality. The use of the internet and cellular phone calls or messages to deliver results might be extraordinarily useful to streamline decision-making even in resource-constrained settings.

Regarding current regimens, efficacy is high and they have the potential to cure most MDR-TB cases under ideal conditions. However, the length and toxicity of them under field and real-life conditions reduces their effectiveness. The largest problem in countries with more than 5 years' experience in MDR-TB management is not mortality but the high levels of patients lost to follow-up. In such cases, reduction from 21 to 9 months of MDR-TB treatment might provide a substantial

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increase in effectiveness. The key issues to focus on are not only the regimens, but also the quality of the delivery, side effects management, social support, motivated human resources and treatment simplification [45].

We have observed that countries starting to implement MDR-TB programs come across similar stages or trends in implementation. The early cohorts programs have many widespread cases with amplified patterns of resistance where many individualized regimens are necessary. These are the most difficult cases (delayed presentation and multi-resistance patterns) in areas where there is reduced experience in clinical and programmatic MDR-TB management. These early cohorts are often small in centralized services and mortality is usually high. At this time is precisely when the aforementioned errors are most frequent. After 3 or 4 years, programs usually gain clinical and management background, errors are less common, cure rates increase and the number of patients under treatment also increases. MDR-TB management starts to be decentralized or even becomes ambulatory or community based. Some years later, basic clinical errors are minimized and the number of patients under treatment can substantially increase. However, the levels of human resources or funding do not increase at the same speed. Mortality declines because patients are identified earlier and put under suitable regimens but treatment defaults increases especially in the continuation phase. Delivery errors began to be rather more frequent than diagnosis or regimen errors. Each country or setting should identify in which phase of implementation it is and the potential errors may occur.

Five-year view

We are currently witnessing changes in TB management; in the near future, we will see even more exciting moments in the TB landscape. For the first time in more than 40 years, a new drug (bedaquiline) has been approved for TB use [103]. Another drug, delamanid, will probably appear for compassionate use in less than 2 years. There are a cluster of new compounds under evaluations and in clinical trials [46] and potential salvage treatments are under study in order to give hope to many XDR or even TDR (totally drug resistant)-TB patients.

In 5 years, we will have the final results of the STREAM trial, which uses a similar combination of drugs than the Bangladesh regimen [36] to ascertain the efficacy of a 9-month regimen based on fourth-generation high-dose fluoroquinolones as the core drug. Reducing the regimen from 21 to 9 months with a 4-month period of injectables would be a great advance capable of reducing regimen design and delivery errors due to shorter, cheaper and less toxic regimens. In the meantime, new regimens for susceptible TB are also in the pipeline in order to try to simplify and shorten treatment. There are three trials (Oflotub, REMox and RIFAQUIN) testing regimens for new TB cases that include a fourth-generation fluoroquinolone. Final results will appear in less than 2–4 years; it is not yet clear whether reducing the regimen from 6 to 4 months will be superior to the potential risk of fluoroquinolone resistance amplification. If this was to become the case standard management of MDR-TB which is currently based on fluoroquinolones as the core drugs would substantially change into individual regimens and would be more expensive and difficult to deliver in developing countries. On the other hand, it remains unknown the most appropriate rifampicin dose [47] or if high dose of rifampicin in addition to high-dose isoniazid could also reduce the treatment time to 4 months. Efforts are being made by many to optimize current drugs for MDR-TB management [48]. Moreover, understanding the role of low-level mutations might open the door for the treatment of MDR-TB patients with high doses of rifampicin in the same way we use high INH doses for those strains presenting inh A mutation. There are ongoing studies investigating the role of high-dose rifampicin and even high-dose quinolones and their capacity to overcome low-level resistances. Genotypic mutation mapping may change our perceptions toward TB treatment similarly to how it has changed individual HIV treatment design. Combining the new resistance genetic test, new ways to use current drugs and the incorporation of new drugs in 5–10 years, the management of TB will finally be slightly comparable with the treatment of HIV. Overall, we expect that in 5 years, most of MDR-TB settings will gain enough experience and training to avoid the mentioned errors in diagnosis and regimen design, especially, if new diagnosis technologies and shorter and less toxic standard MDR-TB treatments are embraced. Most of the common errors will probably remain in the field of programmatic constrains, particularly in treatment delivery as it happens nowadays in HIV, or in susceptible TB management where drug availability and adherence is the key factor for cure. Whatever happens, resistance is likely to continue increasing and hence making the most of current drugs and new drugs is much needed.

Acknowledgements

The authors would like to thank National TB Programs and healthcare workers with whom they have worked side by side facing challenges in technical assistance and training. Through their daily work they have laid the foundation for better scientific knowledge in MDR-TB in developing countries.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

No writing assistance was utilized in the production of this manuscript.

doi: 10.1586/17476348.2014.856758
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Key issues

- Errors in clinical or programmatic management of multidrug-resistant tuberculosis are frequent especially in new or recent settings implementing drug-resistant treatments.
- Most errors could be avoided with timely and appropriate training.
- Whenever possible, confirmation of resistance to isoniazid and rifampicin is desirable when using second-line drug regimens.
- Drug susceptibility testing with the proportion method is not 100% reliable. It is more reliable for isoniazid, rifampicin, quinolones and second-line drug injectables. Reliability for other drugs is reduced and results should be validated according to patient history.
- To create resistance, two conditions are necessary: high bacillary load (e.g., cavitary lesions, bilateral disease); and monotherapy. It is necessary to avoid as much as possible real monotherapies, masked monotherapies or weak combinations. An adequate regimen should comprise at least three or four effective drugs.
- Not all anti-tuberculosis drugs have the same efficacy: core drugs for multidrug-resistant tuberculosis are fluoroquinolones and injectables. The other companion drugs will support and prevent resistance acquisition.
- Correct drug dosage according to weight is essential for a curative regimen. Maintain as much as possible drugs and dosage and in case of side effects consider in the first instance treating the side effect rather than withdrawing drugs or reducing dosage.
- Second-line drug forecasting and timely acquisition is crucial. Stock-outs of medication usually lead to considerable clinical problems.
- Training and management of patients (including side-effect assessment and treatment) during the continuation phase is often not planned. This is key to avoid defaulting, limit transmission and increasing the cure rates.
- Overall, the goal is to avoid the creation of new resistant cases or the amplification of existing drug resistance by applying proficient clinical management.
- Basic administrative infection control measures need to be ensured to avoid the transmission of already resistant strains.

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