TREATMENT OF TUBERCULOSIS

Guidelines for treatment of drug-susceptible tuberculosis and patient care

2017 UPDATE

World Health Organization

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Abbreviations & acronyms

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral treatment
ATS	American Thoracic Society
BMI	body mass index
CDC	United States Centers for Disease Control and Prevention
DOT	directly observed treatment
E	Ethambutol
FDC	fixed-dose combination
GDG	Guideline Development Group
Gfx	Gatifloxacin
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GTB	Global TB Programme
HIV	human immunodeficiency virus
IDSA	Infectious Diseases Society of America
IRIS	Immune Reconstitution Inflammatory Syndrome
KNCV	Royal Dutch Tuberculosis Foundation
MDR-TB	multidrug-resistant tuberculosis
Mfx	Moxifloxacin
NGO	non-governmental organization
PICO	Patients, Intervention, Comparator and Outcomes
RIF or R	Rifampicin
RFP	Rifapentine
SAT	self-administered treatment or unsupervised treatment
SMS	Short Message Service or text message
TB	tuberculosis
The Union	International Union Against Tuberculosis and Lung Disease
USAID	United States Agency for International Development
VOT	video-observed treatment
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

Acknowledgements

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1   WHO/GTB staff members were also invited to be part of the development of the ATS/CDC/IDSA guideline.

Declaration and management of conflict of interest

The scope for the update of the *Guidelines for treatment of drug-susceptible tuberculosis and patient care* and the composition of the Guideline Development Group (GDG), as well as the External Review Group, were established in line with WHO's policy on conflict of interest. All contributors completed a WHO Declaration of Interest form. All stated declarations of interest were evaluated by three members of the steering group for the existence of any possible financial or intellectual conflict of interest. In some cases there was possible conflict of interest justifying the exclusion from membership of the GDG, and the Director of the WHO Global TB Programme, the WHO Guidelines Review Committee and the WHO Legal Office were consulted on this and a decision was made. Diversity and broad representation in the GDG were sought in an effort to address and overcome any potential intellectual conflicts of interest. The GDG was composed of representatives of technical partners and academia, a GRADE methodologist, national TB programme managers from different WHO regions, representatives of civil society organizations, experts from WHO collaborating centres, professional organizations and a representative from the International Organization for Migration (see Annex 1).

The biographies of the GDG members were made public ahead of the meeting, and the WHO Guidelines Steering Committee, which was formed in preparation for the update of the guidelines, reviewed the completed forms at the beginning of the meeting with everyone present.

I.   Guidelines Development Group (GDG)

The following members declared no interests: Si Thu Aung; Frank Bonsu; Jeremiah Chakaya; Lucy Chesire; Daniela Cirillo; Poonam Dhavan; Kathy Fiekert; Andrei Mariandyshev; Nguyen Viet Nhung; Ejaz Qadeer; Abdul Hamid Salim; Holger Schünemann; Pedro Suarez; Justin Wong Yun Yaw.

The following GDG members declared interests that were judged not to be in conflict with the policy of WHO, or the objectives of the meeting:

Kelly Dooley declared that she did not receive any salary support from drug companies for her work in the following roles and activities: Co-chair of the AIDS Clinical Trials Group (ACTG) study assessing bedaquiline and delamanid for MDR-TB; principal investigator, assessing pretomanid for tuberculosis trial, assessing pretomanid (PA-824, investigational drug) for treatment of drug-sensitive TB; investigator on trials assessing rifapentine for pregnant women with latent TB infection, rifapentine for treatment shortening in patients with pulmonary TB, high-dose rifampicin and levofloxacin for pediatric TB meningitis, high-dose isoniazid for MDR-TB, and delamanid for MDR-TB in children with and without HIV.

Mike Frick declared that his organization received noncommercial support 1) to track investment made in TB research and development; 2) to host a symposium at the Union meeting; 3) advocate for increased funding for TB research and development, research and access to evidence-based interventions; and 4) management of community research advisors group.

Simon Schaaf declared receiving grants for pharmacokinetic drug studies in children of second-line drugs and for studying preventive therapy in MDR-TB.

Carrie Tudor declared that her organization receives funding from Eli Lilly Foundation for activities related to TB and MDR-TB projects.

II.   External Review Group

The following External Review Group members declared no interest related to the objectives of this meeting: Riitta Dlodlo, Celine Garfin, Lee Reichman, Vaira Leimane, Rohit Sarin, Fraser Wares, and Dalene von Delft. The following WHO staff from the Regional Offices reviewed the final draft of the guideline document: Masoud Dara (Europe), Mirtha Del Granado (Americas), Daniel Kibuga (Africa), Md Khurshid Alam Hyder (South-East Asia), Mohamed Aziz (Eastern Mediterranean), and Nobuyuki Nishikiori (Western Pacific).

III.   Evidence reviewers

The researchers who undertook the systematic reviews of evidence for this revision were the following:

- Narges Alipanah, Cecily Miller, Payam Nahid (team leader for PICO 1, 2 & 7-10), University of California, San Francisco, United States of America; and Leila Chaisson, Johns Hopkins Bloomberg School of Public Health, Baltimore, United States of America.

- Richard Menzies, McGill University, Montreal, Canada (team leader for PICO 3, 4 & 6); and James Johnston, University of British Columbia, Vancouver, Canada.

- Gregory Fox (team leader for PICO 11) and Jennifer Ho, University of Sydney, Sydney, Australia.

The evidence reviewers did not participate in the formulation of the policy recommendations.

The following reviewers declared no interest related to the objectives and their attendance of the meeting: Narges Alipanah, Jennifer Ho and James Johnston.

The following reviewers declared interests that were judged not to be in conflict with the policy of WHO, or the objectives of the meeting:

Payam Nahid declared that his research unit received support from the United States Centers for Disease Control and Prevention through a federal contract to support clinical trial units in San Francisco, USA, and in Hanoi, Viet Nam.

Executive summary

The update of the *Guidelines for treatment of drug-susceptible tuberculosis and patient care* is important in the context of the End TB Strategy, which recommends treatment and patient support for all people with TB. This update by WHO aims to use the best available evidence on the treatment of drug-susceptible TB and interventions to ensure adequate patient care and support in order to inform policy decisions made in these technical areas by national TB control programme managers, national policy-makers and medical practitioners in a variety of geographical, economic and social settings.

The objectives of the updated *Guidelines for treatment of drug-susceptible tuberculosis and patient care* are:

1) to provide updated recommendations based on newly emerged evidence on the treatment of drug-susceptible TB and patient care; and

2) to provide a summary of changes in the new guidelines together with all the existing and valid WHO recommendations on the treatment of drug-susceptible TB and TB patient care.

The Global TB Programme of the World Health Organization (WHO) convened a meeting of a Guidelines Development Group (GDG) on 11–13 July 2016 in order to review the evidence available on key aspects of the treatment of drug-susceptible TB, as well as of patient care, and to formulate recommendations for the update of the fourth edition of the *Guidelines for treatment of tuberculosis* published in 2010 *(1)*. The GDG was composed of a multidisciplinary group of TB experts external to WHO.

The scope of the update for the 2017 *Guidelines for treatment of drug-susceptible tuberculosis and patient care* was

1) to update the previous evidence-based policy recommendations published in 2010; and

2) to have additional GRADE-based recommendations on some issues relevant to patient care, regardless of whether the disease is drug-susceptible or drug-resistant (in this context even the model of care for patients with drug-resistant TB was reviewed to assess the quality of the evidence available).

Prior to the meeting, the WHO Steering Committee identified several key questions that were extensively discussed during four online meetings with the GDG members. The PICO (Population, Intervention, Comparator, Outcomes) format of these questions was finalized during the same online meetings, in order to proceed to the commissioning of systematic reviews by several research teams.

At the time of preparing for the update, the American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America (ATS/CDC/IDSA) were also developing new clinical practice guidelines on the treatment of drug-susceptible TB, in which WHO staff were involved *(2)*. The available material was shared not only with

WHO but also with reviewers from University of California San Francisco and from McGill University in Montreal, who contributed to the ATS/CDC/IDSA guidelines and have also been major contributors of the reviews used to prepare the WHO guidelines.

Three PICO questions on the treatment of drug-susceptible TB (PICO 1, 2 & 9) and two questions on patient care (PICO 10 & 11) were proposed by the GDG for systematic reviews, while the other six PICO questions proposed by the GDG (PICO 3-8) were addressed by the evidence derived from the systematic reviews conducted for the recently updated ATS/CDC/IDSA guidelines *(2)*.

The PICO questions considered by the GDG focused on the priority areas of drug-susceptible TB treatment such as 4-month fluoroquinolone-containing regimens, effectiveness of fixed-dose combination formulations, dosing frequency, ART initiation and the duration of TB treatment for TB patients living with HIV, effectiveness of adjuvant corticosteroids for treatment of TB pericarditis and meningitis, management of patients who require retreatment; and on priority areas of patient care such as effectiveness of treatment supervision and treatment adherence interventions, and the multidrug-resistant TB (MDR-TB) decentralized model of care.

The recommendations were formulated by the GDG using the GRADE approach, except in the special case of the recommendation on category II treatment regimen for which available evidence generated by the GRADE approach was insufficient for the GDG to make the decision. Consequently, a good practice statement approach was used for formulating the recommendation.

The guidelines were reviewed by the External Review Group which was composed of experts and end-users from all WHO regions.

The recommendations are the following:

1. Treatment of drug-susceptible tuberculosis

1.1. The effectiveness of shortened fluoroquinolone-containing regimens when compared to the standard 6-month treatment regimen of 2HRZE/4HR in patients with drug-susceptible pulmonary TB disease

Recommendation:
In patients with drug-susceptible pulmonary TB, 4-month fluoroquinolone-containing regimens[2] should not be used and the 6-month rifampicin-based regimen 2HRZE/4HR remains the recommended regimen (Strong recommendation, moderate certainty in the evidence).

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2   Fluoroquinolone-containing regimens include: 4MfxHRZ, 4MfxRZE, 2MfxRZE/2(Mfx+RFP)2, 2MfxRZE/4(Mfx+RFP)weekly, 2GfxHRZ/2GfxHR, 2(GfxHRZ)3/2(GfxHR)3, 2(MfxHRZ)3/2(MfxHR)3,

1.2. The effectiveness of TB treatment using fixed-dose combination tablets when compared to separate drug formulations in patients with drug-susceptible TB disease

Recommendation:

The use of fixed-dose combination (FDC) tablets is recommended over separate drug formulations in treatment of patients with drug-susceptible TB (Conditional recommendation, low certainty in the evidence).

1.3. The effectiveness of intermittent dosing (thrice weekly) of TB medications, both in the intensive phase and in the continuation phase of treatment, when compared to daily treatment

Recommendation:

In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing is not recommended in both the intensive and continuation phases of therapy, and daily dosing remains the recommended dosing frequency (Conditional recommendation, very low certainty in the evidence).[3]

1.4. Initiation of antiretroviral treatment (ART) in TB patients living with HIV

Recommendation:

1.4.1. ART should be started in all TB patients living with HIV regardless of their CD4 cell count (Strong recommendation, high certainty in the evidence).

1.4.2. TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment (Strong recommendation, high certainty in the evidence). HIV-positive patients with profound immunosuppression (e.g. CD4 counts less than 50 cells/mm3) should receive ART within the first 2 weeks of initiating TB treatment.

1.5. The effectiveness of a TB treatment period of greater than 8 months compared to the standard 6-month treatment period for HIV co-infected patients with drug-susceptible pulmonary TB

Recommendation:

In patients with drug-susceptible pulmonary TB who are living with HIV and receiving antiretroviral therapy during TB treatment, a 6-month standard treatment regimen is recommended over an extended treatment for 8 months or more (Conditional recommendation/very low certainty in the evidence).

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3   Twice-weekly dosing is totally not recommended. See Guidelines for treatment of tuberculosis, fourth edition. Geneva: World Health Organization; 2010 (http://www.who.int/tb/publications/2010/9789241547833/en/, accessed 27 February 2017).

1.6. The use of adjuvant steroids in the treatment of extrapulmonary TB disease

Recommendation:

1.6.1. *In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8 weeks should be used (Strong recommendation, moderate certainty in the evidence).*

1.6.2. *In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used (Conditional recommendation, very low certainty in the evidence).*

1.7. The empirical use of the WHO category II regimen[4] in patients who require retreatment for TB

Recommendation

In patients who require TB retreatment, the category II regimen should no longer be prescribed and drug-susceptibility testing should be conducted to inform the choice of treatment regimen (Good practice statement).

2. Patient care and support

2.1. Cross-cutting interventions for drug-susceptible TB and drug-resistant TB: effectiveness of patient care and support interventions

Recommendations:

2.1.1. *Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment (Strong recommendation, moderate certainty in the evidence).*

2.1.2. *A package of treatment adherence intervention[5] may be offered for patients on TB treatment in conjunction with the selection of a suitable treatment administration option[6] (Conditional recommendation, low certainty in the evidence).*

2.1.3. *One or more of the following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health-care providers:*

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4   Regimen previously recommended by WHO for TB patients who require retreatment due to treatment interruption or recurrence of disease: 2HRZES/1HRZE/5HRE or 2HRZES/1HRZE/5(HRE)3,

5   Treatment adherence interventions include social support such as material support (e.g. food, financial incentive, and transport fee); psychological support; tracers such as home visit or digital health communication (e.g. SMS, telephone call); medication monitor; and staff education. The interventions should be selected on the basis of the assessment of individual patient's needs, provider's resources and conditions for implementation.

6   Treatment administration options include DOT, VOT, non-daily DOT (e.g. not every dose supervised treatment, weekly or a few times per week supervision), or unsupervised treatment).

a) tracers[7] or digital medication monitor[8] (Conditional recommendation, very low certainty in the evidence);

b) material support to patient[9] (Conditional recommendation, moderate certainty in the evidence);

c) psychological support[10] to patient (Conditional recommendation, low certainty in the evidence);

d) staff education[11] (Conditional recommendation, low certainty in the evidence).

2.1.4 The following treatment administration options may be offered to patients on TB treatment:

a) Community- or home-based directly observed treatment (DOT) is recommended over health facility-based DOT or unsupervised treatment (Conditional recommendation, moderate certainty in the evidence);

b) DOT administered by trained lay providers or health-care workers is recommended over DOT administered by family members or unsupervised treatment (Conditional recommendation, very low certainty in the evidence);

c) Video observed treatment (VOT) can replace DOT when the video communication technology is available and can be appropriately organized and operated by health-care providers and patients (Conditional recommendation, very low certainty in the evidence).

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7   Tracers refer to communication with the patient including via SMS, telephone (voice) calls, or home visit.

8   A digital medication monitor is a device that can measure the time between openings of the pill box. The medication monitor may have audio reminders or send an SMS to remind patient to take medications, along with recording when the pill box is opened.

9   Material support can be food or financial support such as: meals, food baskets, food supplements, food vouchers, transport subsidies, living allowance, housing incentives, or financial bonus. This support addresses indirect costs incurred by patients or their attendants in order to access health services and, possibly, tries to mitigate consequences of income loss related to the disease.

10 Psychological support can be counselling sessions or peer-group support.

11 Staff education can be adherence education, chart or visual reminder, educational tools and desktop aids for decision-making and reminder.

2.2. Model of care for drug-resistant TB: the benefits of treating MDR-TB patients within a decentralized compared to centralized model of care

Recommendation:

A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment (Conditional recommendation, very low certainty in the evidence).

It is critical that national TB programmes and public health leaders consider these recommendations in the context of countries' TB epidemics, the strengths and weaknesses of health systems, and the availability of financial, human and other essential resources. In adapting these guidelines, care must be exercised to avoid undermining current treatment programmes, to protect access for the populations most in need, to achieve the greatest impact for the greatest number of people, and to ensure sustainability. It is similarly important to ensure that the adaptation of these guidelines does not stifle ongoing or planned research, since the new recommendations reflect the current state of knowledge and new information for sustainability and future modifications of existing guidelines will be needed.

Summary of changes in the new guidelines 2017 and policy recommendations on treatment of drug-susceptible TB and patient care in other existing WHO guidelines that remain valid

Guidelines for treatment of tuberculosis, 2010[12] *(1)*	Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update
Duration of rifampicin in new TB patients	
New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR (Strong recommendation, high grade of evidence)	Remains valid*
The 2HRZE/6HE treatment regimen should be phased out (Strong recommendation, high grade of evidence)	Remains valid*
Effectiveness of shortened fluoroquinolone-containing regimens	
NO EXISTING SPECIFIC RECOMMENDATION	UPDATED* In patients with drug-susceptible pulmonary TB, 4-month fluoroquinolone-containing regimens[13] should not be used and the 6-month rifampicin-based regimen 2HRZE/4HR remains the recommended regimen (Strong recommendation, moderate certainty in the evidence)

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12 Guidelines for treatment of tuberculosis, fourth edition. Geneva: World Health Organization; 2010 (http://www.who.int/tb/publications/2010/9789241547833/en/, accessed 27 February 2017).

13 Fluoroquinolone-containing regimens which have been used in the four trials were the following: 4MfxHRZ, 4MfxRZE, 2MfxRZE/2(Mfx+RFP)$_2$, 2MfxRZE/4(Mfx+RFP)$_1$, 2GfxHRZ/2GfxHR, 2(GfxHRZ)$_3$/2(GfxHR)$_3$, 2(MfxHRZ)$_3$/2(MfxHR)$_3$.
(E: ethambutol, Gfx: Gatifloxacin, H: isoniazid, Mfx: moxiflicacin, R: rifampicin, RFP: rifapentine, Z: pyrazinamide. The number prior to the regimen or treatment phase presents the number of months of the therapy. Subscript number following the drug or combination of drugs presents dosing frequency per week).

Use of fixed-dose combination formulations or separate drug formulations NO EXISTING SPECIFIC RECOMMENDATION	The use of FDC tablets is recommended over separate drug formulations in the treatment of patients with drug-susceptible TB (Conditional recommendation, low certainty in the evidence)

Dosing frequency of TB treatment in new TB patients

Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy (Strong recommendation, high grade of evidence)	Remains valid*
New patients with pulmonary TB may receive a daily intensive phase followed by a three-times-weekly continuation phase [2HRZE/4(HR)$_3$], provided that each dose is directly observed (Conditional recommendation, high and moderate grade of evidence)	UPDATED* In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing is not recommended in both the intensive and continuation phases of therapy, and daily dosing remains the recommended dosing frequency (Conditional recommendation, very low certainty in the evidence).
Three-times-weekly dosing throughout therapy [2(HRZE)$_3$/4(HR)$_3$] may be used as another alternative to Recommendation 2.1, provided that every dose is directly observed and the patient is NOT living with HIV or living in an HIV-prevalent setting (Conditional recommendation, high and moderate grade of evidence)	
New patients with TB should not receive twice-weekly dosing for the full course of treatment unless this is done in the context of formal research (Strong recommendation, high grade of evidence)	Remains valid*

Dosing frequency of TB treatment in persons living with HIV[14] (3)

TB patients with known positive HIV status and TB patients living in HIV-prevalent settings should receive at least 6 months of rifampicin-containing treatment regimen (Strong recommendation, high quality of evidence). The optimal dosing frequency is daily during the intensive and continuation phases (Strong recommendation, high quality of evidence).	Remains valid*

Duration of TB treatment for TB patients living with HIV

It is recommended that TB patients who are living with HIV should receive at least the same duration of TB treatment as HIV-negative TB patients (Strong recommendation, high grade of evidence)	Remains valid*

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14   From WHO's *Policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders.* Geneva: World Health Organization; 2012 (http://www.who.int/tb/publications/2012/tb_hiv_policy_9789241503006/en/, accessed 27 February 2017).

In TB patients who are living with HIV and receiving antiretroviral therapy during TB treatment, is there a need to prolong duration of TB treatment longer than 6 months? NO EXISTING SPECIFC RECOMMENDATION	UPDATED* In patients with drug-susceptible pulmonary TB who are living with HIV and receiving antiretroviral therapy during TB treatment, a 6-months standard treatment regimen is recommended over an extended treatment for 8 months or longer (Conditional recommendation, very low certainty in the evidence)

Initial regimen in countries with high levels of isoniazid resistance

In populations with known or suspected high levels of isoniazid resistance, new TB patients may receive HRE as therapy in the continuation phase as an acceptable alternative to HR (Conditional recommendation, insufficient evidence, expert opinion)	Remains valid* [15]

Treatment extension in new pulmonary TB patients

In new pulmonary TB patients treated with the regimen containing rifampicin throughout treatment, if a positive sputum smear is found at completion of the intensive phase, the extension of the intensive phase is not recommended[16] (Strong recommendation, high grade of evidence)	Remains valid*

The use of steroids in the treatment regimen of tuberculous meningitis and tuberculous pericarditis

NO EXISTING SPECIFC RECOMMENDATION	UPDATED* In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8 weeks should be used (Strong recommendation, moderate certainty in the evidence) In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used (Conditional recommendation, very low certainty in the evidence)

Treatment of previously treated TB patients

Specimens for culture and drug-susceptibility testing should be obtained from all previously treated TB patients at or before the start of treatment. Drug-susceptibility testing should be performed for at least isoniazid and rifampicin	Remains valid*
In settings where rapid molecular-based drug-susceptibility testing is available, the results should guide the choice of regimen	Remains valid*

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15   Further WHO guidance on treatment for patients with isoniazid mono-resistance is in development.

16   Instead, the continuation phase should start even though smear is positive at the completion of the intensive phase or at the end of 2 month.

In settings where rapid molecular-based drug-susceptibility testing results are not routinely available to guide the management of individual patients, TB patients whose treatment has failed or other patient groups with high likelihood of MDR-TB should be started on an empirical MDR regimen	Remains valid*
In settings where rapid molecular-based drug-susceptibility testing results are not routinely available to guide the management of individual patients, TB patients returning after defaulting or relapsing from their first treatment course may receive the retreatment regimen containing first-line drugs 2HRZES/1HRZE/5HRE if country-specific data show low or medium levels of MDR in these patients or if such data are unavailable	UPDATED* In patients who require TB retreatment, the category II regimen should no longer be prescribed and drug-susceptibility testing should be conducted to inform the choice of treatment regimen (Good practice statement)
In settings where drug-susceptibility testing results are not yet routinely available to guide the management of individual patients, the empirical regimens will continue throughout the course of treatment	Remains valid*
National TB control programmes should obtain and use their country-specific drug resistance data on failure, relapse and loss to follow-up of patient groups to determine the levels of MDR-TB.	Remains valid*

Patient care and support: treatment supervision (e.g. DOT, VOT), social support and digital health interventions NO EXISTING SPECIFC RECOMMENDATION	UPDATED* 1. Health education about the disease and counselling on treatment adherence should be provided to patients on TB treatment (Strong recommendation, moderate certainty in the evidence) 2. A package of treatment adherence interventions may be offered to patients on TB treatment in conjunction with the selection of a suitable treatment administration option (Conditional recommendation, low certainty in the evidence) 3. One or more of the following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health-care providers: a) tracer or digital medication monitor (Conditional recommendation, very low certainty in the evidence) b) material support to patient (Conditional recommendation, moderate certainty in the evidence); c) psychological support to patient (Conditional recommendation, low certainty in the evidence); d) staff education (Conditional recommendation, low certainty in the evidence). 4. The following treatment administration options may be offered to patients on TB treatment: a) Community or home-based DOT is recommended over health facility-based DOT or unsupervised treatment (Conditional recommendation, moderate certainty in the evidence); b) DOT administered by trained lay providers or health care workers is recommended over DOT administered by family members or unsupervised treatment (Conditional recommendation, very low certainty in the evidence); c) Video observed treatment (VOT) can replace DOT when the video communication technology is available and it can be appropriately organized and operated by health care providers and patients (Conditional recommendation, very low certainty in the evidence).

Consolidated guidelines on the use of antiretroviral drugs, 2016[17] (4)

Initiation of HIV antiretroviral treatment in HIV-infected patients with TB

HIV antiretroviral medications should be started in all TB patients living with HIV regardless of their CD4 cell count (Strong recommendation, high certainty in the evidence)	Remains valid*
TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment (Strong recommendation, high certainty in the evidence) HIV-positive TB patients with profound immunosuppression (e.g. CD4 cell counts less than 50 cells/mm3) should receive ART within the first 2 weeks of initiating TB treatment	Remains valid*

Guidelines for the programmatic management of drug-resistant tuberculosis – 2011 update[18] (5)

Models of MDR-TB care: ambulatory versus hospitalization

Patients with MDR-TB should be treated using mainly ambulatory care rather than with models of care based principally on hospitalization (Conditional recommendation, very low quality of evidence).	Remains valid*

Models of MDR-TB care: decentralization versus centralization

NO EXISTING SPECIFC RECOMMENDATION	UPDATED* A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment (Conditional recommendation, very low certainty in the evidence)

### Guideline: nutritional care and support for patients with tuberculosis[19]	The recommendations on nutritional care from these guidelines remain valid with the additional considerations reported in the section on patient care and support
### Guidance for national tuberculosis programmes on the management of tuberculosis in children[20]	The recommendations on management of childhood TB from these guidelines remain valid

*These recommendations should be read with the accompanying remarks in the relevant documents. "Remains valid" recommendations were defined as such by the Guidelines Steering Committee on the basis of its assessment of literature (not by comprehensive systematic reviews) that found that insufficient evidence had emerged since the release of the previous guidelines, and there were no other reasons that make recommendations no more valid.

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17   Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2016 (http://www.who.int/hiv/pub/arv/arv-2016/en/, accessed 27 February 2017).

18   Guidelines for the programmatic management of drug-resistant tuberculosis – 2011 update. Geneva: World Health Organization; 2011 (http://apps.who.int/iris/bitstream/10665/44597/1/9789241501583_eng.pdf, accessed 27 February 2017)

19   Guideline: nutritional care and support for patients with tuberculosis. Geneva: World Health Organization; 2013 (http://www.who.int/nutrition/publications/guidelines/nutcare_support_patients_with_tb/en/, accessed 27 February 2017).

20   Guidance for national tuberculosis programmes on the management of tuberculosis in children, second edition. Geneva: World Health Organization; 2014 (http://www.who.int/tb/publications/childtb_guidelines/en/, accessed 27 February 2017).

Introduction

In order to support countries in their effort to respond to the challenges posed by the TB epidemic over the years, WHO has produced and regularly updated guidelines for the treatment of different forms of TB disease. The latest WHO evidence-based guidelines for the treatment of drug-susceptible TB were published in 2010 and the recommendations therein were developed using the GRADE method for assessment of quality of evidence. Over the past six years several important developments have occurred, while the evidence available for some of the recommendations has remained unchanged; this requires and justifies both the revision of some of the recommendations and the updating of the evidence already available for others.

In addition, several interventions to support patients in their adherence to TB treatment have been implemented by national TB programmes for many years (e.g. direct observation of treatment, or DOT, and social support), while others have been recently introduced (e.g. digital health interventions such as SMS messages, telephone calls or other reminders, and video observation of treatment, or VOT), but these models of care have never been assessed using the GRADE methodology. WHO has therefore not yet issued guidelines with evidence-based recommendations for a variety of patient care and support interventions.

The update of the treatment guidelines for drug-susceptible TB and patient care is an important element in the context of the End TB Strategy, which recommends treatment and patient support for all people with TB.

Objectives

The present guideline update aims to use the best available evidence on the treatment of drug-susceptible TB, as well as on interventions to ensure adequate patient care and support, in order to inform policy decisions made in these technical areas by national TB control programme managers, national policy-makers, and medical practitioners in a variety of geographical, economic and social settings.

The objectives of the updated *Guidelines for treatment of drug-susceptible tuberculosis and patient care* are:

1) to provide updated recommendations based on newly emerged evidence on the treatment of drug-susceptible TB and patient care; and

2) to provide a summary of changes in the new guidelines together with all existing and valid WHO recommendations on the treatment of drug-susceptible TB and patient care.

Methods used to update the guidelines

Scope of the guideline update

The scope of the 2017 update for the drug-susceptible TB treatment guideline is to update the previous evidence-based policy recommendations in the *Guidelines for treatment of tuberculosis* released in 2010 *(1)*. The 2017 guideline update is broader than the 2010 guidelines as it includes additional evidence-based policy recommendations on cross-cutting issues relevant to patient care and support for patients with drug-susceptible TB or drug-resistant TB. In the context of patient care for this guideline update, the decentralized model of care for drug-resistant TB patients, which had never previously been addressed by any WHO TB guidelines, was also included for assessment of the available evidence. This is part of the plan of WHO's Global TB Programme to produce consolidated guidelines that will include all the recommendations on management of both drug-susceptible TB and drug-resistant TB.

The WHO Guidelines Steering Group and the Guidelines Development Group (GDG) considered priority questions for the update by focusing on important areas of drug-susceptible TB treatment and care that had not been addressed by previous guidelines and for which evidence was likely to be available by the time of the guideline update. A further priority was those areas that were already addressed by previous guidelines but for which new evidence had emerged that was likely to lead to a change in the existing recommendation. The WHO Guidelines Steering Group and the GDG agreed to limit the scope of the *Guidelines for treatment of drug-susceptible tuberculosis and patient care* to the following priority areas:

1. **Treatment of drug-susceptible TB**

   1.1 Effectiveness of TB treatment with the use of 4-month fluoroquinolone-containing regimens

   1.2 Effectiveness of FDC formulations for treatment of new TB patients

   1.3 Frequency of dosing in intensive and continuation phases for treatment of new patients with pulmonary TB

   1.4 Initiation of antiretroviral therapy in TB patients living with HIV

   1.5 Duration of TB treatment for HIV co-infected patients with drug-susceptible pulmonary TB

   1.6 Effectiveness of adjuvant corticosteroids in patients with tuberculous pericarditis and tuberculous meningitis

   1.7 Treatment regimen and management of patients with a previous history of TB treatment (i.e. treatment interruption or recurrence of disease) who require retreatment

2. **Patient care and support**

2.1 Effectiveness of treatment supervision (e.g. DOT, VOT) and other treatment adherence interventions

2.2 Effectiveness of a decentralized model of care for MDR-TB.

The 2017 update of the guidelines does not cover the aspects of policy guidance on treatment of drug-susceptible TB for which no new evidence has been published since the 2010 revision *(1)*. However, in the updated guidelines there is a section referring to existing WHO policy recommendations on the treatment of drug-susceptible TB and patient care for which no new evidence has emerged since they were released and which are therefore still valid. These existing recommendations will be included in the guidelines with clear reference to the previous guidelines where GRADE assessments and summaries of evidence were presented.

The key audience for these guidelines is policy-makers in ministries of health or managers of national TB programmes who formulate country-specific TB treatment guidelines or who plan TB treatment programmes. In addition, health professionals – including doctors, nurses and educators working both in government services and in nongovernmental organizations, such as technical agencies that are treating patients and organizing treatment services – are expected to use these guidelines. The guidelines included GRADE-assessed recommendations while aiming at a wide variety of health workers and other audiences who may have widely different needs that are unlikely to be met with the same guidance. Separate "how to" guidance, which will be developed subsequently, will include additional information on how to implement the recommendations. As noted, WHO's Global TB Programme also aims to consolidate the essential guidance on management of drug-susceptible and drug-resistant TB into a single guideline.

Key questions

The PICO questions were grouped into two sets – drug-susceptible TB treatment and patient care. There were 9 PICO questions devoted to the treatment of drug-susceptible TB and 2 PICO questions on patient care and support (see Scope of the guideline update, above. and Annex 2 for the full version of all PICO questions).

Certainty of evidence and strength of recommendations

The recommendations in these guidelines qualify both their strength and the certainty in the evidence on which they are based. The certainty (quality) of the evidence is categorized into four levels (Table 1). The criteria used by the evidence reviewers to qualify the quality of evidence are summarized in the GRADE tables annexed to these guidelines (Annex 3, online). A number of factors may increase or decrease the quality of evidence (see tables 12.2b and 12.2c in the *WHO handbook for guideline development (6).* The highest quality rating is usually assigned to evidence from randomized controlled trials, while evidence from observational studies is usually assigned a low or very low quality value at the start.

A recommendation may be strong or conditional. Apart from the quality of evidence, the strength of a recommendation is determined by the balance between desirable and undesirable effects, values and preferences, and costs or resource allocation. For strong recommendations, the GDG is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects. For conditional recommendations, the GDG considers that desirable effects probably outweigh the undesirable effects. The strength of a recommendation has different implications for the individuals affected by these guidelines (Table 2).

Table 1. Certainty in the evidence

Certainty in the evidence	Definition
High ($\oplus\oplus\oplus\oplus$)	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate ($\oplus\oplus\oplus\bigcirc$)	Further research is likely to have an important impact on our confidence in the effect and may change the estimate.
Low ($\oplus\oplus\bigcirc\bigcirc$)	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 ($\oplus\bigcirc\bigcirc\bigcirc$)	Any estimate of effect is very uncertain.

The text of the recommendation itself should be read along with the accompanying remarks which summarize the evidence upon which the recommendation was made, the anticipated desirable and undesirable effects of the interventions to assess the balance of expected benefits to risks, and other considerations which are important to the implementation of the policy.

Assessment of evidence and its grading

The development of these guidelines required a substantial evidence review and assessment using the GRADE process, as stipulated by the WHO Guidelines Review Committee *(6)*. The systematic reviews focused primarily on the randomized controlled trials with direct comparison between the intervention and comparator. However, data on the outcomes from the observational cohort studies were also summarized and assessed by the GDG, especially when limited or no evidence from randomized controlled trials was available.

The systematic reviews were commissioned by independent reviewers. The evidence reviewers are listed in Annex 2. Contributors to this work were not members of the GDG so that the latter can provide independent oversight of recommendations based on evidence assessment. The WHO Steering Group and methodologists supervised the contractors' performance of the reviews, including assessing and providing feedback on the protocol for each systematic review and the evidence tables.

Teams of experts were commissioned to assess the evidence for the PICO questions and their outcomes through systematic literature reviews following a standard methodology. Titles, abstracts and full text of potentially relevant literature were screened using key subject words and text words. Authors or experts in the field were contacted to identify missing studies or studies in progress.

For the systematic reviews that were conducted for the updated ATS/CDC/IDSA TB treatment guidelines, the same groups of reviewers who conducted the reviews also prepared GRADE evidence profiles and presented them to the GDG for the WHO guidelines for assessment prior to and during the GDG meeting. The GDG revised the quality of the evidence assigned by the evidence reviewers on the standard criteria (e.g. directness, precision) using the automated function on the GRADEpro platform.

Table 2. 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 adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

Source: Adapted from Guyatt et al. *(7)*

Relative effects (relative risks or odds ratios of an event) were calculated from pooled data in individual or aggregated formats from the included studies. Absolute effects and risk differences were used to express the magnitude of an effect or difference between the intervention and comparator groups. Where possible, adjustments were made to reduce risk of bias and confounding. More details are provided in the notes on the GRADE evidence profiles that were used to summarize the results of systematic reviews done for each question (online Annex 3). The evidence profiles were prepared using GRADEpro software – an online tool to create guideline materials.[21] The certainty of the evidence was assessed using the following criteria: study design, limitations in the studies (risk of bias), imprecision, inconsistency, indirectness, publication bias, magnitude of effect, dose–effect relations and residual confounding.

The GDG membership represented a broad cross-section of future users of the guidelines as well as affected persons (including the patient). Ahead of the GDG meeting held at the WHO headquarters in Geneva, Switzerland, 11–13 July 2016, one or more discussants were identified from among the GDG members to assess the evidence for each of the PICO questions and to present his or her perspective on the implications of the findings during the meeting. Evidence profiles and drafts of the review reports (online Annexes 3 and 5)

21   See: http://gdt.guidelinedevelopment.org.

were shared with the GDG members ahead of the meeting. During the meeting and in the following weeks additional analyses were shared with the group upon demand. The GRADE evidence profiles were discussed by the GDG ahead of formulating the recommendations.

The GDG used the "Evidence to Decision" tables via the GRADEpro interface to capture the content of the discussions (Annex 4, online). During the meeting on 11–13 July 2016, GDG members formulated the first draft of the recommendations on the basis of their assessment of evidence. The GDG discussed the proposed wording of the recommendations and the rating of strength (strong or conditional) considering not only the nature and quality of evidence but also assessing the balance between benefits and harms, as well as patients' values and preferences, resource implications, equity and human rights, acceptability and feasibility.

In the case of the question on use of the category II regimen for treatment of previously treated TB, the available evidence generated by the GRADE approach was insufficient for the GDG to make a decision on a recommendation. A good practice statement approach was considered more appropriate in this case and was therefore used in formulating the recommendation.

All decisions on the recommendations were reached by discussion and consensus, including their strength of the recommendations and, where appropriate, the conditions to be attached to the recommendations. The Chair facilitated the discussions in order to reach consensus during the meeting; consequently there was no need to vote on any of the recommendations. An additional analysis was conducted by the reviewers after the GDG meeting, addressing a gap in information that was identified in PICO question 10 on treatment adherence interventions. The additional evidence led to a slight revision of two recommendations on treatment supervision options. All evidence provided, and the revised recommendations, were shared with all GDG members for review and endorsement.

External review

The process of peer review involved the External Review Group which was composed of experts and end-users from national programmes, technical agencies and WHO regional offices. These persons provided their review and inputs on the completed draft guidelines after all comments by GDG members were incorporated.

Publication, dissemination, implementation, evaluation and expiry

These guidelines are published on the WHO Global TB Programme (WHO/GTB) website and are freely downloadable (as pdf and in other electronic formats). The main text of the guidelines will be made available in a print version in early 2017 and will be widely distributed to WHO regional and country offices as well as to national TB programmes. This document will appear in six languages: Arabic, Chinese, English, French, Russian and Spanish. It is also expected that the evidence reviews and recommendations will be published in peer-reviewed journals to improve dissemination of the main messages. The updates of policy guidance will also be reflected in the implementation guidance on TB management and the revision of the WHO implementation handbook on programmatic management of drug-resistant TB *(8)*.

WHO will work closely with its regional and country offices, as well as technical and funding agencies and partners, to ensure wide communication of the updated guidance in technical meetings and training activities. WHO at different levels will work with technical partners to support national TB programmes in adopting new recommendations in national TB policies and guidelines. The evaluation of implementation of the recommendations by the countries or end-users will be conducted by WHO/GTB and partners several years following publication. WHO/GTB will also review and update the guidelines some 4–5 years after their publication, or earlier if new evidence becomes available, and these changes will be reflected in the implementation guidance documents.

WHO policy recommendations

1. Treatment of drug-susceptible tuberculosis

1.1. The effectiveness of 4-month fluoroquinolone-containing regimens when compared to the standard 6-month treatment regimen of 2HRZE/4HR in patients with drug-susceptible pulmonary TB disease

> **Recommendation**
>
> *In patients with drug-susceptible pulmonary TB, 4-month fluoroquinolone-containing regimens should not be used and the 6-month rifampicin-based regimen 2HRZE/4HR remains the recommended regimen*
> *(Strong recommendation, moderate certainty in the evidence).*

Remark

Fluoroquinolone-containing regimens which have been used in the four trials *(9-12)* were the following: 4MfxHRZ, 4MfxRZE, 2MfxRZE/2(Mfx+RFP)$_2$, 2MfxRZE/4(Mfx+RFP)$_1$, 2GfxHRZ/2GfxHR, 2(GfxHRZ)$_3$/2(GfxHR)$_3$, 2(MfxHRZ)$_3$/2(MfxHR)$_3$.

Justification

Although shortening the duration of TB therapy is a desirable global research target, the GDG strongly recommended against the use of a fluoroquinolone-containing regimen of less than 6 months and recommended the use of the standard 6-month rifampicin-containing regimen (2HRZE/4HR). The data presented to the GDG synthesized findings from several studies *(9-12)* and found that that shorter fluoroquinolone-containing regimens of 4 months are associated with significantly higher rates of relapse at 18 months follow-up compared with the standard 6-month rifampicin-containing regimen, even though at 2 months the fluoroquinolone-containing regimens had slightly higher (not statistically significant) rates of culture conversion. Additionally, the evidence showed no reduction of adverse events with the fluoroquinolone-containing regimen and no difference in all-cause and TB-related mortality. Specifically, when moxifloxacin replaced ethambutol or isoniazid in a four-month regimen of HRZ or RZE, respectively, favourable outcomes were statistically significantly lower in these experimental arms compared to the standard 6-month regimen *(9)*. These unfavourable outcomes were driven by higher rates of relapse, despite faster culture conversion, in the experimental arms *(9)*. Similarly, when a regimen of 2 months of gatifloxacin, isoniazid, rifampicin and pyrazinamide followed by 2 months of gatifloxacin, isoniazid and rifampicin *(10)* – or when moxifloxacin combined with RZE for 2 months, followed by moxifloxacin and rifapentine twice weekly for 2 months *(11)* – was compared to the standard regimen, the experimental arms failed to show non-inferiority; again this was driven by higher rates of recurrence in the experimental arm *(10, 11)*. Finally, a study comparing a 4-month regimen containing gatifloxacin or moxifloxacin

combined with 4HR and 2 initial months of pyrazinamide was stopped early due to increased rates of relapse in the experimental arms *(12)*.

An additional concern (although not addressed specifically in these data) with using fluoroquinolones in drug-susceptible TB treatment, especially given higher rates of relapse in the four month fluoroquinolone-containing regimens, is that this may lead to a rise in fluoroquinolone resistance and consequently the loss of fluoroquinolone as part of the drug-resistant TB treatment regimen. From a public health perspective, the trials currently underway, involving subgroups of patients with pauci-bacillary and non-cavitary disease, will require careful evaluation before updating of the decision to reserve fluoroquinolone for treatment of drug-resistant TB.

Therefore, the reduction of treatment duration (2 months less) with no reduction in adverse events or mortality, combined with the increased risk of relapse at 18 months, led the GDG to support the standard 2HRZE/4HR regimen and to recommend against the use of 4-month fluoroquinolone-containing regimens for treatment of drug-susceptible TB. As work on the goal of shortening treatment of drug-susceptible TB is ongoing, any new evidence will be reflected in the next version of the guidelines.

The GDG also acknowledged that, within the comparator, shorter fluoroquinolone-containing regimens were varied with respect to the fluoroquinolone used, the drug that the fluoroquinolone replaced and the other drugs in the regimen. However, the GDG still believes that all fluoroquinolone-containing regimens at the doses tested had similar outcomes and those outcomes were inferior to the standard rifampicin-containing regimen.

Subgroup considerations

The recommendation applies to all subgroups.

Implementation considerations

There are no implementation concerns, as the 6-month rifampicin-based regimen is the standard regimen for the treatment of drug-susceptible tuberculosis.

Monitoring and evaluation

There is no new monitoring or evaluation concern beyond the standard recommendations.

1.2. The effectiveness of TB treatment using fixed-dose combination tablets when compared to separate drug formulations in patients with drug-susceptible TB disease

> **Recommendation**
>
> *The use of fixed-dose combination tablets is recommended over separate drug formulations in treatment of patients with drug-susceptible TB*
> *(Conditional recommendation, low certainty in the evidence).*

Justification

The evidence presented to the GDG was based on a systematic review of randomized controlled trials done by Albanna et al. *(13)* and by a recent Cochrane review *(14)*. This evidence showed that the FDCs are non-inferior and as effective as separate drug formulations in terms of treatment failure, death, treatment adherence and adverse events. There was a small increase in 2-month culture conversion with FDC treatment; however, there was no difference in culture conversion rates by the end of treatment. Patient satisfaction was higher among people who were treated with FDCs. A slightly higher rate of disease relapse and acquired drug resistance among patients treated with FDCs compared with the separate drug formulations was not statistically significant.

Patient treatment satisfaction with FDCs was considered the most important factor for making decisions on the recommendation.

Studies in these reviews did not evaluate bioavailability of the drugs in the FDCs but previous studies did not indicate that the FDC formulations used had significant bioavailability issues *(13)*. As no pharmacokinetic studies were done on these FDC formulations, the bioavailability of drugs within the FDCs versus the separate drug formulations remains an important consideration that indicates the need to procure FDCs of demonstrated bioavailability *(15-17)*. This area requires further research.

FDCs may provide programme benefits by making the ordering of medication easier, simplifying supply chain management, reducing the occurrence of stock-outs, and facilitating drug delivery and prescription preparation. FDCs may also provide benefits, especially in settings with a large number of TB patients and a limited number of health-care workers, by reducing the need for additional health-care staff and training in dosing and dispensing of medications, as well as contributing to a lower pill burden for patients. However, national TB programmes are advised to have a quantity of separate drug formulations available for certain treatment conditions. Having single drug formulations available would be beneficial to programmes when designing MDR-TB regimens that include some first-line drugs (i.e. pyrazinamide, ethambutol, high-dose isoniazid), when providing preventive therapy, and in cases of adverse reactions to TB medications when drugs must be reintroduced one at a time.

The GDG acknowledged that greater patient satisfaction is an advantage of FDCs over separate drug formulations.

Subgroup considerations

The reduced pill burden afforded by using FDCs may be especially valuable in patients with co-morbidities (notably HIV infection) and paediatric patients (who may have a some difficulty in swallowing large amounts of medications).

Patients with some specific medical conditions (e.g. intolerance to certain TB drugs, liver or renal function impairment) are likely to require individual medication dose adjustment which can be done with separate drug formulations only.

Implementation considerations

There are no specific implementation considerations as the use of FDC formulations is already widespread.

Monitoring and evaluation

There are no specific new recommendations for monitoring and evaluation as the use of both types of drug formulation is already widespread.

1.3. The effectiveness of intermittent dosing (thrice weekly) of TB medications,[22] both in the intensive phase and in the continuation phase of treatment, when compared to daily treatment

> **Recommendation**
>
> *In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing is not recommended in both the intensive and continuation phases of therapy and daily dosing remains the recommended dosing frequency*
> *(Conditional recommendation, very low certainty in the evidence).*

Justification

The use of intermittent dosing of TB medications has been adopted in some geographical settings in an effort to improve treatment adherence and to reduce the burden on the health-care system due to daily DOT. However, it was unclear how this intermittent dosing may affect treatment outcomes. In addition to the evidence from the systematic review of treatment regimens with intermittent dosing schedules conducted in 2009 *(18)*, this systematic review was updated with the most recent randomized controlled trials *(4, 9, 10, 19-22)*.

Evidence showed that when thrice-weekly dosing throughout therapy was compared to daily dosing throughout therapy, patients who received thrice-weekly dosing had a higher risk of treatment failure, disease relapse and acquired drug resistance in both drug-susceptible disease and when the strain susceptibility was unknown. Consequently, thrice-weekly dosing in the intensive phase should never be used.

Likewise, when thrice-weekly dosing during the continuation phase only is compared to daily dosing throughout, there were higher rates of treatment failure and relapse in the

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22 Twice-weekly dosing is not recommended. See: Guidelines for treatment of tuberculosis, fourth edition. Geneva: World Health Organization; 2010 (http://www.who.int/tb/publications/2010/9789241547833/en/, accessed 27 February 2017)

patients that received thrice-weekly treatment during the continuation phase. In this case, acquired drug resistance rates did not differ. If thrice-weekly dosing during the continuation phase is used, it is essential to make sure that patients do not miss any dose of medications and that DOT is used.

In this review, the use of twice-weekly dosing in the continuation phase only was also reviewed. Twice-weekly dosing in the continuation phase only had higher rates of treatment failure, disease relapse and drug resistance than thrice-weekly dosing in the continuation phase only. As a result, twice-weekly dosing should never be used during any part of TB therapy.

Adherence to treatment was not addressed adequately enough in the reviewed studies to be included as an outcome. However, in most studies included in the systematic review, intermittent dosing used DOT, while the use of DOT during daily dosing was variable.

The GDG also considered that health equity would be adversely affected with intermittent dosing because more vulnerable populations would have inferior treatment if intermittent dosing were used. This is because people living in more resource-constrained settings would be more at risk of missing doses of medication, both because of their own difficulty in reaching a clinic and the risk of medication stock-outs in clinics. Additionally, patients who are co-infected with HIV or have other comorbidities may not absorb TB medications well, so in fact they receive less medication than they are ingesting. In order to be used as part of a treatment regimen, no doses must be missed with thrice-weekly intermittent dosing during the continuation phase because the rates of unfavourable outcomes then rise. Consequently, more vulnerable populations are at risk of missing medication doses or not absorbing the doses well, and intermittent dosing puts them in a situation with an increased risk of unfavourable outcomes.

Intermittent dosing could also create problems on the national and international level by leading to requirements for different drug manufacturing and packaging and a reduced drug supply buffer, leading to an increased risk of TB medication stock-outs.

Given the findings in this review, all countries are encouraged to use exclusively daily dosing in both the intensive and continuation phases of treatment. Although two separate evidence assessments were conducted on thrice-weekly dosing in the intensive phase and the continuation phase, both the formulated recommendations were conditional and there was very low certainty in the evidence. A combined recommendation for both intensive and continuation phases was formulated to make it more convenient for use by the end-users.

Subgroup considerations

This recommendation is the same for HIV-negative people and for people living with HIV.

The data used in this review examined only patients with drug-susceptible pulmonary TB and who had no extenuating circumstances such as adverse reactions which might require modification of the dosing schedule.

Children were not considered specifically in this review. However, there is no biologically plausible reason why this recommendation should not apply to children as well. It is

recommended that all children receive daily dosing of TB medications during the intensive and continuation phases of therapy for the same reason as adults. Please see the WHO's 2014 *Guidance for national tuberculosis programmes on the management of tuberculosis in children (24)* for recommendations on the daily dosing of children with drug-susceptible tuberculosis.

Implementation considerations

There are no new implementation considerations as the recommended daily treatment is already widespread practice. However, intermittent dosing is still used in some countries. In such exceptional cases, implementation of the recommendation to use exclusively daily dosing in the intensive and continuation phases of TB therapy is likely to have implications for drug procurement, practitioner training, change of programme practice and patient support.

Monitoring and evaluation

There are no new monitoring and evaluation recommendations as the standard of care (daily dosing of medications during the intensive and continuation phases of therapy) is being recommended.

1.4. Initiation of antiretroviral treatment (ART) in TB patients living with HIV

> ### Recommendation
>
> *1.4.1. **ART should be started in all TB patients living with HIV regardless of their CD4 cell count (Strong recommendation, high certainty in the evidence).***
>
> *1.4.2. **TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment (Strong recommendation, high certainty in the evidence). HIV-positive patients with profound immunosuppression (e.g. CD4 cell counts less than 50 cells/mm³) should receive ART within the first 2 weeks of initiating TB treatment.***

Justification

These recommendations are from those published in the WHO publication *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection (4)*.[23] Below is the rationale and justification from this publication.

Early initiation of ART for patients with HIV-associated TB is critical in reducing morbidity and mortality. Since 2010, WHO has recommended that ART be started as soon as possible within the first 8 weeks of TB treatment in all TB patients living with HIV, regardless of CD4 cell count. Since then, several additional results from randomized controlled trials have been published. In 2015, a systematic review was conducted to reassess the optimal timing of ART initiation among people living with HIV and active TB to minimize death, AIDS-defining events, severe treatment-related adverse events and incidence of immune reconstitution inflammatory syndrome (IRIS).

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23   See: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Geneva: World Health Organization; 2916 (http://www.who.int/hiv/pub/arv/arv-2016/en/, accessed 27 February 2017).

The review of evidence focused on the relative benefits of early ART started within 2 weeks (defined as "earlier initiation") or 8 weeks (defined as "early initiation") of TB treatment initiation, compared to ART initiated after 8 weeks (defined as "delayed initiation"). Early and earlier initiation were also compared to delayed ART, initiated after 8 weeks but before completion of TB treatment. Particular consideration was given to people with profound immunosuppression (CD4 cell count less than 50 cells/mm^3).

High-quality evidence from eight trials *(23, 26–32)* showed that, across the CD4 strata, early ART (within 8 weeks of TB treatment) is associated with a reduction in overall mortality, compared with ART initiated after 8 weeks of TB treatment or after TB treatment is completed. In a sub-analysis of patients with a CD4 cell count of less than 50 cells/mm3, the reduction in mortality was statistically significant *(26, 29, 33, 34)*. High-quality evidence from four trials also demonstrated a reduction in mortality when ART was started within 2 weeks of starting TB treatment, compared with delayed initiation but during TB treatment, across all CD4 cell counts *(26–28, 29)*. Similarly, earlier ART for patients with a CD4 cell count of less than 50 cells/mm3 was associated with a reduction in mortality *(26, 34)*. Furthermore, one trial found a significant reduction in the combined outcome of AIDS-defining illness or death among this group *(28)*.

Overall, the systematic review found similar levels of grade 3 or 4 non-IRIS adverse events among patients starting ART early or earlier with all CD4 cell counts compared to delayed ART *(4)*. Sub-analysis of patients with a CD4 cell count of less than 50 cells/mm^3 showed similar findings when comparing early ART with delayed ART within 24 weeks of starting TB treatment.

The evidence showed a tendency towards reduction in AIDS-defining illnesses across all CD4 strata when early and earlier ART were compared with delayed initiation during TB treatment. Sub-analysis of patients with a CD4 cell count of less than 50 cells/mm^3 showed similar findings with early ART *(26)* and earlier ART compared with delayed ART within 24 weeks of starting TB treatment.

However, overall there was a statistically significant, higher incidence of IRIS in patients who initiated ART within 8 weeks when compared with delayed ART initiation across the CD4 strata and in the sub-analysis of CD4 cell count less than 50 cells/mm^3. A separate sub-analysis was conducted of high-quality evidence from five randomized controlled trials to assess IRIS-related mortality. While there was a statistically significant increase in IRIS-related mortality associated with early ART, the absolute number of deaths was small (9/335) in comparison with overall deaths *(28–30, 32, 35, 36)*.

Subgroup considerations

On the basis of this evidence, ART should be started in all TB patients living with HIV regardless of CD4 cell count because of the overall benefit of early ART. A direct comparison of the effect of starting ART within 2 weeks compared with after 2 weeks but within 8 weeks of TB treatment was not feasible. However, ART initiation within 2 weeks is important in people with CD4 cell counts less than 50 cells/mm^3 because mortality in this group is

particularly high. Inability to measure CD4 cell count should not be a barrier to starting ART earlier.

Data from the reviewed studies primarily included adults and adolescents and were not disaggregated according to age, so it was not possible to measure the effect of early ART among children with HIV-associated TB. However, data from one observational study in South Africa showed increased mortality and poorer virological response in children with HIV-associated TB when ART was initiated more than 8 weeks after starting TB treatment, particularly in children with severe immunosuppression *(37)*. The existing strong recommendation developed in 2010 that was based on low-quality evidence is therefore maintained in these guidelines.

Caution is needed regarding people living with HIV with TB meningitis, as immediate ART is significantly associated with more severe adverse events when compared with initiation of ART 2 months after the start of TB treatment *(38)*.

These recommendations also apply to patients with suspected or confirmed MDR-TB.

Implementation considerations

Patients should be closely followed up to assess the occurrence of side-effects related to co-treatment and of TB-associated IRIS, which is common in patients with TB started on ART but is usually self-limited. Stakeholders and service providers should establish mechanisms to ensure that people living with HIV receive TB treatment along with ART, emphasizing integrated and patient-centred care, preferably at the same location. See section 6.10.2 on "Delivering ART in TB treatment settings and TB treatment in HIV care settings" from *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infections (4)*.

1.5. The effectiveness of a TB treatment period of greater than 8 months compared to the standard 6-month treatment period for HIV co-infected patients with drug-susceptible pulmonary TB

> **Recommendation**
>
> *In patients with drug-susceptible pulmonary TB who are living with HIV and receiving antiretroviral therapy during TB treatment, a 6-month standard treatment regimen is recommended over an extended treatment for 8 months or more (Conditional recommendation, very low certainty in the evidence).*

Justification

All persons living with HIV, and especially those with TB, should be receiving antiretroviral therapy (ART). Persons living with HIV who are responding to ART need not expect a more unfavourable outcome to a treatment episode than an uninfected person. Therefore persons with drug-susceptible TB who are living with HIV should require only 6 months of rifampicin-containing TB treatment. See WHO's *The use of antiretroviral drugs for treating and preventing HIV infection (4)* and *WHO policy on collaborative TB/HIV activities:*

guidelines for national programmes and other stakeholders (3).

Adverse consequences of an extended period of TB treatment include the increased burden of an additional 2 or more months of medications, the increased risk of toxicity and drug-drug interactions with prolonged treatment, and the risk of HIV-related stigma if it is revealed that a patient is on a regimen recommended for persons living with HIV.

Subgroup considerations

If TB patients living with HIV are not yet receiving ART, ensuring the early start of ART should be prioritized.

In a systematic review of TB treatment outcomes in HIV-coinfected patients *(25)*, when the subgroup of TB patients living with HIV who were not being treated with ART were examined, relapse rates were significantly higher among people who received treatment with regimens that contained 6 months of rifampicin as opposed to those who received treatment with regimens that contained greater than or equal to 8 months of rifampicin. However, when people received at least some treatment with ART, these differences disappeared. Rates of failure and death did not differ between persons treated with 6 months of rifampicin-containing regimens versus those treated for a period greater than or equal to 8 months. This held true whether the persons were on ART or not.

Implementation considerations

There are no new implementation considerations beyond the current standard of care. National TB programmes may need to work closely with HIV programmes to further expand HIV testing and ART coverage among TB patients in order to apply this recommendation safely.

Monitoring and evaluation

There are no new monitoring and evaluation considerations beyond the current standard of care. In view of above subgroup considerations, national tuberculosis programmes may consider monitoring specifically for relapse in this group of TB patients.

1.6. The use of adjuvant steroids in the treatment of extrapulmonary TB disease

> **Recommendation**
>
> *1.6.1.* ***In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8 weeks should be used (Strong recommendation, moderate certainty in the evidence).***
>
> *1.6.2.* ***In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used (Conditional recommendation, very low certainty in the evidence).***

Justification

In patients with tuberculous meningitis, evidence from randomized controlled trials in the systematic review *(39-43)* showed lower rates of mortality, death or severe disability, and disease relapse when patients were treated with steroids in addition to anti-TB treatment.

The mortality benefit increased with increasing TB meningitis stage (i.e. increasing severity of disease). Additionally, rates of adverse events and severe adverse events, including severe hepatitis, were lower in the patients receiving steroids.

In patients with tuberculous pericarditis, evidence from studies in the systematic review *(44-51)* showed a benefit to steroid treatment with regard to death, constrictive pericarditis and treatment adherence. When the studies were considered individually, the largest (1400 patients) and most recent study – the IMPI study *(46)* – showed no benefit of steroids. However, a factor complicating these findings is HIV infection. In the IMPI study, 67% of subjects were HIV-positive and only 14% were on ART. This raises the question as to whether immunosuppressed patients may have had a different benefit from steroids when compared to HIV-negative people or persons living with HIV who are on ART. In the IMPI study, a supplemental analysis was done of the HIV-negative patients only, and a small mortality benefit was shown with steroid treatment. However, the relationship between HIV infection and steroids is complex; in another smaller study of 58 subjects, in which all were HIV-positive, steroids were found to reduce mortality *(47)*. It is of note that the other studies in the review did not address HIV and mortality.

The panel considered that the benefit in preventing constrictive pericarditis outweighed the potential harms of corticosteroid therapy.

Subgroup considerations

Steroids should be given regardless of the severity of meningitis.

With regard to the use of steroids in tuberculous pericarditis, in one study an increase in HIV-related cancers (non-Hodgkins' lymphoma and Kaposi sarcoma) was observed *(46)*. However, this increase appears to be caused by co-administration of immunotherapy (*M. indicus pranii*).

Implementation considerations

Practitioners should give oral steroids if intravenous formulations are not available.

Monitoring and evaluation

There are no additional recommendations beyond the standard of care.

1.7. The empirical use of the WHO category II regimen[24] in patients who require retreatment for TB

> **Recommendation**
>
> *In patients who require TB retreatment, the category II regimen should no longer be prescribed and drug susceptibility testing should be conducted to inform the choice of treatment regimen (Good practice statement).*

Justification

The systematic review *(52-72)* conducted for this guideline found only indirect evidence from observational studies (cohort analysis of retreatment cases) and not randomized controlled trials. In none of the studies was a comparator available to allow direct comparison between the category II regimen and another regimen in treatment of previously treated TB patients. The systematic review demonstrated that the empiric use of the category II regimen in patients requiring retreatment for their TB disease when isoniazid and rifampicin resistance was unknown led to unacceptably low rates of treatment success (median treatment success rates of 68%). Given the global goals of TB treatment success, 68% success rates are unacceptable. In addition, other systematic reviews of randomized controlled trials and cohort studies (one originally done in 2009 and one updated for this guidelines meeting) *(73, 74)* showed that when patients were treated with category II, those with confirmed isoniazid resistance had significantly higher rates of acquired drug resistance than those who remained susceptible to isoniazid. This demonstrates how category II continues to drive drug resistance.

Although adverse events were not sufficiently well reported in the literature, it is well known that streptomycin causes a high rate of adverse events, including ototoxicity and nephrotoxicity. Furthermore, since the adverse effects of the aminoglycosides are cumulative over a lifetime, giving streptomycin as part of an ineffective regimen (i.e. the category II regimen) raises the probability of adverse effects for a patient if that patient requires treatment later on with a second-line injectable for drug-resistant tuberculosis.

The available evidence generated by the systematic reviews was insufficient for the GDG to formulate a GRADEd recommendation in this case. Following thorough discussion, members of the GDG felt that a good practice statement was best to express the GDG position on this option. As described in the literature *(75)*, a good practice statement may take the place of a GRADE approach, and is in fact superior to a GRADE approach when several conditions are met. The GDG believed that, given the dire consequences of using a category II regimen for the reasons given below and given that the indirect evidence clearly does not favour continued use of the category II regimen, carrying out randomized controlled trials to compare the outcomes of category II against another treatment regimen would be unethical.

This good practice statement should be adopted as a policy and patients should no longer receive a category II regimen.

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24 The regimen previously recommended by WHO for TB patients who require retreatment due to treatment interruption or recurrence of disease, namely: 2HRZES/1HRZE/5HRE or 2HRZES/1HRZE/5(HRE)₃.

There are several reasons why the category II regimen should no longer be used. With the advent of widespread drug-susceptibility testing, the standard of care is to perform a drug-susceptibility test on persons who have had treatment interruption or recurrence of disease and then to treat accordingly based on the patient's drug resistance profile. Not carrying out drug-susceptibility testing and instead empirically treating with the substandard category II regimen would create a situation of inequity in the treatment of different patients, delay proper treatment for drug-resistant TB (which fuels drug resistance and leads to worse outcomes for the drug-resistant TB patients and for the community) and, if patients have drug-susceptible disease, expose them unnecessarily to the toxicities of streptomycin.

One of the basic principles of TB treatment is that a single drug should not be added to an unsuccessful regimen. Adding streptomycin to the previously unsuccessful regimen of isoniazid, rifampicin, ethambutol and pyrazinamide violates this principle and fuels the development of drug resistance, leading to the loss of streptomycin as a second-line agent in MDR-TB therapy. Patients who have interrupted first-line TB treatment or have had recurrence of disease tend to have a higher risk of drug resistance than new TB patients. Using a category II regimen for these patients runs contrary to this basic treatment principle and will accelerate drug resistance.

The GDG expressed concern regarding treatment of patients with isoniazid mono-resistant TB. Xpert® MTB/RIF is the most common method for rifampicin drug-susceptibility testing but it lacks the ability to test for isoniazid resistance. Patients with isoniazid resistance are at higher risk of developing additional drug resistance. Providers must be vigilant about the possibility of isoniazid resistance and, if it is suspected, they must test for isoniazid susceptibility and treat accordingly, and a category II regimen should not be used. Further WHO guidance on treatment for patients with isoniazid mono-resistance, particularly addressing the use of fluoroquinolone, is in development.

Subgroup considerations

None

Implementation considerations

Patients eligible for retreatment should be referred for a rapid molecular test or drug-susceptibility testing to determine at least rifampicin resistance, and preferably also isoniazid resistance status.

On the basis of the drug susceptibility profile, a standard first-line treatment regimen (2HRZE/4HR) can be repeated if no resistance is documented; and if rifampicin resistance is present, an MDR-TB regimen should be prescribed according to WHO's recent drug-resistant TB treatment guidelines.

In patients who have had treatment interruption, the reason for the interruption, such as medication stock-outs, adverse effects from medicines or need for greater patient/provider education should be addressed.

Monitoring and evaluation

There are no additional recommendations beyond the standard of care.

2. Patient care and support

2.1. Cross-cutting interventions for drug-susceptible TB and drug-resistant TB: effectiveness of patient care and support interventions

> **Recommendations**
>
> *2.1.1 Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment (Strong recommendation, moderate certainty in the evidence)*
>
> *2.1.2 A package of treatment adherence interventions[25] may be offered to patients on TB treatment in conjunction with the selection of a suitable treatment administration option[26] (Conditional recommendation, low certainty in the evidence)*
>
> *2.1.3 One or more of the following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health-care providers:*
>
> *a) tracers[27] and/or digital medication monitor[28] (Conditional recommendation, very low certainty in the evidence)*
>
> *b) material support[29] to patient (Conditional recommendation, moderate certainty in the evidence)*
>
> *c) psychological support[30] to patient (Conditional recommendation, low certainty in the evidence)*
>
> *d) staff education[31] (Conditional recommendation, low certainty in the evidence).*

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25 Treatment adherence interventions include social support such as material support (e.g. food, financial incentives, transport fees), psychological support, tracers such as home visits or digital health communications (e.g. SMS, telephone calls), medication monitor, and staff education. The interventions should be selected based on the assessment of the individual patient's needs, provider's resources and conditions for implementation.

26 Treatment administration options include DOT, non-daily DOT, VOT, or unsupervised treatment.

27 Tracers refer to the communication with the patient, including home visits or via SMS, telephone (voice) call.

28 A digital medication monitor is a device that can measure the time between openings of the pill box. The medication monitor can have audio reminders or send SMS to remind patient to take medications along with recording when the pill box is opened.

29 Material support can be food or financial support: meals, food baskets, food supplements, food vouchers, transport subsidies, living allowance, housing incentives, or financial bonus. This support addresses indirect costs incurred by patients or their attendants in order to access health services and, possibly, tries to mitigate consequences of income loss related to the disease.

30 Psychological support can be counselling sessions or peer-group support.

31 Staff education can be adherence education, chart or visual reminder, educational tools and desktop aids for decision-making and reminder.

> ### Recommendations
>
> *2.1.4 The following treatment administration options may be offered to patients on TB treatment:*
>
> *a) Community- or home-based DOT is recommended over health facility-based DOT or unsupervised treatment (Conditional recommendation, moderate certainty in the evidence).*
>
> *b) DOT administered by trained lay providers or health-care workers is recommended over DOT administered by family members or unsupervised treatment (Conditional recommendation, very low certainty in the evidence).*
>
> *c) Video observed treatment (VOT) may replace DOT when the video communication technology is available and it can be appropriately organized and operated by health-care providers and patients (Conditional recommendation, very low certainty in the evidence).*

Justification

Treatment supervision

Currently WHO defines DOT as any person observing the patient taking medications in real time. The treatment observer does not need to be a health-care worker, but could be a friend, a relative or a lay person who works as a treatment supervisor or supporter. Observed treatment may also be achieved with real-time video observing and video recording. However, in this document, DOT refers to treatment administered under direct observation by another person. Video observation is referred to as video observed treatment (VOT).

Adherence definitions varied across the studies. However, in general adherence was defined as taking > 90% of medications under conditions of direct observation by another person.

The systematic review conducted in support of this guideline was based on synthesis of data from randomized controlled trials *(76-83)* and from observational studies *(84-97)* with preference given to the results of randomized controlled trials. Outcomes from DOT and self-administered treatment (SAT) given under standard TB practice and without any additional support were compared. DOT could be administered by a health-care worker, a family member or a community member and either at home, in the patient's community or at a clinic. DOT was generally administered daily. The GDG focused preferentially on randomized controlled trial data from the systematic review. When the data from randomized controlled trials were limited or not available, observational data were examined and their results were presented. Interpretation of the associations, however, needs caution due to limitations of the observational data when the associations are confounded by different factors. In uncontrolled observational studies, for instance, patients with more severe disease or higher risk of non-adherence are likely to be assigned DOT and less sick or less likely incompliant patients are assigned SAT. The same may apply to the selection of DOT location, DOT provider or other interventions in cohort studies.

When DOT alone was compared with SAT, patients who were on DOT had better rates of treatment success, adherence and 2-month sputum conversion; and also had slightly lower rates of loss to follow-up and acquired drug resistance. However, patients on DOT had a slightly higher relapse rate. The GDG considered that, overall, the evidence was inconsistent in showing clear advantages of DOT alone over SAT or vice versa. However, the evidence showed that some subgroups of patients (e.g. TB patients living with HIV) with factors affecting treatment adherence, are likely to benefit from DOT more than other patients; or specific types of DOT delivery (e.g. locations of DOT or DOT providers) are likely to work better than the others. The evidence also showed that when patients receiving treatment adherence interventions (e.g. different combinations of patient education, staff education, material support, psychological support, tracer and use of medication monitor) in conjunction with DOT or SAT, the treatment outcomes were significantly improved compared to DOT or SAT alone (see below).

Only cohort studies were available to examine DOT and SAT in HIV-positive TB patients (98-114), and many of these studies were conducted in the pre-ART era or shortly after the introduction of early ART for HIV-positive TB patients *(110–113)*. As above, DOT could have been administered by a variety of people in a variety of settings, including homes and clinics, and occasionally during initial intensive phase treatment it was hospital-based. A few studies provided incentives and enablers or provided DOT only for persons considered to be at higher risk of loss to follow-up. HIV-positive TB patients on SAT had lower rates of treatment success, treatment completion and cure. They had higher rates of mortality, treatment failure and loss to follow-up. The evidence showed that HIV-positive TB patients, as a subgroup, benefit more from DOT than general TB patients do, and that SAT alone is not advisable in HIV-positive TB patients. Reasons such as increased rates of drug-drug interactions and more severe disease in this cohort may cause DOT to offer a significant advantage over SAT.

DOT and SAT in MDR-TB patients were also examined in the systematic review. However, very limited data were available from a cohort study *(100)*. There were higher rates of mortality and non-adherence and lower rates of treatment completion in MDR-TB patients on SAT compared with those on DOT although the differences were not significant.

DOT provider

Randomized controlled trials *(78, 80-82)* and observational studies *(85, 86, 89, 91, 96, 99, 104, 106, 107, 109, 110, 114)* were available for examination of the effect of DOT providers versus SAT. Providers were grouped as health-care workers, lay providers and family members. The health-care worker group was varied and included personnel working at different levels of health-care systems and who had received health training. Health-care workers could be nurses, physicians or trained community health workers. Lay providers were also varied and could include teachers, community volunteers or traditional healers. DOT by lay provider had higher rates of treatment success and cure, and a slightly lower rate of loss to follow-up compared with SAT. However, in one cohort study there was a higher rate of treatment completion with SAT compared to DOT with lay providers. Patients receiving DOT from a family member had higher rates of treatment success and lower rates

of loss to follow-up compared with patients using SAT. When DOT provided by a health-care worker was compared to SAT, there were higher rates of cure and adherence and lower rates of relapse and acquisition of drug resistance with health-care worker DOT. However, there was a higher rate of treatment completion with SAT compared to health-care worker DOT in cohort studies.

The effect that different types of DOT provider had on outcomes was also examined. DOT provided by health-care workers and DOT provided by lay persons were compared. Only observational studies were available in the literature *(86, 89, 106, 116-120)*. There were no significant differences although slightly higher rates of success, and lower rates of mortality, failure and loss to follow-up were observed among patients who had DOT administered by a lay provider versus a health-care worker.

When provision of DOT by a family member was compared to health-care worker provision of DOT, there were higher rates of mortality, loss to follow-up and failure, and lower rates of successful treatment, cure and treatment adherence among patients who had DOT administered by family members. Therefore, although DOT by a health-care worker, trained lay provider and family member showed advantages compared to SAT, provision by trained lay providers and health-care workers are the preferred options for DOT and the least preferred DOT provider is a family member.

DOT location

Randomized control trials *(78, 80, 82, 96, 121-124)* and observational studies *(84, 91 104, 106, 109, 110, 125-158)* examined how DOT location affected treatment outcome. Locations were grouped by community- or home-based DOT and health facility-based DOT. Community- or home-based DOT was defined as DOT delivered in the community that is close to the patient's home or workplace. In general, community- or home-based DOT was provided close to the patients. Health facility-based DOT was defined as DOT delivered at a health centre, clinic or hospital. There were some instances of community- or home-based DOT being provided by health-care workers. When comparing DOT locations, community- or home-based DOT had higher rates of treatment success, cure, treatment completion and 2-month sputum conversion. Community or home-based DOT also had lower rates of mortality and lower rates of unfavorable outcomes compared with health facility-based DOT.

When comparing community/home-based DOT or health facility-based DOT with SAT, there were no significant differences across the outcomes in randomized controlled trials. However, cohort studies showed higher rates of treatment success and adherence, and a lower rate of loss to follow-up, with community/home-based DOT compared with SAT.

Observational data from cohort studies also showed lower rates of treatment completion, and slightly higher rates of failure and loss to follow-up in health-facility DOT compared to SAT.

Therefore, the community- or home-based DOT is the preferred option rather than health facility-based DOT and SAT.

Combining the evidence on DOT provider and DOT location, DOT should preferably be delivered at home or in the community and by a health-care worker or trained lay provider. DOT delivered at a health facility, DOT provided by a family member and unsupervised treatment are not preferable options.

Video observed treatment (VOT)

For VOT there were only two cohort studies from high-income countries and no data from low- and middle-income countries *(159, 160)*. These studies compared in-person DOT with VOT done in real time. Patients who were provided with VOT had no statistically significant difference in treatment completion and mortality compared to patients who had in-person DOT.

Although there is some concern as to the indirectness of evidence for VOT, given that the studies were conducted in high-income countries and the uncertainty of evidence surrounding the use of VOT, the results from the two cohort studies showed that in-person DOT was not better than VOT. DOT has been the standard of care that many programmes aim for, even if in practice they have to resort to SAT in many patients because of lack of resources. The advantages of using VOT are its potential to observe adherence to treatment from a distance – and even when people travel and cannot visit or be visited by a DOT provider. VOT is also more flexible to people's schedules by offering virtual observation at different times of the day. VOT could help achieve better levels of patient interaction at a much lower cost and less inconvenience when compared with in-person DOT. VOT can be used as an additional to, or interchangeable with, in-person DOT or other treatment administration options. For instance, it is not expected that a patient receives VOT as the sole option of supervision during the whole duration of treatment.

Furthermore, the technology required for VOT (broadband Internet and smartphone availability) is becoming increasingly available in resource-constrained settings. Moreover, VOT delivery options are evolving (e.g. enhanced possibility for real-time communication in addition to recorded video), and therefore evidence and best practices are likely to develop further in the coming years, especially from the ongoing randomized controlled trials. The benefits of VOT may become more apparent as programmes are able to choose forms of VOT that best meet their needs. In fact, VOT may be particularly useful for easing the burden on the health-care system in low- and middle-income countries.

Package of combined treatment adherence interventions

There were randomized controlled trials *(160-165)* and observational studies *(125-131, 166)* examining the effects of combined treatment adherence interventions. When patients receiving combined treatment adherence interventions along with DOT or SAT were compared to those receiving DOT or SAT alone, patients who received combined treatment adherence interventions had higher rates of treatment success, treatment completion, cure and adherence, and lower rates of mortality and loss to follow-up. The mixture of types of adherence interventions was varied (Table 3). These included different combinations of patient education, staff education, material support (e.g. food, financial incentives, transport fees, bonuses for reaching treatment goals), psychological support and counselling. The

treatment adherence interventions also included tracer such as home visits, use of digital health communication (e.g. SMS, telephone calls) or a medication monitor. The interventions should be selected on the basis of the assessment of individual patient's needs, providers' resources and conditions for implementation.

Table 3. Treatment adherence interventions

Treatment adherence intervention	Description
Patient education	Health education and counselling.
Staff education	Education, chart or visual reminder, educational tool and desktop aid for decision-making and reminder.
Material support	Food or financial support such as meals, food baskets, food supplements, food vouchers, transport subsidies, living allowance, housing incentives or financial bonus. This support addresses indirect costs incurred by patients or their attendants in accessing health services and, possibly, tries to mitigate the consequences of income loss related to the disease.
Psychological support	Counselling sessions or peer-group support.
Tracer	Communication with the patient, including home visit or via mobile telephone communication such as SMS or telephone (voice) call.
Digital medication monitor	A digital medication monitor is a device that can measure the time between openings of the pill box. The medication monitor can give audio reminders or send SMS to remind patient to take medications, along with recording when the pill box is opened.

Tracers and digital health interventions rather than VOT

Varied tracers were included in randomized controlled trials *(167-174)* and observational studies *(159, 160, 175-179)*. These interventions could include SMS, telephone calls or automated telephone reminders. For patients who missed appointments or failed to collect their medication received reminder letters or home visits by health-care workers. Medication monitors or computer systems in the clinic to aid health-care workers in tracing patients were also used. Medication monitors can measure the time between openings of the pill box, give audio reminders, record when the pill box is opened or sent SMS reminders to take medications.

There were higher rates of treatment success, treatment adherence and 2-month sputum conversion, and lower rates of mortality, loss to follow-up and drug resistance acquisition with tracers, either through home visits or mobile telephone communication (SMS or telephone call).

When mobile telephone interventions (SMS or telephone call) were examined separately, there were higher rates of treatment success, cure and 2-month sputum conversion and lower rates of treatment failure, loss to follow-up, poor adherence and unfavourable outcomes with mobile telephone reminders as opposed to no intervention.

Medication monitors had better rates of adherence and favourable outcomes, and combined interventions of SMS and medication monitors also showed better adherence compared to no intervention.

It should be noted, however, only a small number of studies were available for all digital health interventions. There was only one small randomized controlled trial *(168)* on which these data are based. With all the digital interventions and tracers, including VOT, patient support and the ability of patient to interact with health-care workers should be preserved. In fact, these interventions should be considered as tools to enable better communication with the health-care provider rather than as replacements for other adherence interventions. In practice, it is expected that SMS, telephone calls and VOT may replace in-person DOT for periods of time rather than for the entire duration and that they promote patient-centered approaches to care.

Mobile telephone interventions, tracers and VOT may also increase health equity if the need to travel to a health clinic or to a patient's home is reduced. However, the ability of patients to participate in these programmes depends on the patients living in an area with a good telecommunication infrastructure.

Material support for patients

The effects of material support were examined both with randomized controlled trials *(138-141)* and observational studies *(147, 180-187)*. The interventions included giving meals with DOT, monthly food vouchers, food baskets, food supplements and vitamins. Food support for patients and family members is an important incentive for TB patients and it also helps protect patients from the catastrophic costs associated with TB. Food may be an incentive but it may also improve outcome biologically due to reduction in malnutrition and consequent improvement in immune function. Other material support could be financial support in the form of financial incentives, transport subsidies, living allowance, housing incentives, or financial bonuses after reaching treatment targets.

There were higher rates of treatment success, completion, and sputum conversion with patients who received material support, and lower rates of treatment failure and loss to follow-up compared with patients who did not receive material support. It is of note that all of these studies were in low- and middle-income countries, so presumably these incentives were of significant value to the patients in these settings. However, the material support would be of significant value to TB patients even in higher-income countries, especially in countries that do not have a good social welfare system, as TB is a disease of poverty.

The studies in this review found that material support was usually given to the most vulnerable groups, and therefore health equity was presumably improved by this intervention. However, if these incentives are not applied equitably, health disparities may be increased. The distribution of material support is likely to depend on the country context and may have different effects within and between countries.

Patient education or educational counselling

Analysis of the benefit of patient education included randomized controlled trials *(133-136)* and observational studies *(144)*. Patients who received education or educational counselling had better rates of treatment success, treatment completion, cure and treatment adherence, and had lower rates of loss to follow-up. It should be noted in this case that "counselling"

refers to educational counselling and not psychological counselling. Patient education could include oral or written education via health-care workers or pharmacists. The education could be one-time at discharge from the intensive phase of therapy or at each presentation for follow-up care. The educational session might include only the health-care worker or it might involve the patients' social network and family members. It is important to make sure that education and counselling are done in a culturally appropriate manner. Additionally, specific marginalized populations may require special educational efforts.

Staff education

Staff education may include peer training, visual aids to help initiate conversations with patients, other tools to aid in decision-making and as reminders, and also the education of laboratory staff. This intervention was examined in both randomized controlled trials (137, 138, 187) and observational studies (189). There were higher rates of treatment success and slightly lower rates of mortality and loss to follow-up with staff education. With better staff education, treatment for patients is likely to improve and any stigma that health-care workers may hold towards patients would decrease, as health-care workers better understand TB disease and TB treatment.

Psychological support

Psychological support was varied and could include self-help groups, alcohol cessation counselling and TB clubs (125, 143, 190). Patients who had access to psychological support had higher rates of treatment completion and cure, as well as lower rates of treatment failure and loss to follow-up. However, the GDG had concerns about confounding in these studies due to the severity of illness in the groups receiving support. Additionally, allocation of patients to the support groups was not always randomized.

When considering this data, it should also be noted that psychological support types are very broad and may not be adequately represented in this review. To maximize health equity, psychological support should be targeted at the most marginalized populations.

Subgroup considerations

Although the reviewed evidence did not allow for conclusions about the advantages of DOT over SAT or vice versa for TB patients, in a subgroup analysis of TB patients living with HIV, DOT showed clear benefit with significantly improved treatment outcomes. It is likely that DOT may be not beneficial for all patients but that it is likely to have more benefit in certain subgroups of TB patients. Apart from HIV-positive TB patients, other factors or groups of patients that were more or less likely to result in treatment adherence and therefore require DOT were not examined in the scope of the systematic review.

Implementation considerations

Treatment adherence interventions

As treatment supervision alone is not likely to be sufficient to ensure good TB treatment outcomes, additional treatment adherence interventions need to be provided. Patient education should be provided to all patients on TB treatment. A package of the other

treatment adherence interventions also needs to be offered to patients on TB treatment. The interventions should be selected on the basis of an assessment of the individual patient's needs, provider's resources and conditions for implementation.

With regard to telephone or video-assisted interventions, there may be reluctance to use new technology, making implementation more difficult. There may be privacy concerns surrounding security of telephone data, so encryption and other measures to safeguard privacy will need to be considered. The feasibility of implementing these types of interventions depends on telecommunication infrastructure, telephone availability and connection costs. Multiple organizations have initiated programmes such as these, so TB programmes may find it helpful to collaborate and communicate with other medical service delivery programmes that have already set up infrastructure.

There may be reluctance on the part of implementers (e.g. national or local governments, health partners) to pay for incentives. Implementers may be more willing to pay for material support for smaller subgroups with particularly high risk (e.g. patients with MDR-TB). However, one of the components of the End TB Strategy *(191)* is to provide "social protection and poverty alleviation" for patients with TB. This publication specifically calls for measures to "alleviate the burden of income loss and non-medical costs of seeking and staying in care". Included in these suggested protections are social welfare payments, vouchers and food packages. The benefit of material support found in this review supports these components of the End TB Strategy *(191)*.

In order to distribute the material support, government and/or NGO infrastructure would need to be in place, including anti-fraud mechanisms (e.g. reliable unique personal identifiers) and appropriate accounting to ensure that incentives are distributed equitably and to the people who need them most. Countries should choose incentives that are the most appropriate for their situation.

Treatment administration

Community-based or home-based DOT has more advantages than health facility-based DOT while family members should not be the first or only option for administering DOT. DOT is better provided at home or in the community and by trained lay providers or health-care workers. There may be challenges in providing community- or home-based DOT by health-care workers because of the increased number of health-care workers required and the increased costs for staff time and daily travel to the community or patient's home. DOT provision in the community or at home by trained local lay persons is more feasible. A combination of lay provider and health-care worker for provision of community- or home-based DOT is also an option. Community-based or home-based DOT is more likely to be acceptable and accessible to patients than with other forms of DOT. However, stigma may continue to be an issue with community- or home -based DOT. Having a health-care worker coming regularly to a patient's house may be stigmatizing and the feeling of being "watched over" may be disempowering to patients. Other forms of DOT (e.g. administered by an emotionally supportive relative or close friend) may be more acceptable but may still be stigmatizing.

Given complex family social dynamics, family members may not always be the best people to supervise treatment and the suitability of such treatment adherence supervisors needs to be carefully analysed in each national or local context. If family members are providing DOT, careful identification and training of those persons is required. Additional supervision of local supporters or health-care workers is still needed, as family members cannot be depended on as the only option for care. Patients will continue to need social support, even if family members are providing DOT.

Assessment of potential risk factors for poor adherence must be taken into account by health-care workers at the start of treatment in order to decide which treatment administration option should be selected for the patient. Some groups of patients who are less likely to adhere to treatment may benefit more from DOT than others do. Another factor to consider when selecting treatment administration options is that some patients with inflexible work or family responsibilities may not be able to do DOT. Any option of treatment administration offered to a patient must also be provided in conjunction with proper medical care, including regular pick-up of TB drugs, consultations with a physician or other health-care workers when necessary, TB treatment that is free of charge, and provision to the patient of essential information on TB treatment.

Monitoring and evaluation

Programmes should attempt to measure whether the provision of incentives improves programme performance.

2.2. Model of care for drug-resistant TB: the benefits of treating MDR-TB patients within a decentralized compared to centralized model of care

Recommendation

A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment (Conditional recommendation, very low certainty in the evidence).

Justification

As the use of Xpert® MTB/RIF expands, more patients will be diagnosed and enrolled on MDR-TB treatment. Having treatment and care provided in decentralized health-care facilities is a practical approach to scale up treatment and care for patients who are eligible for MDR-TB treatment. Therefore, a systematic review of the treatment and care of bacteriologically confirmed or clinically diagnosed MDR-TB patients in decentralized versus centralized systems was conducted to gather evidence on whether the quality of treatment and care is likely to be compromised with a decentralized approach. Data from both randomized controlled trials and observational studies were analysed, the majority being from low- and middle-income countries *(190-200)*. The review provided additional value to the recommendation in the previous guidelines *(5)* on ambulatory over hospitalized models of care for MDR-TB patients where the evidence was examined only for treatment and care of patients outside or inside hospitals.

In the review, decentralized care was defined as care provided, in the local community where the patient lives, by non-specialized or peripheral health centres, by community health workers or nurses, non-specialized doctors, community volunteers or treatment supporters. Care could occur at local venues or at the patient's home or workplace. Treatment and care included DOT and patient support, plus injections during the intensive phase. In this group, a brief phase of hospitalization of less than one month was accepted for patients who were in need in the initial phase of treatment or when they had any treatment complications.

Centralized care was defined as inpatient treatment and care provided solely by specialized drug-resistant TB centres or teams for the duration of the intensive phase of therapy or until culture or smear conversion. Afterwards, patients could have received decentralized care. Centralized care was usually delivered by specialist doctors or nurses and could include centralized outpatient clinics (outpatient facilities located at or near the site of the centralized hospital).

Analysis of the data showed that treatment success and loss to follow-up improved with decentralized care versus centralized care. The risk of death and treatment failure showed minimal difference between patients undergoing decentralized care or centralized care. There were limited data on adverse reactions, adherence, acquired drug resistance and cost.

Both HIV-negative and HIV-positive persons were included in the reviewed studies; however, the studies did not stratify patients on the basis of HIV status.

There was some discussion regarding the quality of the data. The GDG expressed concerns that health-care workers may have selected for the centralized care groups the patients who they thought might have a worse prognosis. None of the studies controlled for this risk of bias.

Subgroup considerations

Decentralized care may not be appropriate for patients with severe TB disease, extremely infectious forms of the disease, serious co-morbidities or patients for which treatment adherence is a concern.

Measures to protect the safety of patients on MDR-TB regimens, especially those containing new or novel medicines, need to be maintained in the outpatient settings.

These recommendations for decentralized care should not preclude hospitalization if appropriate. This review did not include patients requiring surgical care.

Implementation considerations

National TB programmes should have standardized guidelines regarding which patients are eligible for decentralized care. Patient preference should be given a high value when choosing centralized or decentralized care.

Decentralized care for MDR-TB patients requires appropriate treatment supervision, patient education and social support, staff training, infection control practices and quality assurance. The optimal treatment supervision options and treatment adherence interventions recommended in section 2.1. should be considered for MDR-TB patients on decentralized care.

Several of the studies in the review addressed treatment costs. However, the cost estimates were found to vary widely and no concrete recommendations could be made on the basis of cost. The resource requirements are likely to vary because TB treatment programmes are highly variable, so costs for these programmes vary across different countries. The GDG raised several issues for TB programmes to consider. Although hospitalization is generally thought to be more expensive than outpatient care, the costs of good outpatient programmes can also be significant. Additionally, outpatient costs may vary significantly according to the services provided. A cost-saving measure to consider in decentralized care is that patients may be able to receive treatment faster. Financial benefits of decentralized care would include finding patients before they are very ill and require more medical care, while treating people before TB can be transmitted to contacts would be a public health benefit.

If a patient is living with a person from a high-risk group (i.e. HIV-positive or a young child), there may be complications in sending the patient home for treatment. However, the risk posed to these high-risk groups varies significantly, depending on whether the TB programme gives preventive treatment to high risk persons. Studies involving preventive therapy for MDR-TB therapy are ongoing.

An additional implementation issue to consider is that it may be illegal in some settings to treat MDR-TB patients in a decentralized setting, especially when the treatment involves injections. Such legal concerns need to be addressed.

Monitoring and evaluation

There are no monitoring and evaluation considerations beyond those outlined in WHO's "*WHO treatment guidelines for drug-resistant tuberculosis; 2016 update" (201), "The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance" (202)* and "*The use of delamanid in the treatment of multidrug-resistant tuberculosis: interim policy guidance" (203).*

Research priorities

The GDG discussed research priorities and highlighted a number of priorities.

1. *The effectiveness of 4-month fluoroquinolone-containing regimen when compared to the standard 6-month treatment regimen of 2HRZE/4HR in patients with drug-susceptible pulmonary TB disease*
    - Certain subgroups may do equally well with a 4-month fluoroquinolone-containing regimen (i.e. people with body mass index (BMI) greater than 18, people with non-severe, non-cavitary disease) *(204)*. Therefore further research to assess if a 4-month fluoroquinolone-containing regimen could be non-inferior to the standard regimen in these populations may be warranted.
    - The optimal dosing of fluoroquinolone needs to be determined. Higher doses may affect outcomes.
    - To determine why certain groups are more likely to do worse with a 4-month fluoroquinolone-containing regimen.
    - To explore biological mechanisms behind *Mycobacterium TB* persistence and the recurrence of disease despite more rapid culture conversion with certain regimens.
    - More qualitative research and systematic reviews are required on patient values and preferences with regard to TB treatment regimens.

2. *The effectiveness of fixed-dose combination TB treatment when compared to separate drug formulations in patients with drug-susceptible TB disease*
    - Additional research on the reasons why FDC formulations did not show a clear benefit over separate drug formulations.
    - Pharmacokinetic studies of the bioavailability of FDCs versus separate drug formulations and better development of weight banding categories for drug dosing.
    - The optimal dose of rifampicin, including the use of different drug formulations.
    - Additional qualitative studies detailing medication adherence.
    - Additional work on FDC formulations to further decrease the pill burden, especially among patients with co-morbidities.

3. *The effectiveness of intermittent dosing of TB medications, both in the intensive phase and in the continuation phase of treatment, when compared to daily treatment*
    - The utility and efficacy of 5 days of treatment per week versus 7 days of treatment per week in the intensive phase of therapy (i.e. sparing weekend dosing).
    - The optimal duration of the intensive phase of therapy.
    - Additional research on the benefit of thrice-weekly dosing in the continuation phase, as effect differences seen in this review between the thrice-weekly dosing in the continuation phase and daily dosing during the continuation phase are small.

4. *The effectiveness of a TB treatment period greater than 8 months compared to the standard 6-month treatment period for HIV co-infected patients with drug-susceptible pulmonary tuberculosis*
    - What are the factors that may cause people, especially people living with HIV, to not respond well to TB treatment (e.g. starting ART late, low CD4 cell counts, TB drug resistance, cumulative drug toxicity, drug–drug interaction with newer ARV drugs).
    - Explore and describe etiological factors leading to higher death rates and rates of adverse events in HIV-positive TB patients.

5. *The use of steroids in the treatment regimen of extrapulmonary TB disease*
    - The optimal steroid dose for TB meningitis (including different drug formulations).
    - The optimal steroid duration for TB meningitis, and if this duration differs between different grades of meningitis.
    - The different effects of steroids on people who are HIV-positive or HIV-negative, or who are being treated with ART or not.
    - The relationship between steroid treatment and cancer risk – with reference to the Mayosi et al. study on pericarditis *(46)*.

6. *The effectiveness of different forms of interventions to improve treatment adherence*
    - The patient support and treatment supervision interventions that are best suited to particular populations.
    - The patient support interventions that are most effective in low- and middle-income countries.
    - Analysis of the cost-effectiveness of different types of incentives.
    - Research into the effectiveness of VOT in low- and middle-income countries, as the available data is from high income countries.
    - Which types of psychological support are most appropriate.

7. *The benefits of treating MDR-TB patients within a decentralized compared to centralized model of care*
    - Evaluating the risk of TB transmission in different settings – i.e. does treatment centered on hospital care or outpatient clinics pose a higher risk of transmission?
    - Additional cost-effectiveness studies of decentralized versus centralized care.
    - Many programmes are providing decentralized care, but very few have published the data. Programmes should be encouraged to publish or even just systematically collect their data.

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Annexes

Annex 1: Experts involved in the development of the guidelines

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3	Riitta Dlodlo	International Union Against Tuberculosis and Lung Disease. France	Technical agency/ programme implementation
4	Celine Garfin	Ministry of Health Philippines	National programme/end-user
5	Mirtha del Granado	WHO Americas Regional Office	WHO
6	Daniel Kibuga	WHO Africa Regional Office	WHO
7	Md Khurshid Alam Hyder	WHO South-East Asia Regional Office	WHO
8	Vaira Leimane	Riga East University Hospital, Centre of Tuberculosis and Lung Diseases. Latvia	Clinician/end-user
9	Nobuyuki Nishikiori	WHO Western Pacific Regional Office	WHO
10	Lee Reichman	Rutgers New Jersey Medical School. The United States	Clinician/end-user
11	Rohit Sarin	National Institute of TB & Respiratory Diseases, Ministry of Health India	National programme/end-user
12	Dalene von Delft	TB Proof South Africa	Patient representative
13	Fraser Wares	Royal Dutch Tuberculosis Foundation (KNCV). The Netherlands	Technical agency/ programme implementation

Annex 2. PICO questions

1. **In new TB patients, is a less than 6-month fluoroquinolone-containing treatment regimen as effective as the standard 6-month treatment regimen (2HRZE/4HR)?**

Population	Intervention	Comparator	Outcomes

TB patients:
• New
• HIV co-infected
• Children
	First-line oral agents plus moxifloxacin or plus gatifloxacin or plus levofloxacin	Regimen 2HRZE/4HR (isoniazid plus rifampicin plus pyrazinamide plus ethambutol in 2 months of the intensive phase; and isoniazid plus rifampicin in 4 months of the continuation phase)	• Cure or treatment completion
			• Treatment failure
			• Disease relapse
			• Time to sputum culture or smear conversion
			• Clinical or radiological improvement at 8 weeks and at the end of treatment
			• Death
			• Drug adverse events:
			  » Serious adverse events
			  » Adverse effects associated with fluoroquinolones

2. **In patients with active TB, is the use of fixed-dose combination (FDC) formulations as effective as the use of separate drug formulations?**

Population	Intervention 2HRZE/4HR (FDC)	Comparator 2HRZE/4HR (no FDC)	Outcomes
Pulmonary tuberculosis patients treated with first-line drugs (2HRZE/4HR)	FDC formulation with isoniazid plus rifampicin plus pyrazinamide plus ethambutol	Separate drug formulation: isoniazid, rifampicin, pyrazinamide and ethambutol	• Cure or completion of treatment • Treatment failure or disease relapse • Death • Smear conversion after 2 months of treatment • Acquired drug resistance • Adverse drug reaction • Patient adherence and satisfaction

3. Does intermittent dosing in the intensive phase have outcomes similar to daily dosing in the intensive phase for treatment of drug-susceptible pulmonary tuberculosis?

Population	Intervention	Comparator	Outcomes
Pulmonary tuberculosis patients on intensive phase of treatment for drug-susceptible TB	3-times-weekly dosing of drugs throughout duration of treatment	Daily dosing of drugs throughout duration of treatment	• Cure or treatment completion • Treatment failure • Disease relapse • Death • Acquired drug resistance among patients who failed or relapsed

4. Does intermittent dosing in the continuation phase have outcomes similar to daily dosing in the continuation phase in patients with drug-susceptible pulmonary tuberculosis patients?

Population	Intervention	Comparator	Outcomes
Pulmonary tuberculosis patients on continuation phase of treatment for drug-susceptible TB	3-times-weekly dosing of drugs throughout duration of treatment	Daily dosing of drugs throughout duration of treatment	• Cure or treatment completion • Treatment failure • Disease relapse • Death • Acquired drug resistance among patients who failed or relapsed

5. Does initiation of antiretroviral therapy (ART) during tuberculosis treatment, compared to initiation at the end of tuberculosis treatment, improve outcomes among tuberculosis patients co-infected with HIV?

Population	Intervention	Comparator	Outcomes
Pulmonary tuberculosis patients co-infected with HIV	Early initiation of ART	Late initiation of ART	• IRIS • Mortality • AIDS-defining illness or death • Treatment success • Treatment completion • Disease relapse • Drug adverse effects

6. Does extending treatment beyond 6 months improve outcomes compared to the standard 6-month treatment regimen among pulmonary tuberculosis patients co-infected with HIV?

Population	Intervention	Comparator	Outcomes
Pulmonary tuberculosis patients co-infected with HIV	6 months of rifampicin-containing regimen	8 months or longer of rifampicin-containing regimen	• Treatment failure • Disease relapse • Death

7. Does the use of adjuvant corticosteroids in tuberculous pericarditis provide mortality and morbidity benefits?

Population	Intervention	Comparator	Outcomes
Patients with tuberculous pericarditis	First-line oral agents plus systemic corticosteroid therapy	First-line oral agents plus placebo	• Death • Adherence • Constrictive pericarditis

8. Does the use of adjuvant corticosteroids in tuberculous meningitis provide mortality and morbidity benefits?

Population	Intervention	Comparator	Outcomes
Patients with tuberculous meningitis	First-line oral agents plus systemic corticosteroid therapy	First-line oral agents plus placebo	• Cure or treatment completion • Survival • Staying disease-free after treatment; sustaining a cure • Acquisition or amplification of drug resistance • Smear or culture conversion during treatment • Drug adverse events

9. For patients with a previous history of treatment with first-line anti-TB drugs being considered for re-treatment (due to treatment interruption or recurrence) in the absence of isoniazid or rifampicin resistance testing, does empiric re-treatment with five first-line drugs HRZES (WHO category II regimen) lead to acceptable outcomes?

Population	Intervention	Comparator	Outcomes
Patients with active tuberculosis and a previous history of treatment with first-line anti-TB drugs who have interrupted treatment or have a recurrent disease and are therefore in need of re-treatment	Four first-line oral drugs plus streptomycin injectable[32]	No comparator is available. No randomized controlled trials are available for this evaluation; only observational studies (cohort analyses of re-treatment cases) are available	• Cure or treatment completion • Survival • Staying disease-free after treatment; sustaining a cure • Acquisition or amplification of drug resistance • Smear or culture conversion during treatment • Drug adverse events

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32 The intervention (known as category II regimen) was recommended in the previous WHO TB treatment guideline for TB patients who adjure re-treatment due to treatment interruption or recurrence of disease. 2HRZES/1HRZE/5HRE or 2HRZES/1HRZE/5(HRE)₃

10. In patients with TB, are any interventions to promote adherence to TB treatment more or less likely to lead to the outcomes listed below?

Population	Intervention	Comparator	Outcome
- Patients on treatment for drug-susceptible TB - Patients on treatment for MDR-TB - Children (0-14 years) and adults - HIV-infected and HIV-uninfected TB patients	Any intervention to promote treatment adherence - Supervision of treatment (DOT, virtual (video) observed therapy) - Measures to improve treatment adherence (e.g. medication monitors and/or SMS or telephone call reminders) - Social support (educational, psychological, material) - Combinations of the above interventions	Routine practice[33]	- Adherence to treatment (or treatment interruption due to non-adherence) - Conventional TB treatment outcomes: cure or treatment completion, failure, relapse, survival/death - Adverse reactions from TB drugs (severity, type, organ class) - Cost to the patient (including direct medical costs as well as others such as transportation, lost wages due to disability) - Cost to health services

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33 Routine practice: regular TB drugs pick-up and consultations with physician or other health-care workers are available when necessary; TB treatment is free of charge; essential information/health education in relation to TB treatment is provided.

11. Is decentralized treatment and care for MDR-TB patients more or less likely to lead to the outcomes listed below?

Population	Intervention	Comparator	Outcome
Patients on treatment for MDR-TB	Decentralized treatment and care (provided by non-specialized or periphery health centres; by community health workers, community volunteers or treatment supporters) • DOT and patient support • Injection during the intensive phase • Specialist care for co-morbidities (e.g. HIV, diabetes, chronic lung diseases, or other conditions such as auditory function, renal function, liver function, neurology, ophthalmology)	Treatment and care provided solely by specialized drug-resistant TB centres or teams	• Adherence to treatment (or treatment interruption due to non-adherence) • Conventional TB treatment outcomes: cure or treatment completion, failure, relapse, survival/death • Adverse reactions from TB drugs (severity, type, organ class) • Acquisition (amplification) of drug resistance • Cost to the patient (including direct medical costs as well as others such as transportation, lost wages due to disability) • Cost to health services

Annex 3. GRADE evidence profiles

Annex 4. Evidence-to-decision tables

Annex 5. Reports of the systematic reviews

Are available on the Internet at:
http://www.who.int/tb/publications/
2017/dstb_guidance_2017/en/

World Health Organization