

A basis for the clinical management of complicated MDR-TB cases

Ignacio Monedero and Sandya Holkar summarise best practice in the often lengthy and complex management of multidrug-resistant tuberculosis

Summary

Successful multidrug-resistant tuberculosis (MDR-TB) treatment and programme performance is possible even in complex circumstances. Governments are subject to strong pressure from donors concerning both DOTS (directly observed treatment, short course) expansion initiatives and especially MDR management.¹ Nevertheless, anyone assuming an MDR programme can be launched just with money and drugs is probably labouring under a grave misapprehension. A sound understanding of the clinical management of both susceptible and resistant TB is one of the basic fundamentals. The standard use of second-line drugs is not only measured in low cure rates but in drug resistance amplification in the community, and hence potentially circulating extensively drug-resistant (XDR) TB strains.

From a clinical point of view, MDR management is lengthy and complicated, involving the entire range of problems attendant upon chronic disease plus the high toxicity profile of second-line drugs. In addition, in developing countries with high HIV/TB co-infection levels, the complexity in terms of clinical and drug management issues increases. Poverty and lack of access to care and treatment can reduce adherence and further complicate the recovery process. This paper provides a brief summary of the best practice in MDR-TB patients including the most frequent side-effects and practical advice on managing TB/HIV co-infection based upon the most recent evidence.

Background

Multidrug-resistant tuberculosis (MDR-TB), defined as TB resistant to isoniazid (H) and rifampicin (R) is a major concern in global TB control. It is thought that

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more than half a million MDR-TB cases emerge per year.² The issue is more serious taking into account the length and cost of treatment, the serious side-effects and the low cure rates compared with susceptible cases.

Unfortunately, low cure rates are especially common in those countries with high TB/HIV co-infection rates.³ HIV per se is not a risk factor for MDR-TB.^{4,5} However, it has been widely linked to MDR or even XDR-TB outbreaks.^{6,7} People living with HIV, by reason of their impaired immunity, are more likely to become infected with TB, more than 100 times more likely to develop TB disease from infection, and also more likely to die from it.⁸ Due to this synergy of HIV and TB, Africa demonstrates an unusual scenario whereby the total number of MDR cases remains relatively low but the incidence of new cases is particularly high.⁹

It is thought that airborne XDR/MDR-TB transmission to primary cases is playing a crucial role in high HIV burden countries. The deadly XDR-TB epidemic of Kwa-Zulu Natal in South Africa is probably the most studied example.⁶ Around 98% of the patients died within 2 weeks of diagnosis; most having been infected by the same source. Major efforts towards infection control and appropriate MDR-TB management are urgently needed. Tackling HIV is not easy, and neither is combatting MDR/XDR-TB. Managing both at the same time is even more complex. New anti-TB medications and ideally an effective TB vaccine are desperately needed, but they will not be ready for use in developing countries within the next 10–15 years.¹⁰

There is a pressing need for training of healthcare workers since suboptimal clinical management of a patient can amplify resistance into MDR within a couple of months. However, curing that same patient once they have developed MDR-TB can take up to 2 years.¹¹ Furthermore, the cure rates for MDR-TB and specially XDR-TB tend to be less than 60%^{5,12} and failure and mortality rates are high.¹³

In addition to these challenges, wide-scale MDR-TB management is comparatively a new field. Consequently, not many randomised controlled trials (RCTs) exist



MDR-TB often requires complex drug management

and to some extent this has generated more controversies than useful evidence.¹⁴ It is only recently that a robust consensus on correct management is being achieved.¹¹ However, even in low-income settings with limited human resources, there are many effective measures which can be applied, just using the current knowledge and public health tools.

The aim of this paper is to provide a short catalogue of good practices to manage the majority of complicated MDR cases, describing the most common problems and the most likely solutions according to current literature. Given the urgent need for practical and simple approaches to managing MDR complex conditions, this paper aims to provide rapid and succinct guidance on management of MDR-TB and avoidance of common errors even where resources are most scarce. It is also hoped that it will serve as a starting point for further reading of more specialised MDR-TB guidelines and literature.

Basis for susceptible TB management

Susceptible TB is mainly diagnosed by sputum smear, which is cheap, quick and easy to accomplish even in resource-scarce settings.^{15,16} It is not only highly specific but also informs whether or not a patient is contagious (specificity of 95%). However, it is not very sensitive, as it can only detect approximately 70% of active TB cases in optimal conditions. In high-HIV settings this figure can be further reduced as many people living with HIV (PLHIV) with active TB develop smear-negative forms. Culture offers a considerable increase in sensitivity (diagnoses up to 85% of cases) but in most high-prevalence settings results are unavailable before 1–3 months, and hence are of no use for immediate clinical management.

There are two basic principles for effective TB treatment:^{8,17}

1. Use of *several drugs* to avoid resistance amplification. If a bacillary population is exposed to only one drug, then just by chance and spontaneous mutation 1 out of 1 million of the bacilli will be a natural mutant resistant. In a patient with cavitary disease, the number of bacilli within the patient is approximately 1000 million. Hence if exposed to monotherapy, almost all of those bacilli will die but from 100 to 1000 natural mutant resistants will remain. After a couple of months there will again be 1000 million bacilli but now all will be of resistant strains. To avoid this circumstance, it is recommended that the initial phase of TB treatment contains at least four drugs. First-line drugs are to date the most powerful drugs available to treat TB.
2. Lengthy treatments: *Mycobacterium Tuberculosis* is a very slow growing bacterium. Furthermore, depending on pH and oxygen conditions on the lesions, bacilli could present different metabolic populations. Some of them are metabolically active, like in the cavities, where the bacilli divide and create disease. Conversely without oxygen and favourable pH conditions bacilli turn metabolically inactive or dormant. Dormant bacilli are not easy to kill and if they turn active will eventually create relapses.

Rifampicin (R) is to date the drug with the greatest capacity to kill dormant forms. Thanks to rifampicin, treatment length can be reduced to 6 months. Without its powerful sterilising effect, the duration of TB treatment stretches to 18–24 months.¹¹

Current treatment recommendations^{15,16} are 2 months with four drugs (R, H, pyrazinamide (Z) and ethambutol (E)) plus 4 months with two drugs (RH). Daily treatment is preferred, especially in high-HIV settings where there are demonstrably better outcomes and reduced relapse and death rates.^{18,19} For susceptible disease, this treatment combination can cure up to 97% of patients.⁸

Bases for MDR-TB management

MDR-TB is simply TB disease that can not be cured with the most effective drugs to date, i.e. isoniazid and rifampicin. Diagnosis can not be confirmed with sputum, clinical picture or chest X ray (CXR) but only from drug susceptibility testing (DST). This can be done via culture (liquid or solid), with, however, a likely delay of 1 to 4 months or more. Usually liquid culture is quicker but contamination rates tend to be higher. DST, a technique developed more than 50 years ago, is most reliable for R and H.²⁰ For fluoroquinolones (FQs) and second-line injectables it is very reproducible but less reliable.²¹ This means results can be consistent between different laboratories, however the clinical relevance of the result can be inaccurate. Unfortunately, regular DST is not very reliable for other second-line drugs (SLDs) and in the particular case of Z, cycloserin (Cs), ethionamide (Eth) and PAS, DST can confuse clinicians more than it helps.^{21,22} Consequently, having a detailed history of the previous drug history of the patient is crucial. An important issue to keep in mind is that currently the best predictor of resistance in TB is the use of a drug as monotherapy for more than 1 month.¹⁷ In clinical practice this translates into the most common error in TB clinical practice leading to drug resistance: adding one drug to a failing regimen.

Fortunately, new rapid DST techniques based on PCR technology and genetic mutation detection are able to provide susceptibility results within 2 hours to 5 days. Being not only rapid but also offering more reliable results, these new techniques are starting to be introduced in many different settings with good results under real conditions.²³

Before starting MDR-TB treatment, a DST result demonstrating resistance to R and H plus an accurate history of drugs is mandatory.¹¹ Also, identification of *Mycobacterium* species is fundamental. *Mycobacterium* other than *Tuberculosis* (MOTTs) can have a DST pattern of disease of MDR. These different sorts of bacilli require a different treatment that is less toxic, less expensive, and shorter than MDR-TB treatment. It is thought that in many MDR-TB programmes, a substantial proportion of the patients actually have MOTT rather than MDR-TB especially in high-HIV settings.

The principles for MDR-TB treatment are the same as for susceptible TB:¹¹

1. *At least four effective drugs*: drugs should be chosen starting from the most effective and least toxic (FLDs) and scaling-up to the least effective and more toxic.

Table 1 Rational classification of anti-tuberculosis drugs. Adapted from references 10, 11, and 14

Grouping	Drugs
Group 1 First-line oral agents	Isoniazid (H); rifampicin (R); ethambutol (E); pyrazinamide (Z)
Group 2 Injectable agents	Kanamycin (Km); amikacin (Am); capreomycin (Cm); streptomycin (Sm)
Group 3 Fluoroquinolones (FQs)	Ofloxacin (Ofx); moxifloxacin (Mfx); levofloxacin (Lfx); gatifloxacin (Gfx)
Group 4 Oral bacteriostatic second-line agents	Ethionamide (Eto); prothionamide (Pto); cycloserine (Cs); terizidone (Trd); P-aminosalicylic acid (PAS)
Group 5 Agents with unclear efficacy	Clofazimine (Cfz); amoxicillin/clavulanate (Amx/Clv); linezolid (Lzd); imipenem/cilastatin (Ipm/Cln); thioacetazone (Thz); clarithromycin (Clr); high-dose isoniazid (high-dose H)

Anti-TB drugs are classified according into five different groups (see Table 1). The pillars of category IV treatment are FQ and second-line injectables, which are by far the most bactericidal drugs among second-line drugs. Add drugs from group 4 (weak and toxic drugs) until complete four effective drugs and use all possible first-line drugs to which the patient is or might be susceptible. When over an MDR-TB case, resistance to one FQ or one second-line injectable emerges, the disease is defined as XDR-TB.²⁴ In that case, drugs available are less and consequently prognosis is worst. Usually the use of group 5 drugs is necessary to treat XDR-TB cases. However, as drugs from this group are very weak or have little evidence base, use two drugs from this group, to account one new 'effective drug'.¹¹

2. *Long treatment*: because the sterilisation power of R is lost, treatments are extended to 24 months. Injectables are recommended to be used for at least 4 months after culture turns negative and usually 6 months.¹¹ If there is resistance to FQs the continuation phase is weak after injectable withdrawal and longer treatment with injectables might be needed given the lack of a powerful drug in the continuation phase.
3. The choice between using individualised versus standardised regimens is a long and hotly debated issue. Though in developing countries, for patients who have never used SLDs in the past, standardised regimens can achieve good levels of treatment success with lower cost, less specific training, and reduced risk of treatment improvisations.¹⁴

Surgery is another issue to consider. This option, with the high associated mortality and morbidity, is only indicated in a limited number of patients who meet the following conditions: fewer than three or four effective drugs available for treatment, single and localised lesion, and sufficient respiratory reserve after the resection.^{14,25} Few patients fulfil these criteria.

Clinicians should be alert to the problem of cross-resistance among anti TB drugs.^{11,26} Rifampicin has almost full cross resistance with other rifamycins. Isoniazid and ethionamide may also have cross resistance if there is isoniazid resistance at low isoniazid concentration (inh-

A mutation). Old generation FQs (ciprofloxacin–ofloxacin) are generally cross resistant within them. However, some activity may still remain using new generation FQs (levofloxacin, gatifloxacin, moxifloxacin) even if resistance to old generation FQs exists. Note that ciprofloxacin is currently not recommended to treat MDR-TB due to reduced efficacy.²⁷

Due to the considerations of toxicity and cross resistance, the order of preference for second-line injectables becomes: capreomycin, then kanamycin, and lastly amikacin.^{28,29} Streptomycin is not recommended currently for MDR-TB treatment given the high resistance levels among initial H resistant strains.

Although clinical improvement is useful, monitoring of MDR as a disease can only be done through/by bacteriology. Follow-up of treatment should preferably be based on culture.¹¹ The number of colonies (solid culture) can be help to show progress or risk of failure during the treatment.

Drug side-effects and possible solutions

First-line drugs

The most common side-effects from first-line drugs is hepatotoxicity.⁸ High levels of liver enzymes (particularly ALT) should be an alert. Having levels four times higher than normal is considered as hepatitis and treatment should be stopped until liver enzymes return to normal. The drugs should be reintroduced one by one with gradually increasing dosage over 2 weeks, starting from the least hepatotoxic.^{15,30} In this sense the rational order of introduction is E–R–H–Z.

Rifampicin is an inducer of cytochrome p450, hence can reduce the levels of other drugs including oral contraceptive, protease inhibitors, and nevirapine. Specific advice should be given on this in TB/HIV patient recommending ARV treatments based on efavirenz or tenofovir plus two NRTIs.³¹

Optic neuritis is an infrequent (less than 1 in 500 treatments) but concerning side-effect of ethambutol (E). It usually starts with colour distortion and blurred vision. If this happens, treatment should be stopped immediately. The use of E among children has being an issue of much debate.³² Currently it is widely recommended to them at a 15–20 mg/kg/day dosage, where the occurrence of optic neuritis is less frequent.¹⁵

Table 2 MDR-TB management. Fundamental aspects. Adapted from references 10, 11, and 14

Steps	Considerations
1. Diagnose	Information required? <ul style="list-style-type: none"> History of drugs: 1 month of monotherapy or single drug intake over a failing regimen could be a strong predictor of resistance. DST: most reliable for R and H; also reliable for Km and FQ; less reliable for E and Z; very low reliability for group 4 drugs.
2. Number of drugs	'At least four effective drugs': never used in the past or shown to be susceptible by DST (taking into account DST reliability and cross-resistance)
3. Drug selection	<ul style="list-style-type: none"> Use first-line drugs if are still effective One injectable One FQ Use group 4 drugs until a regimen with four effective drugs has been reached. If necessary, use group 5 drugs to strengthen the regimen or when with previous groups the number of four effective drugs is not reached. One drug from group 5 accounts as 'half effective drug'.
4. Length of the injectable	<ul style="list-style-type: none"> At least 4 months after smear or culture conversion; longer if there are not three effective drugs used during continuation phase or if drugs used are from group 5
5. Surgery	Consider only if: <ul style="list-style-type: none"> few effective drugs are available localised lesions sufficient respiratory reserve
6. Ideal regimen	<ul style="list-style-type: none"> <i>Standardised</i>: if there is no use of second-line drugs in the past <i>Individualised</i>: use of second-line drugs in the past or contact with an MDR patient who used second-line drugs (treat with whichever regimen was effective for the index case)

Second-line drugs

Current evidence indicates that FQs, have a relatively safe profile even in children.³³

Injectables, including streptomycin, have quite a toxic profile, and can cause vestibular toxicity (vertigo), hearing loss and renal insufficiency, plus teratogenicity (safety class C for Cm and class D for Sm, Am, Km).¹¹ Toxicity is mainly by cumulative dosage hence for long treatment, administration can be reduced to three times weekly. Where conditions are suitable, the drug should be administered intravenously to avoid painful injections especially among malnourished patients.

Cycloserin can cause disturbances of the central nervous system ranging from nightmares to depression, psychotic syndrome and suicidal tendencies. These symptoms are rarely but increasingly described.

Ethionamide (Eto) or prothionamide (pto): these effectively identical drugs are badly tolerated because of nausea, vomiting, stomach ache, and diarrhoea.

PAS: probably the worst-tolerated drug having extremely unpleasant (although not life-threatening) gastrointestinal symptoms. If given with Eto/Pto tolerance side-effects are even worse. Concomitant use can also lead to alteration of the equilibrium of thyroid hormones.

Tips for most frequent side-effects

Using category IV treatment, we can predict that side-effects will occur; hence clinicians must be alert to their occurrence. Nevertheless, despite the wide range of adverse events among second-line drugs, the most frequent ones which have the greatest impact on adherence are easy to diagnose and treat.^{11,34}

1. *Nausea, vomiting, and diarrhoea* are the most common side-effects and are relatively easy to control if omeprazol or similar drugs are used at high doses. Antacids are not recommended due to interactions with FQs absorption. Drugs can be given with foods such as milk and banana that do not decrease absorption, while improving tolerance and possibly adherence if given for free at facilities. Drugs that are poorly tolerated such as PAS, Eto/Pto, and Cs can be introduced gradually (drug ramping).¹¹ The patient starts on a one-third dosage and it is increased every 4–5 days, achieving full dosage within 2 weeks.

2. *Arthralgia*, which is also a common side-effect, can be easily tackled with paracetamol or non-steroid anti-inflammatory drugs.

3. *Dizziness, vertigo, and hearing loss* are most commonly caused by second-line injectables. If early symptoms appear, particularly hearing loss (described by the patient or by audiometry), then consider reducing the injectable treatment to three times weekly. Regrettably, hearing loss is irreversible. However, early withdrawal of injectable would be a mistake if the continuation phase is weak or the smears or cultures remain positive, since the patient would probably develop amplification of resistance in the continuation phase and failure. Keep in mind that Category IV is, especially in developing countries, the last chance for this patient to achieve cure.

Other less common side-effects include *numbness and paresthesia*. A suitable approach for these is to provide from 50–150 mg of pyridoxine (Vit B6). To prevent central and peripheral nervous system alteration it is

currently recommended to use 50 mg pyridoxine for each 250 mg of cycloserine (750 mg average Cs dose). In case of seizures, even 300 mg of pyridoxine plus regular anticonvulsive therapy can be used.¹¹ Behavioural changes are also common, especially depression, in which Cs probably plays a major role but nevertheless, other important factors like chronic ill health and poor socioeconomic conditions also contribute. Treatment with an antidepressant plus psychotherapy and socioeconomic support improves the quality of life of the patient and this increases adherence to treatment. Regarding psychotic disorders, neuroleptics such as haloperidol or risperidone plus pyridoxine can be used. In case of hypothyroidism, replace thyroid hormones when necessary. At the end of the treatment and Eto/Pto and PAS discontinuation, hormone levels tend to return to normal.¹¹

Bases for MDR-TB and HIV management

Management of these two diseases concurrently is one of the major challenges for TB control. However, this is the certain reality for many sub-Saharan African countries. Patients are usually diagnosed late in the course of HIV infection with a low CD4 count, presenting with malnutrition and several opportunistic diseases, TB among them.

According to current evidence the best clinical questions to screen for TB among HIV infected patients are: asking about cough of any duration, fever of any duration and night sweats in the last 3 weeks or more.³⁵ Nutrition treatment and vitamin supplementation (especially vitamin B6) should start as soon as possible together with cotrimoxazole preventive therapy which should continue at least until the end of TB treatment.¹⁵ Other opportunistic diseases should be excluded or treated, especially *Cryptococcus meningitis*. Treatment of opportunistic disease also avoids development of immune reconstitution inflammatory syndrome (IRIS) when ARV treatment is commenced.

TB treatment should start as soon as possible to avoid patient death. If patient has susceptible TB disease then Category I treatment is to be order. HIV-infected patients often have problems of malabsorption hence daily treatment with rifampicin is preferred and leads to better cure rates and fewer relapses.^{15,18,19}

ARV initiation is mandatory whenever TB is present, regardless of the CD4 count.¹⁵ The timing for ARV initiation has been a subject of much debate, although currently the best cure and lowest death rates have been demonstrated among those starting ARV shortly after (2 weeks) or concomitant with TB treatment initiation.³⁶ Preventing and treating IRIS (1–2 mg of prednisone/kg/day) resulted in no deaths or serious side-effects in patients in the integrated treatment group. The only exception to this occurs with immune reconstitution due to cryptococcal meningitis; which *must* be treated simultaneously with TB, while in all other cases, the sooner ARVs are started, the better the cure rates obtained.

Regarding drug interactions between TB and HIV, the key issue is rifampicin which is both the best anti-TB drug ever and a powerful inductor of cytochrome P450. Cytochrome P450 reduces the concentration of

many ARVs, especially protease inhibitors (PI) and NVP. Currently the recommendation while using rifampicin are 2 nrti (nucleoside reverse transcriptase inhibitors) plus efavirenz, or alternatively 3 NRTI. Where protease inhibitors are unavoidable, the ritonavir boosting dose should be increased from 100 mg to 400 mg but this regime is often poorly tolerated.³¹

MDR treatment lacking rifampicin avoids the principal interaction problems. Nevertheless, clinical complexities and second-line drug toxicities are added. MDR-TB patients tend to be in the worst clinical situation having spent longer in a deteriorating state, more so if they are HIV infected. Gastrointestinal intolerance is often severe due to malnutrition and parasitic diseases; electrolyte alterations like hypokalaemia (especially when on capreomycin treatment) and overall renal insufficiency are more frequent. Overall, evidence on drug to drug interactions between second-line drugs and ARV are still limited.³⁷

Particular care and monitoring of these patients is needed especially at the beginning of treatment where other opportunistic diseases, serious clinical conditions (malnutrition, cavitory, meningeal and miliary TB), drug intolerance, side-effects, additive toxicities, and IRIS are all occurring within a short time frame. See a basic approach for TB/HIV patients in Box 1.

However, implementing these measures at the community level is not useful if patients and visitors are getting MDR-TB infected during their stay at the hospital. Good understanding of the disease plus effective administrative infection control measures are strongly needed in high-HIV-prevalence countries.³⁸

Other special conditions

Regarding management of children, the same rules apply as for adults. Given that the bacillary load in children is lower, probably three effective drugs and shorter treatments could be used.¹¹ However, there is no robust evidence to support these statements. In terms of

Box 1 Fundamental aspects of TB/HIV patient management

1. Initiate TB treatment as soon as possible and preferably containing rifampicin on a daily basis.
2. Initiate CPT as soon as possible. Keep CPT at least for the whole TB treatment duration.
3. Nutritional support and vitamin replacement.
4. Rule out and treat other opportunistic diseases (especially *Cryptococcal meningitis*).
5. Start ARVs in all PLHIV with TB independently of the CD4 count.
6. Start ARV as soon as possible and in any case earlier than 8 weeks from TB treatment initiation.
7. Adjust ARV treatment in case of susceptible TB and rifampicin use.
8. Prevent IRIS (prednisone 1–2 mg/kg/day for 2 weeks).
9. Closely monitor for side-effects and toxicities.

Note: CPT: Cotrimoxazol preventive therapy; PLHIV: People living with HIV.

side-effects, it appears that SLDs are better tolerated in children.

On the subject of pregnancy and MDR, pregnancy should be avoided if possible. A pregnancy test should be requested at the beginning of treatment and family planning discussed and strongly encouraged. Deferral of treatment to the second trimester is suggested if the clinical condition allows it. Almost all first- and second-line drugs can be used during pregnancy with different levels of safety. Nevertheless, injectables should be avoided (Sm, Km, Am) or if necessary, use capreomycin where available as it has a less teratogenic profile.¹¹

Diabetes mellitus is becoming a more common condition in developing countries and even among MDR-TB cases. Among diabetes patients immunity is slightly reduced, thus creating a greater chance of worse outcomes. Moreover, treatment can be more complicated if a baseline of neuropathy and renal failure exists in addition to potential drug toxicities.

Conclusions

MDR-TB management on a large scale is new for most NTPs. In addition, many countries have to face fundamental challenges such as scarce economic and human resources, weak healthcare systems and high HIV rates. In these challenging conditions clinical and programmatic errors can occur frequently. In that sense, improper TB or MDR-TB schemes are a waste of money and lives. Moreover, it leads to an increase in resistant strains circulating in the community.

Now, more than ever, good cure rates among susceptible cases are vital. Prevention of MDR with good initial treatments and follow-up are the roots of the problem and the solution. This is certainly true if HIV rates are high and infection control measures are not in place. Inappropriate MDR-TB schemes lead to low cure rates and a high number of failures. On the other hand appropriate MDR-TB schemes, which are the last chance for the patient, will result in bad adherence, unless side effects are managed promptly and the continuation phase is supportive.

Clinical MDR-TB management is challenging but feasible even in resource constrained settings. Overall, clinical knowledge is not only crucial but the starting point for an MDR-TB programme. A good working understanding of the disease process is essential.

References

- Seita A. The critical challenge in tuberculosis programmes: are we thinking critically? *Int J Tuberc Lung Dis* 2009;13:1444–6.
- WHO. *Anti-Tuberculosis Drug Resistance in the World. Fourth Global Report*. WHO/HTM/TB/2008.394. Geneva, Switzerland: WHO, 2008.
- Murray J, Sonnenberg P, Shearer SC, Godfrey-Faussett P. Human immunodeficiency virus and the outcome of treatment for new and recurrent pulmonary tuberculosis in African patients. *Am J Respir Crit Care Med* 1999; 159: 733–40.
- Suchindran S, Brouwer ES, Van Rie A. Is HIV infection a risk factor for multi-drug resistant tuberculosis? A systematic review. *PLoS One* 2009; 4: e5561.
- WHO. *Multidrug and Extensively Drug-Resistant Tb (M/Xdr-Tb): 2010 Global Report on Surveillance and Response*. Geneva, Switzerland: WHO, 2010.
- Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet* 2006; 368: 1575–80.
- Wells CD, Cegielski JP, Nelson LJ, et al. HIV infection and multidrug-resistant tuberculosis: the perfect storm. *J Infect Dis* 2007; 196 Suppl 1: S86–107.
- Caminero Luna JA. *A Tuberculosis Guide for Specialist Physicians*. Paris, France: Imprimerie Chirat, International Union Against Tuberculosis and Lung Diseases, 2004.
- Caminero JA. Multidrug-resistant tuberculosis: epidemiology, risk factors and case finding. *Int J Tuberc Lung Dis* 2010; 14: 829–90.
- Monedero I, Caminero JA. MDR-/XDR-TB management: what it was, current standards and what is ahead. *Expert Rev Respir Med* 2009; 3: 133–45.
- WHO. *Guidelines for the Programmatic Management of Drug-resistant Tuberculosis. An Emergency Update*. WHO/HTM/TB/2008.402. Geneva, Switzerland: WHO, 2008.
- Sotgiu G, Ferrara G, Matteelli A, et al. Epidemiology and clinical management of XDR-TB: a systematic review by TBNET. *Eur Respir J* 2009; 33: 871–81.
- Brust JC, Gandhi NR, Carrara H, Osburn G, Padayatchi N. High treatment failure and default rates for patients with multidrug-resistant tuberculosis in KwaZulu-Natal, South Africa, 2000–2003. *Int J Tuberc Lung Dis* 2010; 14: 413–9.
- Caminero JA. Treatment of multidrug-resistant tuberculosis: evidence and controversies. *Int J Tuberc Lung Dis* 2006; 10: 829–37.
- WHO. *Treatment of Tuberculosis: Guidelines*. 4th ed. WHO/HTM/TB/2009.420. Geneva, Switzerland: WHO, 2009.
- IUATLD. *Management of Tuberculosis. A guide to the Essentials of Good Practice*. Sixth edition. Paris, France: International Union Against Tuberculosis and Lung Diseases (The Union); 2010.
- Mitchison DA. Microbial genetics and chemotherapy. *Br Med Bull* 1962; 18: 74–80.
- Menzies D, Benedetti A, Paydar A, et al. Effect of duration and intermittency of rifampin on tuberculosis treatment outcomes: a systematic review and meta-analysis. *PLoS Med* 2009; 6: e1000146.
- Khan FA, Minion J, Pai M, et al. Treatment of active tuberculosis in HIV-coinfected patients: a systematic review and meta-analysis. *Clin Infect Dis* 2010; 50: 1288–99.
- Kim SJ. Drug-susceptibility testing in tuberculosis: methods and reliability of results. *Eur Respir J* 2005; 25: 564–9.
- Kim SJ, Espinal MA, Abe C, et al. Is second-line anti-tuberculosis drug susceptibility testing reliable? *Int J Tuberc Lung Dis* 2004; 8: 1157–8.
- WHO. *Policy Guidance on Drug-Susceptibility Testing (DST) of Second-line Antituberculosis Drugs*. Geneva: World Health Organization, 2008.
- Barnard M, Albert H, Coetzee G, O'Brien R, Bosman ME. Rapid molecular screening for multidrug-resistant tuberculosis in a high-volume public health laboratory in South Africa. *Am J Respir Crit Care Med* 2008; 177: 787–92.
- WHO. *The Global MDR-TB and XDR-TB Response Plan*. WHO/HTM/TB/2007.387. Geneva, Switzerland: WHO, 2007.
- Somocurcio JG, Sotomayor A, Shin S, et al. Surgery for patients with drug-resistant tuberculosis: report of 121 cases receiving community-based treatment in Lima, Peru. *Thorax* 2007; 62: 416–21.
- Zhang Y, Yew WW. Mechanisms of drug resistance in Mycobacterium tuberculosis. *Int J Tuberc Lung Dis* 2009; 13: 1320–30.
- Ziganshina LE, Squire SB. Fluoroquinolones for treating tuberculosis. *Cochrane Database Syst Rev* 2008: CD004795.
- McClatchy JK, Kanes W, Davidson PT, Moulding TS. Cross-resistance in M. tuberculosis to kanamycin, capreomycin and viomycin. *Tubercle* 1977; 58: 29–34.
- Tsukamura M, Mizuno S. Studies on the cross-resistance of Mycobacterium tuberculosis, strain H37Rv, to aminoglycoside- and peptide-antibiotics. *Microbiol Immunol* 1980; 24: 777–87.
- Tostmann A, Boeree MJ, Aarnoutse RE, de Lange WC, van der Ven AJ, Dekhuijzen R. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. *J Gastroenterol Hepatol* 2008; 23: 192–202.
- WHO. *Priority Interventions HIV/AIDS Prevention, Treatment and Care in the Health Sector*. World Health Organization. HIV/AIDS Department. Version 1.2 – April 2009.
- WHO. *Ethambutol Efficacy and Toxicity: Literature Review and Recommendations for Daily And Intermittent Dosage in Children*. WHO/HTM/TB/2006.365, 2006.
- Burkhardt JE, Walterspiel JN, Schaad UB. Quinolone arthropathy in animals versus children. *Clin Infect Dis* 1997; 25: 1196–204.
- Nathanson E, Gupta R, Huamani P, et al. Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. *Int J Tuberc Lung Dis* 2004; 8: 1382–4.
- Cain KP, McCarthy KD, Heilig CM, et al. An algorithm for tuberculosis screening and diagnosis in people with HIV. *N Engl J Med* 2010; 362: 707–16.
- Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med* 2010; 362: 697–706.
- Coyne KM, Pozniak AL, Lamorde M, Boffito M. Pharmacology of second-line antituberculosis drugs and potential for interactions with antiretroviral agents. *AIDS* 2009; 23: 437–46.
- Bock NN, Jensen PA, Miller B, Nardell E. Tuberculosis infection control in resource-limited settings in the era of expanding HIV care and treatment. *J Infect Dis* 2007; 196 Suppl 1: S108–13.