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Principles for constructing a tuberculosis treatment regimen: the role and definition of core and companion drugs

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SUMMARY

Current World Health Organization guidelines for the formulation of treatment regimens for multidrug-resistant tuberculosis (MDR-TB) pay too little attention to the microbiological activity of anti-tuberculosis drugs. Here, we draw lessons from the pioneering work done on shorter MDR-TB treatment regimens and the current knowledge of the bactericidal and sterilizing properties of the drugs to inform the composition of treatment regimens for MDR-TB. We propose to reserve the term 'core drug' for the one drug in a regimen that contributes most to relapse-free cure. The core drug has both moderate to high bactericidal and sterilizing activity, is given throughout treatment, is well tolerated, and has no cross-resistance with the core drug used in the previous regimen. Currently used core drugs include rifampicin in the first-line 6-month regimen, and fourth-generation fluoroquinolones and bedaquiline in regimens for drug-resistant TB. All other drugs are 'companion drugs', used to avert treatment failure due to acquired drug resistance against the core drug. Some also help further reduce the risk of relapse. Moreover, toxic drugs should be avoided if there is an alternative. A regimen must always include the core drug, plus at least one companion drug with high bactericidal activity, a second bactericidal companion drug, plus two sterilizing companion drugs.

KEY WORDS: drug resistance; MDR-TB; DR-TB; second-line drugs

IN 2015, THERE WERE AN ESTIMATED 580 000 new patients with multidrug-resistant/rifampicin-resistant TB (MDR/RR-TB) worldwide, although only 132 000 (22.8%) of these were notified.[1] Outcomes for MDR-TB treatment were poor, with only 54% programmatic treatment success (i.e., treatment cure or completion), strongly associated with regimen composition.[2] The composition of a regimen should be tailored to result in 1) early bactericidal effect (immediate and substantial reduction of metabolically highly active bacilli) to arrest transmissibility, to reduce the risk of selecting resistant mutants, and thus prevent treatment failure, and 2) sterilizing effect (elimination of bacilli with low metabolic activity) to reduce the risk of relapse after successful treatment completion.[3]

The 2016 World Health Organization (WHO) guidelines propose using the so-called ABCD classification to build a regimen for drug-resistant TB (DR-TB), taking into account contra-indications such as drug susceptibility testing (DST) results showing resistance, history of adverse drug events and previous drugs used in a failing regimen. The guidelines recommend to 'include pyrazinamide and four core second-line TB drugs: one chosen from group A (fluoroquinolones), one from group B (second-line injectables) and at least two from group C (ethionamide/prothionamide, cycloserine terizidone, linezolid and clofazimine)'. Moreover, 'if the minimum of effective TB drugs cannot be composed, an agent from group D2 (bedaquiline, delamanid) may be added to bring the total to five'.[4]

From this, it would appear that any drug from groups A, B or C may be considered as a core drug. Hence, when drugs from both group A (the fluoroquinolones [FQs]) and group B (the second-line injectables) are contraindicated, a patient could be prescribed four drugs from group C. For example, a regimen consisting of ethionamide, cycloserine (CS), linezolid (LZD) and clofazimine (CFZ) plus pyrazinamide (PZA) would be an acceptable option. Moreover, drugs from group D2 (bedaquiline [BDQ], delamanid [DLM]) are only considered when a regimen with five likely active drugs cannot be composed.[4] Thus, neither the classification of second-line anti-tuberculosis drugs in groups A, B, C and D, nor the rationale for the composition of a regimen

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Table Activity of anti-tuberculosis drugs and their use

	Characteristics*			Use in a MDR/XDR–TB treatment regimen			
	Bactericidal activity	Sterilizing activity	Resistance prevention	Core drug†	Companion drug used for its high bactericidal effect‡	Companion drug used for its sterilizing effect	Other companion drugs
RMP§	High	High	High				
FQ (GFX/MFX$^{high-dose}$)¶	High	High	High	X			
BDQ	High	High	High	X			
DLM	High	High?	High	?	X		
Second-line injectables#	High	Low	High		X		
LZD	High	Low	High		X		
Imipenem/meropenem + amoxicillin-clavulanate	High	?	High		X		
CFZ**	Low	High	High			X	
PZA††	Low	High	Low			X	
ETH/PTH‡‡	Moderate/high	Low	Moderate				X
INH$^{high-dose}$	Low/moderate§§	Low	High				X
EMB	Low	Low	Moderate				X
CS	Moderate	Low?	Moderate				X
PAS	Low	Low	Moderate				?

* Also depends on susceptibility. In patients with MDR-TB, INH and RMP resistance assumed to be present.
† Core drug: bactericidal and sterilizing, administered throughout treatment.
‡ High early bactericidal activity to rapidly kill existing core drug-resistant mutants and rapidly reduce the bacillary load, to prevent the selection of resistant mutants during bacillary replication. The bactericidal activity of the 'other companion drugs' is less significant.
§ The drug with the highest sterilizing action; used in RMP-susceptible TB.
¶ Among FQs, LVX and ofloxacin are less effective than later generation drugs, which include high-dose GFX (800 mg if >50 kg body weight), high-dose MFX (800 mg if ⩾50 kg) and very high-dose LVX (1500 mg for 55–64 kg, 1750 mg for ⩾65 kg).¶¶
# Early bactericidal effect, but the effect is of short duration.[5] Important as companion drug during the early phase of the treatment, especially to prevent FQ resistance and treatment failure. Moreover, as the cumulative dose is associated with severe adverse drug reactions such as hearing loss, it is prescribed only during the intensive phase.
** A powerful sterilizing drug. Used throughout treatment, it likely contributes substantially to the success of the shorter treatment regimen.
†† Has important sterilizing activity.
‡‡ Included for their bactericidal effect, which is probably not very high, but higher than that of CS or PAS. Also, ETH and PTH are less toxic.
§§ A high dose (15 mg/kg)¶¶ will still have a variable (low to moderate and some still high) effect on most INH-resistant bacilli, depending on the resistance level. For INH-susceptible TB, the bactericidal activity of normal dose INH is high and its sterilizing activity moderate.
¶¶ Dosages only for FQs and isoniazid. Dosages are not shown for drugs administered at normal dosage. The recommendations for the normal standard dosages are published in regularly updated WHO guidelines.
MDR-TB = multidrug-resistant tuberculosis; XDR-TB = extensively drug-resistant; RMP = rifampicin; FQ = fluoroquinolone; GFX = gatifloxacin; MFX = moxifloxacin; BDQ = bedaquiline; DLM = delamanid; LZD = linezolid; CFZ = clofazimine; PZA = pyrazinamide; ETH = ethionamide; PTH = prothionamide, INH = isoniazid; EMB = ethambutol; CS = cycloserine; PAS = para-aminosalicylic acid; LVX = levofloxacin.

for DR-TB, take into consideration the diverse microbiological activity of the different drugs.

We propose that the microbiological activity of drugs should be accorded greater importance when a regimen for DR-TB is composed (Table). The activity of the anti-tuberculosis drugs differs: some have relatively more bactericidal activity, while others greater sterilizing activity, but very few drugs have both.[6] Moreover, most second-line drugs are less effective than most first-line drugs, and DST for many of these remains poorly standardized and not very reliable. In many settings with high DR-TB prevalence, access to DST is so poor that the turnaround time would delay treatment initiation to an unacceptable extent. To build an effective regimen keeping this in mind, we refer to lessons learnt from the sequential adaptation and implementation of the shorter MDR-TB treatment regimens pioneered in Bangladesh,[7,8] and replicated, with modifications, in Niger,[9] Cameroon,[10] and, more recently, on a large scale in nine West African countries.[11] Moreover, we emphasize the bactericidal and sterilizing properties of the currently used second-line anti-tuberculosis drugs to the extent that they are known or generally accepted. We propose to provide a sharper definition for 'core drug', while the term 'companion drugs' will be used to describe all other drugs in the regimen. The 'core drug' drives the regimen, and is indispensable for its efficacy, while 'companion drugs' assist by providing layers of protection against treatment failure due to acquired drug resistance against the core drug; some also help avert relapse after treatment completion. As a result, and conditional on good adherence, a properly designed regimen will have high efficacy and effectiveness.

CHARACTERISTICS OF A CORE DRUG

We reserve the term 'core drug' for a single drug that contributes most to the prevention of treatment failure and relapse in a regimen. Here, the core drug has moderate to high bactericidal and sterilizing activity, both essential for relapse-free cure, and is administered throughout treatment to every patient on the regimen. In patients with DR-TB, the core drug of a new regimen should also be effective against resistance to the core drug used in the previous regimen, i.e., using a regimen cascade strategy.[12] Without the core drug, the regimen substantially, or even almost entirely, loses its efficacy, so as to make the regimen unacceptably inefficacious.[12] Exceptionally, the core drug can be replaced by another core

drug, i.e., when a patient cannot tolerate the initially prescribed core drug.

In the current standard first-line 6-month regimen, rifampicin (RMP) is the core drug, and isoniazid (INH), PZA and ethambutol (EMB) are companion drugs. For example, if PZA is lost the regimen is weakened and treatment duration has to be prolonged.[13] If EMB is lost, the risk of acquiring RMP resistance is increased, as its addition to the RMP-INH-PZA combination does not improve the regimen's effectiveness in drug-susceptible cases, and its role at current dosages is limited to protecting the core drug.[14] The first quality of a core drug is thus that a regimen's efficacy is almost fully dependent on it. If it is lost, an alternative regimen based on another core drug must be chosen.

In the history of anti-tuberculosis chemotherapy, only a few core drugs have emerged that fit the criteria outlined here. Before the introduction of RMP, INH-based regimens (with streptomycin [SM] and thioacetazone, SM and para-aminosalicylic acid [PAS], or SM and EMB as companion drugs) made TB curable,[15,16] but required treatment for 12–18 months with excellent adherence. INH was the driving core drug in that regimen; SM and PAS were companion drugs that added early bactericidal activity and protection against acquisition of drug resistance.

RMP became the next core drug, initially of a regimen that combined RMP and INH with either SM or EMB.[17] The sterilizing activity of RMP is greater than that of INH.[6] RMP therefore led to a reduction in the treatment duration to 9 months.[17] INH remained in the regimen, but its role was now relegated to that of an important companion drug, while RMP became the driving core drug. The addition of PZA helped to further shorten the regimen to 6 months, and was thus a key companion drug, but it did not fundamentally change the regimen.[13] In the shorter MDR-TB treatment regimens, a fourth-generation FQ, such as gatifloxacin (GFX) or moxifloxacin (MFX), is used as the core drug.[7–10,18] When there is resistance to both RMP and the FQs, BDQ is currently being used as the core drug of the regimen in view of its (probably) high bactericidal as well as sterilizing activity.[19,20] The use of BDQ during the entire treatment duration is being studied.[21] Whether DLM will qualify as an additional core drug remains to be confirmed.

CHARACTERISTICS OF COMPANION DRUGS

Although the WHO guidelines recommend group B and C drugs as core drugs, only some of these have a high bactericidal or sterilizing effect, and none have both; they do not therefore meet our proposed definition of a core drug.

Companion drugs are used to ensure that no resistance is acquired to the core drug, and thus prevent its loss. To this end, companion drugs in the intensive phase should preferably have documented high bactericidal activity to reduce the high bacillary load swiftly and effectively, and thus limit the selection of core drug-resistant mutants. Although neither SM nor the second-line injectables seem to have high bactericidal activity on their own,[22,23] in the right combination they may actually be the strongest companion drugs during the critical first days of treatment.[14,22] LZD, which interacts with bacterial 23S rRNA, probably has an effect that is similar to that of second-line injectables, which interact with bacterial 16S rRNA, and might be a viable alternative, i.e., in patients with extensively drug-resistant tuberculosis (XDR-TB).[24] The toxicity of both the second-line injectables and LZD is another reason to use them only for a limited time during the early treatment phase, when their bactericidal effect is highest.[25,26] Other drugs that may be considered for their high early bactericidal activity in MDR-TB, and even more so in XDR-TB, are DLM and the combination of one of the carbapenems (imipenem, meropenem) with clavulanate. However, while promising, these findings need further confirmation.[27] Moreover, as carbapenems must be administered intravenously thrice daily, requiring an implantable venous access device, they are impractical in most endemic settings. Companion drugs with moderate bactericidal activity include the thioamides, high-dose EMB, high-dose INH (for probably most INH-resistant strains)[28] and CS. These are added to maximize regimen protection. As PAS and thioacetazone appear to be purely bacteriostatic, they only protect the core drug against the acquisition of resistance.[22]

Some other companion drugs, such as PZA and CFZ,[14,29,30] likely have relapse-preventing properties, and should be included. PZA may, in addition to its sterilizing effect, enhance the effectiveness of an FQ core drug.[31]

Drugs that have a high potential for toxicity, such as CS and PAS, should be avoided if there is an alternative. The effectiveness of a regimen is determined not only by the efficacy of the drugs, but also substantially by its tolerability: failure- and relapse-free cure is only possible when patients adhere to the treatment. The more toxic a treatment regimen, the larger the proportion of patients lost to follow-up.[7] In addition, regimen modifications due to adverse drug reactions threaten its effectiveness. Moreover, when modifying a regimen due to an adverse drug reaction, clinicians have to be conscious of the bacteriological response at this point, as a single drug should never be added to a failing regimen.

Although the likelihood of resistance to a given drug should be considered for the regimen and population in which it will be used, the individual

assessment of baseline resistance may be counterproductive, because it can be operationally too difficult and result in delayed treatment initiation, compounded by the lack of test reliability for many companion drugs. High-dose INH is usually well tolerated. Although it cannot be considered a key companion drug for every patient with DR-TB, it may still have an important role to play in patients with remaining activity on strains with the *inh*A mutation and on a likely substantial proportion of strains with the frequent *kat*G 315 Thr resistance mutation. However, resistance-conferring mutations in both the *inh*A and *kat*G gene or a deletion of the *kat*G gene are unlikely to be overcome even with high-dose INH.[27] Although most RR-TB isolates are also resistant to INH, an important proportion of patients with RR-TB may still have an INH-susceptible strain, especially when RR-TB is detected in new patients from populations with low RR-TB prevalence. Given the higher proportion of patients cured with an RR/INH-susceptible strain,[12] it is operationally most practical to systematically include high-dose INH in patients diagnosed with RR-TB.[4] The potentially added toxicity is relatively small compared to that from other frequently used companion drugs.

EXEMPLARY COMPOSITIONS OF TREATMENT REGIMENS FOR DRUG-SUSCEPTIBLE AND DRUG-RESISTANT TUBERCULOSIS

The first curative regimen for tuberculosis

The first studies showed that neither SM nor PAS alone or in combination was guaranteed to prevent the emergence of acquired drug resistance and thus treatment failure.[32] The addition of INH allowed for the formulation of triple chemotherapy, and this was thus the first regimen to permit failure-free cure.[15] It nevertheless took the WHO Expert Committee some time to define this regimen as the desired standard.[33] The most important drug in this regimen was INH. Because the main property of INH is bactericidal,[22] rather than sterilizing activity, treatment duration had to be very long to reduce the risk of subsequent relapse. Nevertheless, the extension to two companion drugs in the intensive phase demonstrated for the first time the importance of using a powerful core drug (in this case INH), supplemented and protected by two drugs in the intensive phase to guard against treatment failure resulting from acquired drug resistance.[34]

The current 6-month regimen for drug-susceptible tuberculosis

The discovery of rifamycins in the late 1950s and the introduction of the oral derivative, RMP, in 1966, increased the effectiveness and reduced the duration of chemotherapy.[35,36] In the United States, the US Public Health Service had conducted clinical trials on TB since the introduction of SM. Trial 19, which compared the first regimen with RMP throughout with the then INH-based standard regimen (supplemented by SM and EMB), was intended for 'curative' treatment rather than only 'remission',[37,38] i.e., it formed the basis for subsequent trials that were aimed at preventing not only treatment failure, but also relapse.[39] The long-term follow-up of a French study for up to 100 months post-treatment cessation documented that a 9-month regimen based on the core drug RMP resulted in less than 3% relapses.[40] The subsequent addition of PZA during the first 2 months led to the further reduction of the duration of chemotherapy to 6 months, without loss of efficacy.[41] In addition to shortening the duration of the chemotherapy, it also demonstrated that the choice of the companion drug could substantially influence the prevention of relapse. A British trial comparing two regimens of INH and RMP, supplemented for the first 2 months by PZA plus either SM or EMB, yielded similar results and thus established the current standard first-line regimen with RMP as the core drug, relegating INH to the role of an important, mainly bactericidal companion drug in the regimen.[42]

The minimum 9-month 'Bangladesh regimen' for multidrug-resistant tuberculosis

Given the fact that the full initial resistance profile is generally unknown and that most second-line drugs have substantially poorer activity than many first-line drugs, a regimen for MDR-TB is commonly composed of more drugs than the regimen for drug-susceptible TB. An MDR-TB regimen should include at least a core drug as defined here, plus one drug with high bactericidal activity, another companion drug with bactericidal activity, plus two sterilizing companion drugs (Figure).

The shortest (9–11 months, including a 4–6 month intensive phase) and the most effective treatment regimen in Bangladesh used high-dose GFX as the core drug, while kanamycin was the bactericidal companion drug. In addition, prothionamide (PTH) and high-dose INH were used as a companion pair with possibly still moderate bactericidal activity. The sterilizing activity of CFZ and PZA was to reduce the risk of relapse. Kanamycin, PTH and high-dose INH were stopped after a 4-month intensive phase. The intensive phase was prolonged in case of failure to smear convert. Delayed smear conversion (even if culture was subsequently negative) was used as an indicator of the total bacterial burden at treatment onset. The aim of this prolongation (up to 2 months) was to reduce both the increased risk of selecting persistent drug-resistant mutants and the subsequent risk of relapse, both attributable to the initially higher bacillary load.[7] Apart from a diagnosis of RMP/multidrug resistance, no DST results were available at treatment start. The regimen therefore had to be

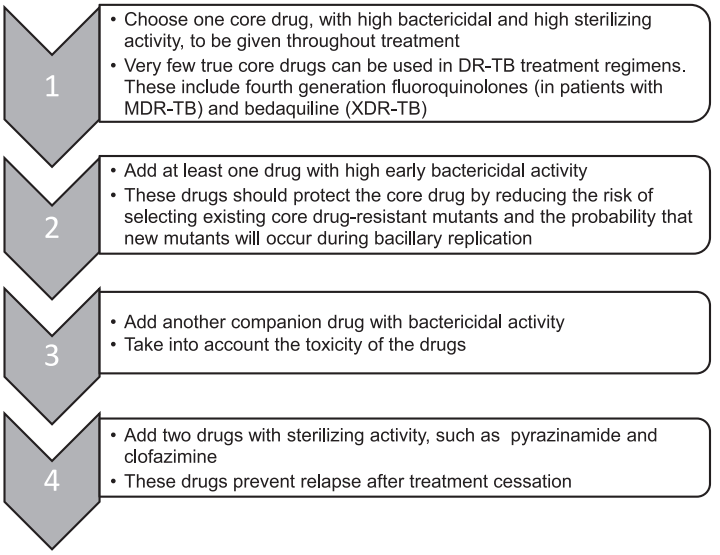

Figure Steps for constructing a DR-TB treatment regimen. To be effective, an anti-tuberculosis treatment regimen should include one core drug, plus at least one drug with high early bactericidal activity, another companion drug with bactericidal activity, plus two drugs with sterilizing activity. DR-TB = drug-resistant tuberculosis; MDR-TB = multidrug-resistant TB; XDR-TB = extensively drug-resistant TB.

sufficiently robust to overcome any additional initial resistance in the regimen. There are indications that both high-dose GFX and the extension of the intensive phase, even when only a few remaining bacilli were detected, have been indispensable in obtaining the observed excellent results.

Applying concept and strategy to create a regimen against extensively drug-resistant tuberculosis

The principles applied in case of drug-susceptible TB and MDR-TB are also relevant when formulating a regimen when there is resistance to both RMP and the FQs: an effective core drug must be complemented by carefully selected companion drugs (Figure). As there are few drugs that meet our criteria for a core drug, such drugs should not be administered simultaneously, to prevent premature exhaustion of all treatment options. FQ-susceptible patients with MDR-TB should therefore not be prescribed BDQ as it could potentially be used as core drug in an XDR-TB regimen. Following this logic, where FQs are used as a core drug, BDQ would be an inappropriate choice as a companion drug. Moreover, FQ may be replaced by BDQ in case of FQ intolerance.

Low-level resistance does not render fourth-generation FQs obsolete.[43] In cases of low-level resistance, high-dose GFX has been shown to retain sufficient activity to act as a very effective core drug.[8] In practice, however, the level of FQ resistance may not be reliably determinable. In the case of high-level FQ resistance, a regimen based on another core drug is indicated.

Given the higher frequency of failure and acquired resistance relative to the Bangladesh study in patients treated with a normal dose of MFX in a West African study,[11] we believe that effective MDR-TB treatment would be best served by making GFX available again.[44] Another option would be to consistently use high-dose MFX. When MFX is used, especially in combination with CFZ, monitoring for cardiotoxicity is indicated. However, as QT interval monitoring is not feasible in many settings, and torsades de pointe may develop without previous electrocardiogram abnormalities, very high-dose levofloxacin (1500 mg for 55–64 kg body weight, 1750 mg if $\geqslant$65 kg) may be a better solution if GFX remains unavailable.

OUTLOOK ON IMPROVED TREATMENT OF DRUG-RESISTANT TUBERCULOSIS

When additional core anti-tuberculosis drugs with sufficiently well characterized properties become available, it may become possible to design MDR-TB regimens containing fewer drugs than seem currently necessary. Although spontaneous mutations may emerge during the course of treatment, simultaneous acquisition of resistance to three regimen drugs during a single course of treatment is unlikely, explaining in part the success of the first-line regimen in patients with RMP-susceptible TB. Current trials are assessing whether all-oral 6-month regimens, consisting of three or four drugs, are efficacious in patients with MDR-TB.

However, regimens composed of fewer drugs may be more vulnerable to unidentified initial resistance. One of the factors that may explain the current outbreak of RR-TB is masked resistance to the other first-line drugs among patients on the 6-month first-

line regimen.[45,46] The same might happen even more rapidly when FQs are used for INH resistance together with RMP, EMB and PZA. RMP resistance is missed more often than previously suspected, as the phenotypic DST gold standard was shown to miss clinically relevant resistance,[47] and the commercially available molecular assays do not cover all *rpo*B mutations that confer resistance.[48] Moreover, PZA does not necessarily protect against the selection of resistant mutants among most actively multiplying bacilli.[49] As resistance remains a 'man-made problem', the risk of acquiring resistance to new potential core drugs should be reduced by using them only for clearly defined indications, embedded in a solid regimen with assured strict treatment adherence.

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RÉSUMÉ

Les directives actuelles de l'Organisation Mondiale de la Santé relatives à la composition du protocole de traitement de la tuberculose multirésistante (TB-MDR) accordent trop peu d'attention à l'activité microbiologique des médicaments de la TB. Nous tirons ici les leçons du travail de pionnier relatif aux protocoles plus courts de traitement de la TB-MDR et des connaissances actuelles en matière de propriétés bactéricides et stérilisantes des médicaments pour guider la composition des protocoles de traitement de la TB-MDR. Nous proposons de réserver le terme de « médicament principal » au médicament du protocole qui contribue le plus à une guérison sans rechute. Le médicament principal a, à la fois, une activité bactéricide et stérilisante modérée à élevée, est administré tout au long du traitement, est bien toléré, et n'a pas de résistance croisée avec le médicament principal utilisé dans le protocole précédent. Les médicaments principaux actuellement utilisés incluent la rifampicine dans le protocole de première ligne de 6 mois et les fluoroquinolones de quatrième génération et la bédaquiline dans les protocoles de TB pharmacorésistante. Tous les autres médicaments sont des « médicaments associés », qui protégent vis-à-vis d'un échec du traitement à travers l'acquisition d'une pharmacorésistance vis-à-vis du médicament principal. Certains médicaments contribuent également à réduire davantage le risque de rechute. Plus encore, les médicaments toxiques doivent être évités s'il y a une alternative. Un protocole doit toujours inclure le médicament principal, ensuite au moins un médicament associé avec une activité bactéricide élevée, un deuxième médicament compagnon bactéricide, puis deux médicaments associés stérilisants.

RESUMEN

Las directrices vigentes de la Organización Mundial de la Salud sobre la composición del esquema terapéutico de la tuberculosis multirresistente (TB-MDR) no prestan mucha atención a la actividad microbiológica de los fármacos antituberculosos. En el presente artículo, se extraen enseñanzas de los trabajos vanguardistas sobre los esquemas de tratamiento más cortos de la TB-MDR y de los conocimientos actuales sobre las propiedades micobactericidas y esterilizantes de los fármacos, con el propósito de documentar la composición de los esquemas de tratamiento de este tipo de TB. Se propone reservar el término 'fármaco básico' al fármaco de un esquema que más contribuye a la curación sin recaída. El fármaco básico posee una actividad micobactericida y esterilizante de moderada a alta, se administra durante todo el tratamiento, exhibe buena tolerabilidad y no presenta resistencia cruzada con el fármaco básico del tratamiento anterior. Los fármacos básicos más utilizados son la rifampicina en el esquema de primera línea de 6 meses y las fluoroquinolonas de cuarta generación y la bedaquilina en los esquemas contra la TB farmacorresistente. Todos los demás medicamentos se consideran 'fármacos complementarios', que protegen contra el fracaso terapéutico que depende del surgimiento de farmacorresistencia al medicamento básico. Algunos fármacos contribuyen también a disminuir aun más el riesgo de recaída. Además, cuando existe una alternativa, se deben evitar los fármacos tóxicos. Un esquema de tratamiento tiene que incluir siempre el fármaco básico y como mínimo un fármaco complementario con alta actividad micobactericida, un segundo fármaco complementario bactericida, más dos fármacos complementarios esterilizantes.