ERJ Express. Published on August 4, 2011 as doi: 10.1183/09031936.00073611

Title

WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update

Authors

D. Falzon, E. Jaramillo, H.J. Schünemann, M. Arentz, M. Bauer, J. Bayona, L. Blanc, J.A. Caminero, C.L. Daley, C. Duncombe, C. Fitzpatrick, A. Gebhard, H. Getahun, M. Henkens, T.H. Holtz, J. Keravec, S. Keshavjee, A.J. Khan, R. Kulier, V. Leimane, C. Lienhardt, C. Lu, A. Mariandyshev, G.B. Migliori, F. Mirzayev, C.D. Mitnick, P. Nunn, G. Nwagboniwe, O. Oxlade, D. Palmero, P. Pavlinac, I. Quelapio, M.C. Raviglione, M.L. Rich, S. Royce, S. Rüsch-Gerdes, A. Salakaia, R. Sarin, D. Sculier, F. Varaine, M. Vitoria, J.L. Walson, F. Wares, K. Weyer, R.A. White, M. Zignol.

**For the list of affiliations refer to the Acknowledgements section.

Correspondence
D. Falzon, Stop TB Department / World Health Organization
20, Av. Appia - CH-1211 Geneva 27 - Switzerland
Email: falzond@who.int

Note: This article reproduces the recommendations of the 2011 update of the WHO guidelines for the programmatic management of drug-resistant tuberculosis released earlier this year.

Abstract

(200 words)
The production of guidelines for the management of drug-resistant tuberculosis fits the mandate of the World Health Organization (WHO) to support countries to reinforce patient care.
WHO commissioned external reviews to summarize evidence on priority questions regarding case-finding, treatment regimens for multidrug-resistant tuberculosis (MDR-TB), monitoring the response to MDR-TB treatment, and models of care. A multidisciplinary expert panel used the GRADE approach to develop recommendations. The recommendations support the wider use of rapid drug susceptibility testing for isoniazid and rifampicin or rifampicin alone using molecular techniques. Monitoring by sputum culture is important for early detection of failure during treatment. Regimens lasting at least 20 months and containing pyrazinamide, a fluoroquinolone, a second-line injectable drug, ethionamide (or prothionamide), and either cycloserine or p-aminosalicylic acid are recommended. The guidelines promote the early use of antiretroviral agents for TB patients with HIV on second-line drug regimens. Systems that primarily employ ambulatory models of care are recommended over others based mainly on hospitalization.
Scientific and medical associations should promote the recommendations among practitioners and public health decision makers involved in MDR-TB care. Controlled trials are needed to improve the quality of existent evidence, particularly on the optimal composition and duration of MDR-TB treatment regimens.

Keywords

[as MeSH terms]
tuberculosis, multidrug-resistant; guideline; drug therapy, combination; diagnosis; ambulatory care facilities

Introduction

Tuberculosis (TB) control in the world today must face the challenge posed by the global spread of *Mycobacterium tuberculosis* strains that are resistant to standard anti-tuberculosis drugs(1),(2). It is estimated that about 3% of incident new TB cases in the world have multidrug-resistant TB (MDR-TB), defined as resistance to at least isoniazid and rifampicin, the two most effective anti-tuberculosis drugs(3). About 440,000 MDR-TB cases (95%C.I. 390,000-510,000) are estimated to emerge annually among new and retreated TB patients. The frequency of MDR-TB varies by region and is much higher among previously treated patients. Among the vast majority of MDR-TB patients, very little is known about their access to quality care. Treatment of MDR-TB is complex, using toxic drugs that must be administered for a longer duration than for drug susceptible TB patients, and with lower likelihood of treatment success(4).
In 2009, in recognition of the threat posed by drug-resistant TB to global public health security, the World Health Assembly urged Member States to achieve universal access for diagnosis and treatment of patients with this form of disease(5). The World Health Organization (WHO) was mandated to provide technical support to countries to develop and implement national frameworks for care of drug-resistant TB patients. The production of guidelines for the programmatic management of drug-resistant tuberculosis fits into this role. WHO has already developed guidelines on this subject in recent years(6),(7), based on an assessment of available evidence and best practice by a large group of TB specialists. In 2008, an Emergency update of the guidelines was published and it expired in 2010. We report here about the 2011 update of the guidelines which was developed through a coordinated process starting in 2009. These guidelines target priority areas in drug-resistant TB care. They followed a careful process of systematic retrieval and synthesis of evidence in preparation for the formulation of recommendations by a multidisciplinary expert panel (Guideline Development Group, see Acknowledgements). This panel included TB practitioners, public health professionals, representatives of professional societies, national TB control programme staff, guideline methodologists, members of civil society and non-governmental organizations providing technical support, as well as WHO staff. A second group composed of national TB control programme staff, WHO Regional Advisers, clinicians and public health experts was appointed to serve in a peer-review capacity as an External Review Group (see also Acknowledgements).

Material and methods

i) Defining the scope of the updated guidelines ('scoping')

The 2008 Emergency update of the guidelines had identified outstanding areas of controversy or for which guidance in policy and practice was to be prioritized in future editions of the guidelines. In early 2009, an evaluation was conducted of the first two versions of the guidelines via a user questionnaire(8). The members of the Guideline Development Group discussed the findings of these two processes and decided to limit the scope of the guidelines to (i) case-finding (rapid molecular tests for drug resistance, and the investigation of contacts and other high risk groups); (ii) MDR-TB treatment regimens and duration in HIV-positive and HIV-negative patients; (iii) monitoring during treatment; and (iv) models of care.

This scope was translated into the following seven specific questions which were formulated in PICO(9) (Population, Intervention, Comparator to the intervention, and Outcome) or similar format:

1. At what prevalence of MDR-TB in any group of TB patients is rapid drug susceptibility testing warranted to detect resistance to rifampicin and isoniazid or rifampicin alone on all patients in the group at the time of TB diagnosis, in order to prescribe appropriate treatment at the outset?
2. Among patients with MDR-TB receiving appropriate treatment in settings with reliable direct microscopy, is monitoring using sputum smear microscopy alone rather than sputum smear and culture, more or less likely to lead to the relevant outcomes listed in Table 1?
3. When designing regimens for patients with MDR-TB, is the inclusion of specific drugs (with or without documented susceptibility) more or less likely to lead to the relevant outcomes listed in Table 1?
4. When designing regimens for patients with MDR-TB, is the inclusion of fewer drugs in the regimen (depending on the drug used, the patient's history of using the drug and isolate susceptibility) more or less likely to lead to the relevant outcomes listed in Table 1?
5. In patients with MDR-TB, is shorter treatment, compared with the duration currently recommended by WHO, more or less likely to lead to the relevant outcomes listed in Table 1?
6. In patients with HIV infection and drug-resistant TB receiving antiretroviral therapy, is the use of drugs with overlapping and potentially additive toxicities, compared with their avoidance, more or less likely to lead to the relevant outcomes listed in Table 1?
7. Among patients with MDR-TB, is ambulatory therapy compared with inpatient treatment more or less likely to lead to the relevant outcomes listed in Table 1?

The External Review Group also provided input into the design and content of the questions. The Guideline Development Group then selected and scored outcomes to determine those which were critical or important for making decisions on recommendations and on which data were to be sought during evidence retrieval and synthesis [Table 1].

ii) Review of evidence

Data sources: Between October 2009 and May 2010, WHO commissioned teams from leading academic centres (see Acknowledgements) to review and compile evidence for each of the questions through a series of systematic reviews of the literature using methods suggested by the Cochrane collaboration(10). The teams screened titles, abstracts and full text of potentially relevant papers using key subject words and text words. The search was not limited by study type or by a time period. In addition, the teams contacted article authors and consulted the Guideline Development Group members to identify missing studies or studies in progress. Individual patient data were collected from authors of published studies to address the questions dealing with bacteriology and treatment regimen (Questions 2-6). Modeling methods were used for Questions 1 and 2. The question on models of care (Question 7) was addressed by a review of published and unpublished studies with economic evaluation of MDR-TB patients on treatment.

Analysis: Where possible, relative effects (hazard ratios, relative risks or odds ratios of an event) were calculated using pooled data from the studies included. In two of the analyses outcome was expressed as the cost per disability-adjusted life year (DALY) averted. The DALY is a summary indicator that expresses the burden of mortality and morbidity into a single value, with perfect health valued at 1 and death at 0 (a year with TB disease is valued at 0.729)(11). For the modeling of drug susceptibility testing (DST), the cost outcomes estimated included total costs for each DST strategy, incremental cost per MDR-TB case prevented, cost per TB-related death avoided and cost per DALY averted. For the analysis of models of care (Question 7), costs included were from any of the following: cost from the health service provider's perspective, cost from the patient's perspective (including direct medical costs and indirect costs related to transportation) and total societal cost. Whenever possible, the following outcomes were included in the outcome: proportion of treatment success, default or long-term deaths

(including secondary, default and relapse cases), and case reproduction rate (transmission from primary cases).

iii) Development of recommendations

Summaries of evidence and GRADE (Grading of Recommendations Assessment, Development and Evaluation) profiles based on the results of the systematic reviews were prepared for each question using a standard approach(12). These summaries presented the effect of the intervention on each outcome and the quality of the evidence for each effect, categorized into four levels (Table 2) (13). The review teams assessed the quality of evidence using the following criteria: study design, limitations in the studies (risk of bias), inconsistency, indirectness[i], imprecision, publication bias, magnitude of effect, dose effect relations and the effect of residual confounding.
The members of the Guideline Development Group met to develop the recommendations at WHO headquarters in Geneva, Switzerland from 25 to 27 October 2010. The teams conducting the reviews presented their findings and the GRADE profiles to the group. The GRADE profiles allowed group members to base their judgments on uniformly summarized evidence. In their deliberations, the Group judged the strength of the recommendations from the perspective of different users of the guideline (Table 3) The higher the quality of evidence, the more likely that it led to a strong recommendation. A strong recommendation was however possible in the presence of very low quality evidence as consideration is given to values and preferences that experts attribute to the target population, the balance between desirable and undesirable consequences of an intervention, and resource implications(13). The Group reached agreement on the recommendations following discussion.

[i] Refers to whether the evidence directly answers the question being addressed. See (12) for an explanation of the two types of indirectness.

Throughout the guideline revision, the Guideline Development Group considered that the proper management of drug-resistant tuberculosis requires a concerted effort from various components of the national TB control programme on all activities of care including case detection, treatment, prevention, surveillance, monitoring and evaluation of programme performance. In the development of the recommendations, the Group attached importance to the following guiding principles: (i) promotion of universal access in low-resource settings, (ii) prevention of death and transmission of MDR-TB through early diagnosis, (iii) avoidance of harm and, (iv) provision of care in a setting acceptable to the patient and which optimizes the use of resources.

Recommendations

Eleven recommendations were made by the Guideline Development Group, regarding diagnosis, treatment, monitoring, and models of care.

Recommendation 1. Rapid drug susceptibility testing (DST) of isoniazid and rifampicin or of rifampicin alone is recommended over conventional testing or no testing at the time of diagnosis of TB, subject to available resources (conditional recommendation, ⊕◯◯◯/very low-quality evidence)

Remarks

- The effect of different DST strategies was simulated using decision analysis modeling(14). This method can only generate very low-quality evidence. Despite limitations, sensitivity analyses showed that the results were fairly consistent under different conditions.
- A DST for isoniazid and rifampicin or rifampicin alone which provides a diagnosis within a day or two of testing was considered rapid for this recommendation. Only molecular tests can detect resistance so fast today, of which two technologies - line probe

assay and Xpert MTB/RIF[ii] - are currently recommended for use by WHO. The basic assumption is that rapid DST would reduce the delay to start of appropriate second line therapy, and thus provide benefit to the patient by increasing cure, decreasing mortality, reducing development of additional drug resistance, and reducing the likelihood of failure and relapse.

- Rapid DST on all patients before the start of treatment was the most cost-effective strategy to avert deaths and prevent the acquisition of additional resistance. Rapid testing for both isoniazid and rifampicin at diagnosis rather than later on during treatment was the most cost-effective testing strategy available, starting from a MDR-TB prevalence greater than 1%, and isoniazid resistance (other than MDR-TB) greater than 2%. Rapid DST for rifampicin alone could also avert many deaths but it could not prevent the acquisition of additional resistance in patients resistant to isoniazid alone.
- The influence on secondary transmission of resistant strains was not included in the model and therefore estimations of reductions in mortality and morbidity from early detection and treatment are likely to be conservative. The increased costs of using the diagnostic test may be offset by a reduction in the amount of conventional laboratory capacity needed.
- The Group considered costs to the TB programme as important but not critical. The recommendation is conditional, in part because of the resources required for implementing it. Programmes that cannot adhere to the recommendation for all patients may still apply it to groups at higher risk of MDR-TB or unfavourable outcomes, particularly patients treated for TB in the past or with HIV-associated TB, as has been recommended previously(15).

[ii] Xpert MTB/RIF refers to the currently available methodology that employs an automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance.

- Detection of rifampicin resistance by Xpert MTB/RIF usually suffices to start a patient on a second-line TB regimen(16). However, the positive predictive value of Xpert MTB/RIF is low in patient groups in which rifampicin resistance is rare. Therefore, to reduce possible harms of false positive results for drug resistance that include wasted resources and avoidable toxicity from the administration of unnecessary second line medications, results need to be confirmed by phenotypic DST or line probe assay in these patient groups. This is an important consideration given that access to Xpert MTB/RIF is expected to expand substantially in low resource countries(17).

Recommendation 2. The use of sputum smear microscopy and culture rather than sputum smear microscopy alone is recommended for the monitoring of patients with MDR-TB during treatment (conditional recommendation, ⊕○○○/very low-quality evidence).

Remarks

- The evidence used to assess how best to monitor treatment in MDR-TB patients with the use of sputum smear microscopy and culture in settings with reliable direct microscopy was based on data pooled from ten published observational studies(18-25) included in two recent reviews(4),(26). Monthly culture monitoring was used as the reference in all the analyses. Random-effects Cox proportional hazards models were used to estimate the hazard ratio of failure, comparing monthly culture to alternative monitoring strategies.
- The use of monthly sputum smear microscopy and culture performed best at identifying failures earlier. Sputum smear microscopy alone resulted in delayed detection of failure: when done at monthly rather than two monthly intervals it increased the detection of failure slightly (not significant). In patients who were smear-negative at the start of treatment, monthly smear monitoring (compared to culture) resulted in a statistically significantly greater risk of delayed detection of failure compared to smear-positive patients. Stratified estimates by HIV serostatus, body mass index, and extent of disease on chest radiograph were not significantly different ($P>0.05$).
- The related end-points of drug resistance, initiation of appropriate treatment and the acquisition of resistance were not measured. There was no information about reversion or reinfection and no data were available to assess the quality of culture and smear testing. Other methods of evaluating response to treatment such as clinical indicators or chest radiography were not evaluated.
- Concomitant use of sputum smear microscopy and culture test results helps identify patients whose bacteriology remains positive or reverts back to positive following initial conversion to negative. This is of use to the clinician in identifying patients likely to fail their treatment as well as to institute infection control measures in a timely manner. There was overall certainty in the Group about the risk of missing or delaying the detection of failure if smear microscopy alone was used instead of culture. Additional benefits would be expected from reducing transmission and development of resistance as well as appropriate changes to the treatment regimens, but these were not explicitly addressed by the analysis.
- Delayed detection of failure is expected to increase transmission and increase the probability of acquisition of resistance. The 2008 Emergency update of the guidelines recommended the monitoring of MDR-TB patients by monthly sputum smear microscopy

and culture examination prior to culture conversion to negative[iii] and quarterly culture with monthly smear examination after conversion(7). Even if monthly culture throughout treatment showed the highest benefit to detect failures, resource implications are important. Cost for sputum smear testing alone is much lower than for culture and ranged between one fourth to a half of the combined cost of culture and smear testing in studies across different settings reviewed for these guidelines(27-33). It is likely that this difference may be higher where culture diagnosis is not readily available. More laboratory resources (staff, equipment, utilities) are required to perform culture and fewer culture laboratories exist in the low-resource conditions of most high-burden countries. In settings where the risk of failure is low, prioritization for monthly culture can be done on selected patients.

- The user should be aware of differences in the quality of culture performance. A false positive result of culture or direct microscopy of sputum smear could lead to unnecessary continuation or modification of a regimen with increased risk of toxicity. A false negative culture result may change a treatment decision which was based on suggestive clinical findings and a positive sputum smear microscopy result.
- A high value was placed on outcomes such as preventing death, decreasing the transmission of MDR-TB that could result from its delayed diagnosis, and avoiding increased use of resources. The recommendation is conditional in part because of the resources required for implementing it. As direct microscopy of sputum smear can identify the most infectious cases within a very short time, it has added value alongside culture for infection control purposes.

[iii] Defined as two consecutive sets of negative results of sputum smear microscopy and culture from samples collected at least 30 days apart.

Recommendation 3. In the treatment of patients with MDR-TB, a fluoroquinolone should be used (strong recommendation, ⊕◯◯◯/very low-quality evidence).

Recommendation 4. In the treatment of patients with MDR-TB, a later-generation fluoroquinolone rather than an earlier-generation fluoroquinolone should be used (conditional recommendation, ⊕◯◯◯/very low-quality evidence).

Recommendation 5. In the treatment of patients with MDR-TB, ethionamide (or prothionamide) should be used (strong recommendation, ⊕◯◯◯/very low-quality evidence).

Recommendation 6. In the treatment of patients with MDR-TB, four second-line anti-tuberculosis drugs likely to be effective (including a parenteral agent[iv]), as well as pyrazinamide, should be included in the intensive phase[v] (conditional recommendation, ⊕◯◯◯/very low-quality evidence).

Recommendation 7. In the treatment of patients with MDR-TB, regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent[iv], ethionamide (or prothionamide), and either cycloserine or PAS (p-aminosalicylic acid) if cycloserine cannot be used (conditional recommendation, ⊕◯◯◯/very low-quality evidence).

Remarks

- The evidence used to address the questions on which drugs to include and the number of drugs to be used in regimens for MDR-TB patients was based primarily on studies included in three systematic reviews(4),(26),(34). Studies published before 1970 and

---

[iv] A second line injectable drug : kanamycin, amikacin or capreomycin

[v] The intensive phase is the initial part of a course of treatment during which a parenteral agent (injectable drug) is used.

those reporting only XDR-TB were excluded. The reviewers for these questions pooled individual patient data for a meta-analysis from 32 studies with over 9000 treatment episodes for which the authors could be contacted and were willing to share their data(35). Cohorts included had to have a minimum of 25 subjects treated for MDR-TB, and one or more of the treatment outcomes meeting the standard definitions(36). Patients with XDR-TB (N=410) were excluded from the analysis as their treatment regimens were considered not to be comparable to those of other MDR-TB patients. None of the cohorts was part of randomized controlled trials and bias was very likely to be substantial (certain drugs may have only been used for sicker patients). The quality of evidence was judged to be low or very low. While the odds ratios in the analysis were adjusted for age, sex, HIV-serostatus, past TB treatment, past MDR-TB treatment, and extent of disease, residual confounding is certainly to be expected. Other limitations included incomplete ascertainment of relapse, the under-representation of certain geographic regions, and missing data for some of the variables examined. In many of the studies included, drug regimens were adjusted based on DST results. Findings from this analysis may not necessarily be generalizable to all populations in settings with high or low prevalence of drug resistance or different levels of resources. Nonetheless, the results of this analysis represented the best available evidence to date for the Group to make recommendations on the composition of treatment regimens.

- Use of drugs to which the strain was reportedly susceptible showed some added benefit when compared with their use regardless of susceptibility patterns. Choice of drug would thus depend on the DST of the strain isolated from the patient or close contacts with MDR-TB, previous use of the drug in the patient, and frequency of use of the drug or documented background drug resistance in the setting. In applying this observation to clinical practice, it is important to underline the uncertainties around the reproducibility and reliability of DST for pyrazinamide (and ethambutol)(37), as well as the second-line anti-tuberculosis drugs other than the parenteral agents and the fluoroquinolones(38).
- The analysis showed that in the intensive phase, a regimen with at least four drugs likely to be effective, when adjusted for clinical covariates, all other drugs used concomitantly as well as the total number of susceptible drugs used throughout treatment, was associated with a statistically significant peak in cure with a plateau thereafter.
- Data from this analysis did not reveal any second-line parenteral agent – kanamycin, amikacin or capreomycin – to be superior in effect to any other. Given its lower cost, kanamycin would be preferred. Amikacin can be used instead of kanamycin. In an analysis comparing patients who were cured or completed treatment to those who failed or relapsed, capreomycin was shown to be effective in case of resistance to kanamycin. The use of streptomycin in MDR-TB patients is not recommended given the greater likelihood of ototoxicity and the frequent occurrence of resistance to it among MDR-TB patients.
- Fluoroquinolones should always be used unless there is a contraindication. They showed a significant association with cure and this effect was more pronounced in later-generation fluoroquinolones (for this analysis meaning levofloxacin [750mg/day or more], moxifloxacin, gatifloxacin and sparfloxacin), and was highest when used against strains known to be susceptible. Estimates of effects for fluoroquinolones were probably conservative given that patients treated with ciprofloxacin were included in the control

group. Ciprofloxacin, even if it may have some anti-tuberculosis activity, should not be used(39).
- Among the oral bacteriostatic drugs, the association with cure was higher with ethionamide than with cycloserine which was higher than with *p*-aminosalicylic acid (PAS). Ethionamide or prothionamide should therefore be included in a regimen unless there is a particular contraindication. Ethionamide showed little effect in patients who were treated previously for MDR-TB. PAS performed the worst in the main analysis. Its use would thus be recommended only if an additional drug is needed to have at least four effective second line drugs in the regimen, and if ethionamide or cycloserine cannot be used or are unlikely to be effective. Studies of the *inhA* promoter region mutation (not assessed in this review) may, at an additional cost, guide treatment by identifying strains that are resistant to ethionamide(40). The data did not allow comparison of outcomes between once daily PAS and divided doses, or the formulation of PAS. Decisions on how to administer PAS should thus rely on a balance between its tolerance in the patient and the resources available to observe doses.
- Patients who were treated with Group 5[vi] drugs were observed to have generally worse outcomes, an effect largely attributed to confounding by indication. When the individual effect of amoxicillin/clavulanate, azithromycin, clarithromycin, clofazimine, roxithromycin and thioacetazone was analyzed, no significant association with cure could be discerned. No separate analysis was possible for linezolid and high-dose isoniazid given the small number of cases treated with these agents.
- Pyrazinamide showed a slightly added benefit in one of the analyses in which adjustment was made for other medication used concomitantly. Ethambutol was

---

[vi] The Group 5 drugs include clofazimine, linezolid, amoxicillin/clavulanate, thioacetazone, clarithromycin, and imipenem. In the analysis for these guidelines, azithromycin, roxithromycin, high dose INH and thioridazine were also included under Group 5 when used.

associated with a marginal but statistically significant reduction in the likelihood of cure among patients not previously treated for MDR-TB. As in the case of Group 5 drugs this effect was attributed to confounding rather than a detrimental effect of ethambutol.

- The main changes from the 2008 Emergency update(7) of the guidelines are shown in Table 4. The meta-analysis performed for the 2011 update indicated that a minimum of four drugs were associated with greater likelihood of success. The decision to recommend an additional drug to the regimen during the intensive phase of treatment was based on expert opinion. It is intended to safeguard against the acquisition of additional resistance, particularly in the case of undetected primary resistance to the four drugs considered to be effective given the unreliable nature of DST for drugs other than parenteral agents and fluoroquinolones. If ethambutol and Group 5 drugs are used in treating MDR-TB patients, they should not be counted among the main drugs making up the MDR-TB regimen, given the inconclusive evidence on their effectiveness. The principle of using additional drugs for extensive disease could not be supported by the data used for this review.
- A slight incremental trend in serious adverse events (SAE) was discerned as the number of drugs in the continuation phase increased from two to five. This association was not observed during the intensive phase. Data were incomplete but SAE were more often attributed to the oral bacteriostatic drugs (14%) than to other drugs evaluated (1–6%). The long-term potential for SAE, particularly in children and for the later-generation fluoroquinolones, remains unknown. However, a Cochrane review assessing fluoroquinolones as additional or substitute drugs in regimens for patients with drug-susceptible and drug-resistant strains found that substituting or adding fluoroquinolones to a regimen had no demonstrable effect on the occurrence of SAE(39).
- As patients with XDR-TB were excluded from the analysis, the current recommendations do not necessarily apply to this subgroup of patients. Until better evidence is available to optimize regimens for the treatment of these patients, the same principles used to design MDR-TB regimens should be used, based where possible on the DST pattern of strains from the individual patient, particularly for later-generation fluoroquinolones and second-line parenteral agents. All MDR-TB patients should thus be tested for susceptibility to these two classes of drugs.
- The recommendations contained in this section aim to increase the likelihood of cure and reduce the risk of failure, relapse and death. A high value was placed on preventing death and transmission of MDR-TB and a lower value on the potential for SAE resulting from long-term treatment. As a result, the long-term use of fluoroquinolones was considered to outweigh the higher cost and any possible long-term SAE. The recommendation is thus strong. While the use of later-generation fluoroquinolones is generally preferred, a separate recommendation on their use was classified as conditional rather than strong because of uncertainty about the risk of SAE from the long-term use of these agents.

Recommendation 8. In the treatment of patients with MDR-TB, an intensive phase of at least 8 months' duration is recommended (conditional recommendation, ⊕◯◯◯/very low-quality evidence).

Recommendation 9. In the treatment of patients with MDR-TB, a total treatment duration of at least 20 months is recommended in patients without any previous MDR-TB treatment (conditional recommendation, ⊕◯◯◯/very low-quality evidence).

Remarks

- The evidence base used to derive these two recommendations was the same as that used for Questions 2 to 4 on regimen composition (Recommendations 3 to 7). All data were from observational studies, and the quality of evidence was classified as very low. Patients with XDR-TB were also excluded from the analysis. Attempts to control for bias and confounding in this review are also unlikely to have adjusted for all important factors. In particular, patients who receive longer therapy may be those who are sicker. These findings may not be generalizable to all populations in settings with high or low prevalence of drug resistance or with different levels of resources.
- The analysis provided evidence for an association between treatment success and the total length of treatment and the length of the intensive phase. The trend in relative risk for cure over successive months of treatment was studied to determine the optimal minimum duration for both total treatment and the intensive phase. The adjusted relative risk for cure peaked at an intensive phase lasting between 7.1 and 8.5 months. For total treatment duration, the peak occurred between 18.6 and 21.5 months for patients who had no previous MDR-TB treatment. While the peak occurred later in patients who had been treated for MDR-TB (27.6–30.5 months), no clear incremental trend in success was observed in this patient group and the number of observations was far fewer than for those who had no previous MDR-TB treatment. Most patients may be expected to receive this length of treatment but in some it may have to be modified depending on their bacteriological status and other indicators of progress on treatment.
The recommendations have thus changed from those contained in the 2008 Emergency update, which recommended treatment duration for MDR-TB patients based on the use of a parenteral agent for a minimum of 6 months and at least 4 months past culture conversion, and a minimum total length of treatment of 18 months after culture conversion. The new recommended duration of intensive phase is 2 months longer than the minimum previously recommended. There is, however, no substantial difference in the total length of treatment being recommended given that conversion typically takes a few months to occur. The data used for this analysis could not inform whether a minimum duration of the intensive phase after conversion was a determinant of outcome.
- The risk of serious adverse events (SAE) was observed to increase beyond the first 12 months of treatment but was not correlated with the length of the intensive phase beyond the first 2 months. These trends should be interpreted with caution as they may be confounded by the number of drugs used (independently correlated with SAE) as well as features of the illness process not accounted for in the measure of extent of disease used in this analysis.
- A high value was placed on preventing death and transmission of MDR-TB as a result of failed treatment as well as avoiding harms and minimizing use of resources. The group

placed a lower value on reducing the duration of treatment, while acknowledging that many patients may place a higher value on avoiding a long treatment course due to burden and inconvenience. When selecting the duration of treatment, the analysis allowed a choice to be made within a narrow margin of a few consecutive months, thus reducing the likelihood of prolonging treatment unnecessarily. While shorter regimens would confer clear benefits and be preferred, evidence for the effectiveness of a 9-month regimen for MDR-TB patients has up to now been limited to data from one setting (included in this review)(22). The Guideline Development Group supports further investigation of safety and effectiveness of shorter regimens using the randomized controlled trial design in order to get stronger evidence for their potential use for the treatment of drug-resistant TB.

Recommendation 10. Antiretroviral therapy is recommended for all patients with HIV and drug-resistant TB requiring second-line anti-tuberculosis drugs, irrespective of CD4 cell-count, as early as possible (within the first 8 weeks) following initiation of anti-tuberculosis treatment (strong recommendation, ⊕◯◯◯/very low-quality evidence).

Remarks

- Evidence was reviewed from ten studies(41-50) to assess patient treatment outcomes when antiretroviral therapy (ART) and second-line anti-tuberculosis drugs were used together. None of the data were from randomized controlled trials. Individual patient data were available for 217 drug-resistant TB patients in total, of whom 127 received ART. The quality of evidence in individual observational studies varied from low to very low quality.
- The pooled individual patient data showed a lower risk of death and a higher likelihood of cure and resolution of TB signs and symptoms in patients using ART compared with those not using ART (low-quality evidence). There is very low-quality evidence for other outcomes which were considered critical or important for decision-making (for example, serious adverse events from second-line drugs for drug-resistant TB, occurrence of conversion of sputum smear or culture, interactions of ART with anti-tuberculosis drugs and default from treatment). Available data did not allow assessment for a number of other outcomes of interest, namely avoiding the acquisition of additional drug resistance, preventing TB transmission, sustaining relapse-free cure, establishing the optimal duration of MDR-TB treatment, avoiding unnecessary MDR-TB treatment, and reducing cost and improving population access to appropriate care.
- The strong recommendation for use of ART is based in part on indirect evidence from its use in any patient with active TB that shows large beneficial effects and a very high mortality when ART is not employed(51), particularly in very immunocompromised patients (CD4 cell-count less than 50 cells/mm^3)(52),(53). In the absence of other data specific to patients with drug-resistant TB receiving second-line anti-tuberculosis medication, the decision on when to start ART should be no different from the approach to the HIV-positive drug-susceptible TB patient. ART should thus be initiated regardless of CD4 cell-count and as soon as anti-tuberculosis treatment is tolerated, ideally as early as 2 weeks and no later than 8 weeks after initiation of anti-tuberculosis treatment(51),(54).

- A high value was placed on outcomes such as preventing early death and TB transmission, and a lower value was placed on the resources required to make ART available to all MDR-TB patients with HIV. The capacity to implement this recommendation will require that more providers be trained specifically in the care of HIV and drug-resistant TB and drug–drug interactions. A substantial increase in the availability of and patient's access to treatment and additional support for ensuring adherence is likely to be necessary. The need for increased integration of HIV and TB care for effective patient management, prompt evaluation of adverse events and case-holding throughout treatment will necessitate more resources. For the benefit of the user, a table of adverse events for which both an ART and an anti-tuberculosis drug have been implicated, and could conceivably interact, is included (Table 5).

Recommendation 11. Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalization (conditional recommendation, ⊕◯◯◯/very low-quality evidence).

Remarks

- Outcomes from models of MDR-TB care based mainly on clinic-based ambulatory treatment were compared with those using mainly hospital-based inpatient treatment. The data used came from published and unpublished cost-effectiveness studies in four countries (Estonia, Peru(23), the Philippines(24) and the Russian Federation [Tomsk Oblast]). The design of these observational studies did not allow direct comparison of effects between models of care. Given that none of the studies were randomized controlled trials the evidence was considered to be of very low quality. Cost-effectiveness was modelled for all possible WHO Member States in a probabilistic analysis of the data from the four countries(55).
- Cost varied widely across the modelled settings. The cost per DALY averted by an ambulatory model in one setting was sometimes higher than the cost per DALY averted by a hospitalization model in another setting. However, cost per DALY averted was lower under outpatient-based care than under inpatient-based care in at least 90% of the settings for which cost-effectiveness was modelled. The variation in cost-effectiveness among settings correlated most strongly with the variation in the cost of general health-care services and other non-drug costs. There was no evidence which showed that treatment in a hospital-based model of care leads to a more favourable treatment outcome.
- The overall cost-effectiveness of care for a patient receiving treatment for MDR-TB can be improved with an ambulatory model. The benefits when compared with hospitalization models include reduced resource use and at least as many deaths avoided among primary and secondary cases. This result is based on clinic-based ambulatory treatment (patients attend a health-care facility); in some settings, home-based ambulatory treatment (provided by a worker in the community) might improve cost-effectiveness even further. One of the studies of ambulatory care dated from a time when the regimen drug combinations were not yet optimized, so the success achieved was probably inferior to what can be accomplished with the regimens in use today.
- In addition to reducing or avoiding hospitalization where possible and prioritizing community-care approaches for TB management, exposure to people who are infectious

can be minimized by reducing the number of outpatient visits and avoiding overcrowding in wards and waiting areas(56). The benefit of reduced transmission with an ambulatory model can only be achieved if proper infection control measures are in place in both the home and the clinic.
- There may be some important barriers to accessing clinic-based ambulatory care, including distance to travel and other costs to individual patients. Shifting costs from the service provider to the patient has to be avoided, and implementation may need to be accompanied by appropriate enablers. While placing patients on adequate therapy would be expected to decrease the bacterial load and transmission of drug-resistant TB, infection control measures for home-based and clinic-based measures will need to be part of an ambulatory model of care to decrease the risk of transmission in households, the community and clinics. TB control programmes will have to consider whether they are capable of reallocating resources from hospital to ambulatory care support in order to undertake the necessary changes in patient management. The choice between these options will affect the feasibility of implementing the recommendation in a particular programme.
- A high value was placed on conserving resources and on patient outcomes such as preventing death and transmission of MDR-TB as a result of delayed diagnosis and inpatient treatment. Admission to hospitals for patients may have important social and psychological consequences which need to be taken into account. However, there should always be provision for a back-up facility to manage patients who need inpatient treatment. This may be necessary in certain patient groups at particular risk, such as children during the intensive phase, among whom close monitoring may be required for a period of time.

Conclusions

As MDR-TB treatment programmes scale up globally, it becomes critical for treating clinicians to base their practice on the best available evidence. The recommendations for MDR-TB care and control in the new guidelines have been developed following the systematic examination of available evidence on the most salient questions in this area. Although the recommendations on composition and duration of treatment are now based on a meta-analysis of a large set of observations, the quality of all evidence in these studies varied from low to very low. The paucity of costing data has limited the number of studies which could be included to assess the performance of different models of care. While there have been no drastic changes in the recommendations from the previous guidelines, some changes and the presentation of the evidence on which the recommendations are based will contribute to the dual goals of improving access to care and treatment success. Rapid molecular testing for isoniazid and rifampicin is advisable even in previously untreated patients if resources make it possible. Monthly culture for the monitoring of treatment response is preferred. An intensive phase of 8 months duration is conditionally recommended instead of the previous minimum of 6 months. The addition of pyrazinamide to a minimum of four second-line anti-tuberculosis drugs likely to be effective is recommended. The use of fluoroquinolones and ethionamide is strongly recommended. Later-generation fluoroquinolones are preferred. The contribution of ethambutol and Group 5 drugs in MDR-TB treatment remains unclear. All patients with drug-resistant TB and HIV who are on second-line anti-tuberculosis

medications should be placed on antiretroviral therapy as soon as they can tolerate it. Systems that primarily employ ambulatory models of care are recommended over others based mainly on hospitalization.

The process of developing these guidelines revealed some important gaps in knowledge that are important to address in future research, particularly in the context of large-scale expansion of treatment for patients with drug-resistant TB. These include a lack of high- or moderate-quality evidence from randomized controlled trials for the optimization of treatment regimens in patients with MDR-TB, particularly to determine the best combination of drugs and treatment duration. In addition, evidence was lacking on:

- treatment of paediatric MDR-TB;
- the best drug regimens for treatment of patients with isoniazid resistance, with XDR-TB or with non-MDR-TB polydrug-resistance;
- effective chemoprophylaxis for contacts of MDR-TB cases;
- therapy for symptomatic relief from adverse reactions linked to second-line anti-tuberculosis drugs.

In anticipation of the availability of new anti-tuberculosis drugs in the near future, and the development of novel diagnostic tools, these recommendations require a strong commitment by the national TB programmes to ensure their implementation at all levels. WHO, in collaboration with its technical and implementing partners, will strive to communicate them through different means. As in the past, the support of the ERS (European Respiratory Society)(57) and other leading scientific groups in respiratory medicine, including the ATS (American Thoracic Society), PATS (Pan African Thoracic Society), the UNION (International Union Against Tuberculosis and Lung Disease), ACCP (American College of Chest Physicians), APSR (Asian Pacific Society of Respirology) and ALAT (Asociación Latinoamericana del Tórax), will be crucial to the effective spread of the key messages and to assist countries to adapt the recommendations and evaluate their implementation.

Statement of interest

J. Bayona, C. Daley, C.D. Mitnick and Ma. I. Quelapio declared that they performed work for Otsuka Pharmaceutical Co Ltd. and abstained from discussions relating to the recommendations on drug regimens. Funding for the meetings and reviews involved in the updating of the guidelines came entirely from the United States Agency For International Development (USAID).

Acknowledgements

The affiliations of the Guideline Development Group (in italics) and other contributors to this manuscript are as follows: World Health Organisation (WHO), Geneva, Switzerland: L. Blanc, *D. Falzon*, C. Fitzpatrick, *H. Getahun, E. Jaramillo, C. Lienhardt, F. Mirzayev*, P. Nunn, M.C. Raviglione, *D. Sculier, F. Wares, K. Weyer, M. Zignol* (Stop TB Department); *C. Duncombe, M. Vitoria* (HIV Department); R. Kulier, (Research Policy and Cooperation). For other authors: *H. Schünemann*: McMaster University Health Sciences, Hamilton, Canada. M. Arentz, P. Pavlinac, J. Walson: University of Washington, Seattle, USA. M. Bauer, R. Menzies, O. Oxlade: University of McGill, Montréal, Canada. *J. Bayona*: Socios En Salud Sucursal, Lima, Peru. *J.A. Caminero*:

University General Hospital of Gran Canaria (Pneumology Dept), Las Palmas, Spain and The UNION, Paris, France. *C.L. Daley*: National Jewish Health, Denver, USA. *A. Gebhard*: KNCV Tuberculosis Foundation, The Hague, Netherlands. *M. Henkens, F. Varaine*: Médecins Sans Frontières, Paris, France. *T.H. Holtz*: CDC, Bangkok, Thailand. *J. Keravec, A. Salakaia*: Management Sciences for Health, Virginia, USA. *S. Keshavjee, M.L. Rich*: Partners In Health, Boston, USA. C. Lu, *C.D. Mitnick*: Harvard Medical School, and R.A. White: Harvard School of Public Health, Boston, MA, USA. *A.J. Khan*: Indus Hospital, Karachi, Pakistan. *V. Leimane*: State Infectology Center, Clinic of Tuberculosis and Lung Diseases, Riga, Latvia. *A. Mariandyshev*: Northern State Medical University, Arkhangelsk, Russian Federation. G.B. Migliori: WHO Collaborating Centre for TB and Lung Diseases, Fondazione S. Maugeri, Tradate, Italy. *G. Nwagboniwe*: Alliance for Hope, Nigeria. *D. Palmero*: Hospital Muniz, Buenos Aires, Argentina. *Ma. I. Quelapio*: Tropical Disease Foundation, Manila, Philippines. *S. Royce*: PATH, Seattle, USA. *S. Rüsch-Gerdes*: National Reference Center for Mycobacteria, Borstel, Germany. *R. Sarin*: LRS Institute of TB and Allied Diseases, New Delhi, India. *E. Skachkova*: Federal Center of TB Monitoring, Moscow, Russian Federation. The academic centres reviewing the evidence for these guidelines were the following: University of McGill, Montréal, Canada (M. Bauer, R. Menzies, O. Oxlade); Harvard Medical School (C. Lu, C.D. Mitnick,) and Harvard School of Public Health (R.A. White), Boston, MA, USA; University of California [San Francisco], USA (G. Kennedy, G. Rutherford, K. Steingart); University of Washington, Seattle, USA (M. Arentz, D. Horne, P. Pavlinac, J.L. Walson).
The following members of the External Review Group also contributed to the production of the guidelines: S. Baghdadi, M. Becerra, V. Bhatia, M. Dara, M. del Granado, R. Granich, L. Mvusi, N. Nair, N. Ndjeka, W. Nkhoma, K. Osuga, H.S. Schaaf, C. van Weezenbeek, I. Vasilyeva, W. Xie Xiu, and R. Zaleskis. At WHO/HQ, M. Grzemska and C. Gunneberg advised the initial stages of the development of the guidelines, K. Ciceri provided editorial support, and C. Chevalley assisted the coordination process of the revision.
The lead authors of this article were D. Falzon, E. Jaramillo, and H. Schünemann. G.B. Migliori contributed to the adaptation of the text from the guidelines and the initial review of the manuscript. All other authors contributed to different degrees in the ideation, development of the questions and outcomes, drafting of the recommendations and by commenting on an advanced draft of this article. The authors are grateful to other workers who contributed data for the reviews as cited in the references, and in particular The Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB(35).

This article reproduces the recommendations of the newly published 2011 update of the WHO guidelines for the programmatic management of drug-resistant tuberculosis [www.who.int/tb/challenges/mdr/programmatic_guidelines_for_mdrtb/], which were developed in compliance with the requirements of the WHO Guidelines Review Committee for evidence gathering, assessment and formulation of recommendations.

Table 1. What are the most important outcomes to consider when making decisions on testing and treatment strategies for drug-resistant-TB?

Members of the Guideline Development Group submitted scores for TB outcomes which they considered to be the most critical when making decisions on drug-resistant TB management. Members were asked to take a societal perspective in rating the outcomes. Rating by relative importance was on an incremental scale:
1-3 points : Not important for making recommendations on choice of testing and treatment strategies for DR-TB*
4-6 points : Important but not critical for making recommendations on choice of testing and treatment strategies
7-9 points : Critical for making recommendations on choice of testing and treatment strategies
* none of the Outcomes was scored in this category

Outcomes (in brackets is the same outcome rephrased as the negative)	**Mean Score**	**Relative importance**
1. Cure (treatment failure)	8.7	Critical
2. Prompt initiation of appropriate treatment	8.3	Critical
3. Avoiding the acquisition or amplification of drug resistance	8.1	Critical
4. Survival (death from TB)	7.9	Critical
5. Staying disease-free after treatment; sustaining a cure (relapse)	7.6	Critical
6. Case holding so the TB patient remains adherent to treatment (default or treatment interruption due to non-adherence)	7.6	Critical
7. Population coverage or access to appropriate treatment of drug-resistant TB	7.5	Critical
8. Smear or culture conversion during treatment	7.4	Critical
9. Accelerated detection of drug resistance	7.4	Critical
10. Avoid unnecessary treatment for MDR-TB	7.2	Critical
11. Population coverage or access to diagnosis of drug-resistant TB	7.1	Critical
12. Prevention or interruption of transmission of DR-TB to other people, including other patients, health care workers	6.9	Important but not critical
13. Shortest possible duration of treatment	6.7	Important but not critical
14. Avoiding toxicity and adverse reactions from TB drugs	6.5	Important but not critical
15. Cost to patient, including direct medical costs as well as others such as transportation, lost wages due to disability	6.4	Important but not critical
16. Resolution of TB signs and symptoms; ability to resume usual life activities	6.3	Important but not critical
17. Interaction of TB drugs with non-TB medications	5.6	Important but not

		critical
18. Cost to the TB programme	5.4	Important but not critical

Table 2. Quality of evidence and definitions

Quality of evidence	**Definition**
High (⊕⊕⊕⊕)	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate (⊕⊕⊕◯)	Further research is likely to have an important impact on our confidence in the effect and may change the estimate.
Low (⊕⊕◯◯)	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low (⊕◯◯◯)	Any estimate of effect is very uncertain.

Table 3.Implications of the strength of a recommendation for different users

Perspective	**Strong recommendation**	**Conditional recommendation**
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guidelines could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients, and that patients must be helped to arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
For policy-makers	The recommendation can be adapted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

Table 4. Main changes to the recommendations in the 2008 emergency update following the 2011 update of the guidelines

2008 emergency update	2011 update
Monitoring response to MDR-TB treatment	
Monitoring of MDR-TB patients by monthly sputum smear microscopy and culture examination prior to culture conversion to negative and quarterly culture with monthly smear examination after conversion.	Monthly sputum smear and culture throughout treatment is recommended, subject to resource implications, given that it has the highest benefit to detect failure.
Regimen composition	
Include at least four anti-tuberculosis drugs with either certain, or almost certain, effectiveness during the intensive phase of treatment.	Include at least four second-line anti-tuberculosis drugs likely to be effective as well as pyrazinamide during the intensive phase of treatment.
Consider adding more drugs in patients with extensive disease or uncertain effectiveness.	No evidence found to support the use of more than four second-line anti-tuberculosis drugs in patients with extensive disease. Increasing the number of second-line drugs in a regimen is permissible if the effectiveness of some of the drugs is uncertain.
The regimen should include pyrazinamide and/or ethambutol, one fluoroquinolone, one parenteral agent and second-line oral bacteriostatic anti-tuberculosis drugs (no preference of oral bacteriostatic second-line anti-tuberculosis drug was made).	The regimen should include pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and cycloserine, or else PAS if cycloserine cannot be used.
Ethambutol may be considered effective and included in the regimen if DST shows susceptibility.	Ethambutol may be used but is not included among the drugs making up the standard regimen.
Treatment with Group 5 drugs is recommended only if additional drugs are needed to bring the total to four.	Group 5 drugs may be used but are not included among the drugs making up the standard regimen.
Duration of treatment	
Use of a parenteral agent for a minimum of 6 months and at least 4 months after	Intensive phase of 8 months' duration is recommended. The duration may be

culture conversion	modified depending on bacteriological status and other indicators of progress on treatment
A minimum total length of treatment of 18 months after culture conversion.	A total treatment duration of at least 20 months is recommended in patients without any previous history of MDR-TB treatment. Patients who have had previous treatment for MDR-TB may need longer treatment. The duration may be modified depending on bacteriological status and other indicators of progress on treatment.
Use of ARVs in DR-TB patients with HIV	
Timing of start of ARVs in part determined by CD4 cell-count	Antiretroviral therapy is recommended for all patients with HIV and drug-resistant TB requiring second-line anti-tuberculosis drugs, irrespective of CD4 cell-count, as early as possible (within the first 8 weeks) following initiation of anti-tuberculosis treatment
Models of care for managing MDR-TB patients	
Programmes are encouraged to incorporate community-based care and support into their national plans	Patients with MDR-TB should be treated using mainly ambulatory care rather than models of care based principally on hospitalization.

Table 5. Potentially overlapping toxicities of antiretroviral and anti-tuberculosis drugs (including first-line anti-tuberculosis drugs)

Potential toxicity	**Antiretroviral drugs**	**Anti-tuberculosis drugs**
Peripheral neuropathy	stavudine didanosine	cycloserine isoniazid ethambutol fluoroquinolones streptomycin kanamycin amikacin capreomycin viomycin ethionamide/prothionamide linezolid
Psychiatric symptoms	efavirenz	cycloserine isoniazid fluoroquinolones ethionamide/prothionamide
Hepatitis	nevirapine ritonavir-boosted protease inhibitors efavirenz etravirine maraviroc	pyrazinamide isoniazid rifampin/rifabutin *p*-aminosalicylic acid ethionamide/prothionamide fluoroquinolones

Table 5 (continued)

Potential toxicity	Antiretroviral drugs	Anti-tuberculosis drugs
Gastro-intestinal intolerance	zidovudine protease inhibitors didanosine	ethionomide/prothionomide *p*-aminosalicylic acid pyrazinamide isoniazid rifampin ethambutol clofazimine
Renal toxicity	tenofovir indinavir	streptomycin kanamycin capreomycin amikacin viomycin Rifampin
Bone marrow toxicity	zidovudine	linezolid rifampin/rifabutin
Lactic acidosis	stavudine didanosine Zidovudine	linezolid
Stevens-Johnson syndrome	nevirapine efavirenz etravirine	thioacetazone cycloserine linezolid ethambutol streptomycin
Arrhythmias / QT prolongation	atazanavir/ritonavir saquinavir/ritonavir lopinavir/ritonavir	fluoroquinolones
Rash/pruritus	nevirapine efavirenz etravirine abacavir	rifampin/rifabutin pyrazinamide

References

1. Towards universal access to diagnosis and treatment of multidrug-resistant and extensively drug-resistant tuberculosis by 2015. WHO progress report 2011. Geneva, World Health Organization, 2011 (WHO/HTM/TB/2011.3).

2. Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response. Geneva, World Health Organization, 2010. (WHO/HTM/TB/2010.3).

3. Global tuberculosis control: WHO report 2010. Geneva, World Health Organization, 2010. (WHO/HTM/TB/2010.7).

4. Orenstein EW, Basu S, Shah NS, Andrews JR, Friedland GH, Moll AP, Gandhi NR, Galvani AP. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. Lancet Infect Dis. 2009 Mar;9(3): 153-61.

5. Resolution WHA62.15. Prevention and control of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis. In: Sixty-second World Health Assembly, Geneva, 18–22 May 2009, Resolutions and decisions; annexes. Geneva, World Health Organization, 2009 (WHA62/2009/REC/1):25–29. Available from: apps.who.int/gb/ebwha/pdf_files/WHA62-REC1/WHA62_REC1-en.pdf; accessed 30 April 2011.

6. Guidelines for the programmatic management of drug-resistant tuberculosis, 1st ed. Geneva, World Health Organization, 2006 (WHO/HTM/TB/2006.361).

7. Guidelines for the programmatic management of drug-resistant tuberculosis, Emergency update 2008. Geneva, World Health Organization, 2008 (WHO/HTM/TB/2008.402).

8. Shukhobodskaya E, Falzon D, Jaramillo E. Evaluation of the WHO Guidelines on programmatic management of drug-resistant tuberculosis. Abstract. 40th UNION World Conference on Lung Health, Mexico. December 2009. Available from: www.worldlunghealth.org/Conf2009/website/assets/files/Abstract_Book_2009_Web.pdf; accessed 30 April 2011.

9. Richardson WS, Wilson MC, Nishikawa J, Hayward RS. The well-built clinical question: a key to evidence-based decisions. ACP J Club. 1995 Nov-Dec;123(3): A12-3.

10. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): John Wiley & Sons, 2008. Available from: www.cochrane-handbook.org (latest version); accessed 30 April 2011.

11. Global burden of disease 2004 update: disability weights for diseases and conditions. Geneva, World Health Organization, 2004. Available from: www.who.int/healthinfo/global_burden_disease/GBD2004_DisabilityWeights.pdf; accessed 30 April 2011.

12. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. What is « quality of evidence » and why is it important to clinicians? BMJ. 2008 May 3;336(7651): 995-8.

13. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, Schünemann HJ; GRADE Working Group. Going from evidence to recommendations. BMJ. 2008 May 10;336(7652): 1049-51.

14. Oxlade O, Falzon D, Menzies D. Evaluation of the potential impact and cost-effectiveness of different strategies to detect drug-resistant tuberculosis. Eur Respir J. 2011 [under review].

15. Guidelines for treatment of tuberculosis. 4th ed. Geneva, World Health Organization, 2009. (WHO/HTM/TB/2009.420).

16. Rapid Implementation of the Xpert MTB/RIF diagnostic test. Technical and operational 'How-to' Practical considerations. Geneva, World Health Organization, 2011. Available from: whqlibdoc.who.int/publications/2011/9789241501569_eng.pdf; accessed 18 May 2011.

17. Boehme CC, Nabeta P, Hillemann D, Nicol MP, Shenai S, Krapp F, Allen J, Tahirli R, Blakemore R, Rustomjee R, Milovic A, Jones M, O'Brien SM, Persing DH, Ruesch-Gerdes S, Gotuzzo E, Rodrigues C, Alland D, Perkins MD. Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med. 2010 Sep 9;363(11): 1005-15.

18. Migliori GB, Lange C, Centis R, Sotgiu G, Mütterlein R, Hoffmann H, Kliiman K, De Iaco G, Lauria FN, Richardson MD, Spanevello A, Cirillo DM; TBNET Study Group. Resistance to second-line injectables and treatment outcomes in multidrug-resistant and extensively drug-resistant tuberculosis cases. Eur Respir J. 2008 Jun;31(6): 1155-9.

19. Cox H, Kebede Y, Allamuratova S, Ismailov G, Davletmuratova Z, Byrnes G, Stone C, Niemann S, Rüsch-Gerdes S, Blok L, Doshetov D. Tuberculosis recurrence and mortality after successful treatment: impact of drug resistance. PLoS Med. 2006 Oct;3(10): e384.

20. Holtz TH, Lancaster J, Laserson KF, Wells CD, Thorpe L, Weyer K. Risk factors associated with default from multidrug-resistant tuberculosis treatment, South Africa, 1999-2001. Int J Tuberc Lung Dis. 2006;10(6): 649-55.

21. CDC, Partners In Health/NTP Peru, Partners In Health/Tomsk Prison & Civilian TB Services, NTP Latvia, NTP Estonia, TDF/NTP Philippines, WHO. Case-based data collection: First 5 DOTS-Plus Projects, 2000-2004 [dataset].

22. Van Deun A, Maug AK, Salim MA, Das PK, Sarker MR, Daru P, Rieder HL. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J Respir Crit Care Med. 2010 Sep 1;182(5): 684-92.

23. Suárez PG, Floyd K, Portocarrero J, Alarcón E, Rapiti E, Ramos G, Bonilla C, Sabogal I, Aranda I, Dye C, Raviglione M, Espinal MA. Feasibility and cost-effectiveness of standardised second-line drug treatment for chronic tuberculosis patients: a national cohort study in Peru. Lancet. 2002 Jun 8;359(9322): 1980-9.

24. Tupasi TE, Gupta R, Quelapio MI, Orillaza RB, Mira NR, Mangubat NV, Belen V, Arnisto N, Macalintal L, Arabit M, Lagahid JY, Espinal M, Floyd K. Feasibility and cost-effectiveness of treating multidrug-resistant tuberculosis: a cohort study in the Philippines. PLoS Med. 2006 Sep;3(9): e352.

25. The feasibility and efficiency of controlling MDR-TB using the DOTS-Plus strategy in the Russian Federation. Geneva, World Health Organization, 2005. (WHO/HTM/TB/2005.357C).

26. Johnston JC, Shahidi NC, Sadatsafavi M, Fitzgerald JM. Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. PLoS One. 2009 Sep 9;4(9): e6914.

27. Dowdy DW, O'Brien MA, Bishai D. Cost-effectiveness of novel diagnostic tools for the diagnosis of tuberculosis. Int J Tuberc Lung Dis. 2008 Sep;12(9): 1021-9.

28. Dowdy DW, Lourenço MC, Cavalcante SC, Saraceni V, King B, Golub JE, Bishai D, Durovni B, Chaisson RE, Dorman SE. Impact and cost-effectiveness of culture for diagnosis of tuberculosis in HIV-infected Brazilian adults. PLoS One. 2008;3(12): e4057.

29. Menzies D, Oxlade O, Lewis M. Costs for tuberculosis care in Canada. Ottawa(ON): Public Health Agency of Canada, 2006.

30. The efficiency of TB laboratory services in the Russian Federation. Policy Brief Number 5. Geneva, World Health Organization, 2005 (WHO/HTM/TB/2005.357E).

31. Albert H. Economic analysis of the diagnosis of smear-negative pulmonary tuberculosis in South Africa: incorporation of a new rapid test, FASTPlaqueTB, into the diagnostic algorithm. Int J Tuberc Lung Dis. 2004 Feb;8(2): 240-7.

32. Kamolratanakul P, Hiransithikul N, Singhadong N. Cost analysis of different types of tuberculosis patients at tuberculosis centers in Thailand. Southeast Asian J Trop Med Public Health. 2002;33: 321-30.

33. The Economics of TB Drug Development. The Global Alliance for TB Drug Development 2001.. Available from: www.tballiance.org/downloads/publications/TBA_Economics_Report.pdf; last accessed 30 April 2011.

34. Akçakır Y. Correlates of treatment outcomes of multidrug-resistant tuberculosis (MDR-TB): a systematic review and meta-analysis. MSc Thesis. 2010. McGill University: Montréal, Canada.

35. The Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB. Specific treatment parameters and treatment outcomes of multidrug-resistant tuberculosis: an Individual Patient Data (IPD) Meta-Analysis of 9153 patients. [in preparation].

36. Laserson KF, Thorpe LE, Leimane V, Weyer K, Mitnick CD, Riekstina V, Zarovska, E, Rich ML, Fraser HS, Alarcón E, Cegielski JP, Grzemska M, Gupta R, Espinal M. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2005 Jun;9(6): 640-5.

37. Framework for Implementing New Tuberculosis Diagnostics. World Health Organization, 2010. Available from: www.who.int/tb/laboratory/whopolicyframework_july10_revnov10.pdf; accessed 30 April 2011.

38. Policy guidance on drug susceptibility testing (DST) of second-line anti-tuberculosis drugs. Geneva, World Health Organization, 2008. (WHO/HTM/TB/2008.392). Available from: whqlibdoc.who.int/hq/2008/WHO_HTM_TB_2008.392_eng.pdf; accessed 30 April 2011

39. Ziganshina LE, Squire SB. Fluoroquinolones for treating tuberculosis. Cochrane Database Syst Rev. 2008 Jan 23;(1): CD004795.

40. Lee H, Cho SN, Bang HE, Lee JH, Bai GH, Kim SJ, Kim JD. Exclusive mutations related to isoniazid and ethionamide resistance among Mycobacterium tuberculosis isolates from Korea. Int J Tuberc Lung Dis. 2000 May;4(5): 441-7.

41. Burgos M, Gonzalez LC, Paz EA, Gournis E, Kawamura LM, Schecter G, Hopewell PC, Daley CL. Treatment of multidrug-resistant tuberculosis in San Francisco: an outpatient-based approach. Clin Infect Dis. 2005 Apr 1;40(7): 968-75.

42. Dheda K, Shean K, Zumla A, Badri M, Streicher EM, Page-Shipp L, Willcox P, John MA, Reubenson G, Govindasamy D, Wong M, Padanilam X, Dziwiecki A, van Helden PD, Siwendu S,

Jarand J, Menezes CN, Burns A, Victor T, Warren R, Grobusch MP, van der Walt M, Kvasnovsky C. Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study. Lancet. 2010 May 22;375(9728): 1798-807.

43. Eker B, Ortmann J, Migliori GB, Sotgiu G, Muetterlein R, Centis R, Hoffmann H, Kirsten D, Schaberg T, Ruesch-Gerdes S, Lange C; German TBNET Group. Multidrug- and extensively drug-resistant tuberculosis, Germany. Emerg Infect Dis. 2008 Nov;14(11): 1700-6.

44. El Sahly HM, Teeter LD, Pawlak RR, Musser JM, Graviss EA. Drug-resistant tuberculosis: a disease of target populations in Houston, Texas. J Infect. 2006 Jul;53(1): 5-11.

45. Leimane V, Dravniece G, Riekstina V, Sture I, Kammerer S, Chen MP, Skenders G, Holtz TH. Treatment outcome of multidrug/extensively drug-resistant tuberculosis in Latvia, 2000-2004. Eur Respir J. 2010 Sep;36(3): 584-93.

46. Migliori GB, Besozzi G, Girardi E, Kliiman K, Lange C, Toungoussova OS, Ferrara G, Cirillo DM, Gori A, Matteelli A, Spanevello A, Codecasa LR, Raviglione MC; SMIRA/TBNET Study Group. Clinical and operational value of the extensively drug-resistant tuberculosis definition. Eur Respir J. 2007 Oct;30(4): 623-6.

47. Palmero D, Ritacco V, Ambroggi M, Poggi S, Güemes Gurtubay J, Alberti F, Waisman J. [Multidrug-resistant tuberculosis in AIDS patients at the beginning of the millennium]. Medicina (B Aires). 2006;66(5): 399-404.

48. Shean KP, Willcox PA, Siwendu SN, Laserson KF, Gross L, Kammerer S, Wells CD, Holtz TH. Treatment outcome and follow-up of multidrug-resistant tuberculosis patients, West Coast/Winelands, South Africa, 1992-2002. Int J Tuberc Lung Dis. 2008 Oct;12(10): 1182-9.

49. Varma JK, Nateniyom S, Akksilp S, Mankatittham W, Sirinak C, Sattayawuthipong W, Burapat C, Kittikraisak W, Monkongdee P, Cain KP, Wells CD, Tappero JW. HIV care and treatment factors associated with improved survival during TB treatment in Thailand: an observational study. BMC Infect Dis. 2009 Apr 13;9: 42.

50. Jamal LF, Guibu IA, Tancredi MV, Ramalho MO, Vasconcelos GM, Cota IN, Estevam DL, Domingues CL. Reliability and usefulness of TB/HIV co-infection data proceeding from developing countries. Int Conf AIDS. 2004 Jul 11-16;15. Available from: gateway.nlm.nih.gov/MeetingAbstracts/ma?f=102280737.html; accessed 30 April 2011.

51. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach. 2010 revision. Geneva, World Health Organization, 2010.

52. Abdool Karim S, Naidoo K, Padayatchi N, Grobler A, Baxter C, Gengiah S, El-Sadr W, Friedland G, Abdool Karim Q. Optimal Timing of ART during TB Therapy: Findings of the SAPiT Trial. 18th Conference on Retroviruses and Opportunistic Infections, Boston, USA, 2011. Available from: www.retroconference.org/2011/Abstracts/42488.htm; accessed 30 April 2011.

53. Havlir D, Ive P, Kendall M, Luetkemeyer A., Swindells S., Kumwenda J, Qasba S, Hogg E, Anderson J, Sanne I, and the A5521 Team. International Randomized Trial of Immediate vs. Early ART in HIV+ Patients treated for TB: ACTG 5221 STRIDE study. 18th Conference on Retroviruses and Opportunistic Infections, Boston, USA, 2011.. Available from: www.retroconference.org/2011/Abstracts/41152.htm; accessed 30 April 2011.

54. Blanc FX, Sok T, Laureillard D, Borand L, Rekacewicz C, Nerrienet E, Madec Y, Marcy O, Chan S, Prak N, Kim C, Lak KK, Hak C, Dim B, Sin CI, Sun S, Guillard B, Sar B, Vong S, Fernandez M, Fox L, Delfraissy JL, Goldfeld AE. Significant enhancement in survival with early (2 weeks) vs. late

(8 weeks) initiation of highly active antiretroviral treatment (HAART) in severely immunosuppressed HIV-infected adults with newly diagnosed tuberculosis. 18th Intl AIDS Conf, Abstract THLBB106, Vienna, Austria, 2010. Available from: www.natap.org/2010/IAS/IAS_91.htm; ; accessed 6 June 2011.

55. Fitzpatrick C, Floyd K. A systematic review of the cost and cost-effectiveness of treatment for multidrug-resistant tuberculosis. Pharmacoeconomics. 2011. [under review]. 56. WHO Policy on TB infection control in health-care facilities, congregate settings and households. Geneva, World Health Organization, 2009. (WHO/HTM/TB/2009.419).

57. Migliori GB, Loddenkemper R, Blasi F, Raviglione MC. 125 years after Robert Koch's discovery of the tubercle bacillus: the new XDR-TB threat. Is « science » enough to tackle the epidemic? Eur Resp J 2007;29(3): 423-427.