American Thoracic Society / Centers for Disease Control / Infectious Diseases Society of America Clinical Practice Guidelines:

Treatment of Drug-Susceptible Tuberculosis

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On behalf of the writing committee

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

AMERICAN THORACIC SOCIETY · 1905 · ATS®

IDSA

ERS EUROPEAN RESPIRATORY SOCIETY

National Tuberculosis Controllers Association


WHERE THE RUBBER MEETS THE ROAD:
Key changes in the ATS/CDC/IDSA TB treatment guidelines and some thoughts on their implementation

Clinical Infectious Diseases

IDSA GUIDELINE

Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis

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The American Thoracic Society, Centers for Disease Control and Prevention, and Infectious Diseases Society of America jointly sponsored the development of this guideline for the treatment of drug-susceptible tuberculosis, which is also endorsed by the European Respiratory Society and the US National Tuberculosis Controllers Association. Representatives from the American Academy of Pediatrics, the Canadian Thoracic Society, the International Union Against Tuberculosis and Lung Disease, and the World Health Organization also participated in the development of the guideline. This guideline provides recommendations on the clinical and public health management of tuberculosis in children and adults in settings in which mycobacterial cultures, molecular and phenotypic drug susceptibility tests, and radiographic studies, among other diagnostic tools, are available on a routine basis. For all recommendations, literature reviews were performed, followed by discussion by an expert committee according to the Grading of Recommendations, Assessment, Development and Evaluation methodology. Given the public health implications of prompt diagnosis and effective management of tuberculosis, empiric multidrug treatment is initiated in almost all situations in which active tuberculosis is suspected. Additional characteristics such as presence of comorbidities, severity of disease, and response to treatment influence management decisions. Specific recommendations on the use of case management strategies (including directly observed therapy), regimen and dosing selection in adults and children (daily vs intermittent), treatment of tuberculosis in the presence of HIV infection (duration of tuberculosis treatment and timing of initiation of antiretroviral therapy), as well as treatment of extrapulmonary disease (central nervous system, pericardial among other sites) are provided. The development of more potent and better-tolerated drug regimens, optimization of drug exposure for the component drugs, optimal management of tuberculosis in special populations, identification of accurate biomarkers of treatment effect, and the assessment of new strategies for implementing regimens in the field remain key priority areas for research. See the full-text online version of the document for detailed discussion of the management of tuberculosis and recommendations for practice.

Keywords. *Mycobacterium tuberculosis*; HIV infections; antitubercular agents; case management; public health.

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Treatment of Drug-Susceptible Tuberculosis
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Treatment of Drug-Susceptible Tuberculosis
Writing Committee Leadership and GRADE Methodology Group

- **Chairs:**, Payam Nahid (ATS), Susan Dorman (IDSA), GB Migliori (ERS), Andrew Vernon (CDC)

- **GRADE Methodology Group:** Narges Alipanah, Jan Brozek, Adithya Cattamanchi, Lelia Chaisson, Richard Menzies, Payam Nahid, Giovanni Sotgiu

Disclosures

- N. Alipanah, J. Brozek, A. Cattamanchi, L. Chaisson, S. Dorman, M. Grzemska, J. Higashi, C. Ho, P. Hopewell, S. Keshavjee, C. Lienhardt, C. Merrifield, R. Menzies, G. Migliori, M. Narita, P. Nahid, R. O'Brien, A. Raftery, G. Sotgui, J. Saukkonen, and S. Schaaf - **all reported that they had no relevant commercial interests.**
- P. Barry relative previously owned stocks or options of Merck.
- R. Chaisson consultant and ownership of stocks or options for Merck.
- C. Daley received research support from Insmed and served on data and safety monitoring boards of Otsuka America Pharmaceutical and Sanofi Pasteur.
- C. Peloquin received research support from Jacobus Pharmaceuticals.
- J. Starke reported service on a data safety and monitoring board of Otsuka Pharmaceuticals.
- A. Vernon reported serving as the chief of a US Centers for Disease Control and Prevention clinical research branch doing clinical trials in tuberculosis. collaborates with pharmaceutical companies, that may provide support such as drug supplies or laboratory funding for pharmacokinetic studies.

American Thoracic Society / Centers for Disease Control / Infectious Diseases Society of America Clinical Practice Guidelines:

Treatment of Drug-Susceptible Tuberculosis

Applies to settings in which mycobacterial cultures, molecular and phenotypic drug susceptibility tests, and radiographic studies, among other diagnostic tools, **are available on a routine basis.**

Approach

1. Panel composed
2. Prioritized topics for PICO questions
3. Formulated PICO questions
4. Methodologists prepared evidence profiles for each question using the GRADE approach and the GRADEpro GDT web-based tool to summarize and present information
5. Assessed risk of bias at the outcome level using Cochrane Collaboration's tool
6. assessed certainty of the evidence (i.e. confidence that the estimated effects are true) using GRADE based on
   - Risk of bias, precision, consistency and magnitude of estimates of effects, directness of evidence, risk of publications bias, presence of dose-effect relationship, effect of residual opposing confounding
   - Categorized into 4 levels (very low, low, medium, high)
7. Prepared evidence profiles that described summary of findings and quality of evidence
8. Prepared evidence-to-decision tables that described the estimates of health effects, values and preferences, and resource use.
9. Guideline panel used 7 and 8 to formulate recommendations

GRADE METHODOLOGY (Grading of Recommendations Assessment, Development, and Evaluation)

Recommendations based on the certainty in the evidence assessed according to the GRADE methodology to address PICO questions, incorporating patient values and costs as well as judgments about tradeoffs between benefits and harms.

PICO = Population, Intervention, Comparison, Outcome

Table 1. Interpretation of "Strong" and "Conditional" Grading of Recommendations Assessment, Development, and Evaluation-Based Recommendations

Implications for:	Strong Recommendation	Conditional Recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
Policy	The recommendation can be adopted as policy in most situations.	Policymaking will require substantial debate and involvement of various stakeholders.

Source: Grading of Recommendations Assessment, Development and Evaluation Working Group [1, 2].

Example of Evidence Profile

Quality assessment							Events / № of patients Pooled estimate		Effect		Certainty in the Evidence	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Early	Late ART	Relative (95% CI)	Absolute (95% CI)		
IRIS	PICO: Does initiation of ART during TB tx compared to at the end of tx improve outcomes among TB pts with HIV?											
8 [a,b,c,d,e,f,g,h]	randomized trials	not serious	serious [1]	not serious	not serious	strong association	371/2416 (15.4%)	195/2173 (9.0%)	**RR 1.88 (1.31 to 2.69)**	79 more per 1000 (from 28 more to 152 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Mortality												
8 [a,b,c,d,e,f,g,h]	randomized trials	not serious	not serious	not serious	not serious	none	175/2349 (7.4%)	207/2041 (10.1%)	**RR 0.76 (0.57 to 1.01)**	24 fewer per 1000 (from 1 more to 44 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
AIDS-defining illness or death												
4 [a,c,d,h]	randomized trials	not serious	not serious	not serious	not serious	strong association	121/1136 (10.7%)	141/891 (15.8%)	**RR 0.66 (0.47 to 0.91)**	54 fewer per 1000 (from 14 fewer to 84 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Treatment success												
4 [a,b,d,h]	randomized trials	not serious	not serious	not serious	not serious	none	857/1039 (82.5%)	653/811 (80.5%)	**RR 1.02 (0.98 to 1.07)**	16 more per 1000 (from 16 fewer to 56 more)	⨁⨁⨁⨁ HIGH	CRITICAL
Grade 3-4 adverse event												
5 [a,c,d,e,f]	randomized trials	not serious	not serious	not serious	not serious	none	597/1961 (30.4%)	561/1747 (32.1%)	**RR 0.95 (0.87 to 1.04)**	16 fewer per 1000 (from 13 more to 42 fewer)	⨁⨁⨁⨁ HIGH	CRITICAL
Relapse												
4 [b,e,h,i]	randomized trials	not serious	not serious	not serious	very serious [2]	none	31/1268 (2.4%)	30/1237 (2.4%)	**RR 0.97 (0.52 to 1.83)**	1 fewer per 1000 (from 12 fewer to 20 more)	⨁⨁◯◯ LOW	IMPORTANT

The end result

- Executive summary (13 pages)
- Complete text (27 pages)
- Appendix A: Methods
- Appendix B: GRADE Evidence Profiles
- Appendix C: Drugs in Current Use

Strived to incorporate the required methodologic rigor (centered around circumscribed PICO questions) in a document that included foundational principles of TB treatment as well as important practical clinical information, and was approachable/easy to read.

2016 ATS/CDC/IDSA TB Guidelines Key Changes/Updates from 2003 edition

- Early initiation of ART in HIV/TB patients
- Duration of TB treatment in HIV w/o ART extended
- Evidence base for intermittent therapy reviewed
  - Once weekly regimen NOT recommended
- Evidence base for case management (patient education, incentives, enablers, DOT) reviewed
- TB treatment in pregnancy, language updated for PZA
- Steroids not routinely recommended for TB pericarditis

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Nahid, et al., Clin Infect Dis. Oct 2016

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PICO 6. Does initiation of anti-retroviral therapy during TB treatment compared to at the end of TB treatment improve outcomes among TB patients co-infected with HIV?

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Recommendation: We recommend initiating antiretroviral therapy during tuberculosis treatment.

By 8-12 weeks of tuberculosis treatment initiation for patients with CD4 cell counts ≥50/mm^3

Within the first 2 weeks of tuberculosis treatment for patients with CD4 cell counts <50/mm^3 *

(Strong recommendation / High certainty in the evidence).

***Note: an exception is patients with HIV infection and tuberculous meningitis**

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PICO 5. Does extending treatment beyond 6 months improve outcomes compared to the standard 6-month regimen among tuberculosis patients co-infected with HIV?

PICO 5. Does extending treatment beyond 6 months improve outcomes compared to the standard 6-month regimen among tuberculosis patients co-infected with HIV?

Recommendation (a): For **HIV-infected patients receiving antiretroviral therapy**, we suggest using the standard 6-month daily regimen *(Conditional recommendation / Very low certainty in the evidence).*

Recommendation (b): In **uncommon situations** in which HIV-infected patients do NOT receive antiretroviral therapy during tuberculosis treatment, we suggest extending the continuation phase to 7 months in duration, corresponding to a total of 9 months of therapy *(Conditional recommendation / Very low certainty in the evidence).*

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Systematic review of published trials of adults with PTB treated with 6-month rifamycin-containing regimens of varying dosing schedule: odds of relapse relative to daily regimens:

INTENSIVE PHASE	CONTINUATION PHASE	OR	95% CI
Daily	3 times per week	1.6	0.6-4.1
Daily	2 times per week	2.8	1.3-6.1
3 times per week	3 times per week	2.8	1.4-5.7
Daily	Once weekly RPT	5.0	2.5-10.5
3 times per week	Once weekly RPT	7.1	3.3-15.3

Overall dose-response relationship

In the presence of cavitation, only the following attained best-estimate relapse risk <5%:

- Daily x 6 months
- Daily intensive phase plus 3 times per week continuation phase

PICO 3: Does intermittent dosing in the *intensive* phase have similar outcomes compared to daily dosing in the *intensive* phase?

(in other words…) Should tuberculosis medications be dosed daily or intermittently in the intensive phase of treatment?

PICO 3: Does intermittent dosing in the *intensive* phase have similar outcomes compared to daily dosing in the *intensive* phase?

(in other words…) Should tuberculosis medications be dosed daily or intermittently in the intensive phase of treatment?

Recommendation 3a: We recommend the use of daily rather than intermittent dosing in the intensive phase of therapy for drug-susceptible pulmonary tuberculosis *(Strong recommendation / Moderate certainty in the evidence)*

Recommendation 3b: Use of thrice-weekly therapy in the intensive phase may be considered in patients who are not HIV infected and are also at low risk of relapse (noncavitary and/or smear-negative at start of treatment) *(Conditional recommendation / Low certainty in the evidence)*

Recommendation 3c: In situations where daily or thrice-weekly DOT therapy is difficult to achieve, use of twice-weekly therapy after an initial 2 weeks of daily therapy may be considered for patients who are not HIV infected and are also at low risk of relapse *(Conditional recommendation / Very low certainty in the evidence)*

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PICO 4. Does intermittent dosing in *continuation* phase have similar outcomes compared to daily dosing in *continuation* phase?

(In other words…) Should tuberculosis medications be dosed daily or intermittently in the continuation phase of treatment?

PICO 4. Does intermittent dosing in *continuation* phase have similar outcomes compared to daily dosing in *continuation* phase?

(In other words…) Should tuberculosis medications be dosed daily or intermittently in the continuation phase of treatment?

Recommendation 4a: We recommend the use of daily or three times weekly dosing in the continuation phase of therapy for drug-susceptible pulmonary tuberculosis (Strong recommendation / Moderate certainty in the evidence).

Recommendation 4c: We recommend against the use of once-weekly INH900/RPT600 mg in continuation phase (Strong recommendation / High certainty in the evidence)

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PICO 1. Does adding case management interventions to curative therapy improve outcomes compared to curative therapy alone?

In other words, should case management be provided to patients receiving curative tuberculosis therapy to improve outcomes?

*Case management: patient education/counseling, field/home visits, integration/coordination of care with specialists and medical home, patient reminders, incentives/enablers.

Recommendation 1: We suggest using case management interventions during treatment of patients with tuberculosis. (Conditional recommendation/low certainty in the evidence)

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PZA in pregnancy

- H, R, E, Z previously all classified as 'C'
  - C: "animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks"
  - 2003 US TB guidelines: "PZA can probably be used safely during pregnancy"
    - But most programs did not use PZA during pregnancy
  - WHO recommends use of PZA (standard tx) during pregnancy
  - 2016 TB guidelines:

"We suggest that clinicians evaluate the risks and benefits on a case-by-case basis…" [discuss with patient]

"Potential benefits warrant use of the drug in pregnant women despite potential risks."

"Expert opinion is that in pregnant women with TB/HIV, extrapulm TB, or severe TB, it is more beneficial to include PZA in the regimen than to not include PZA"

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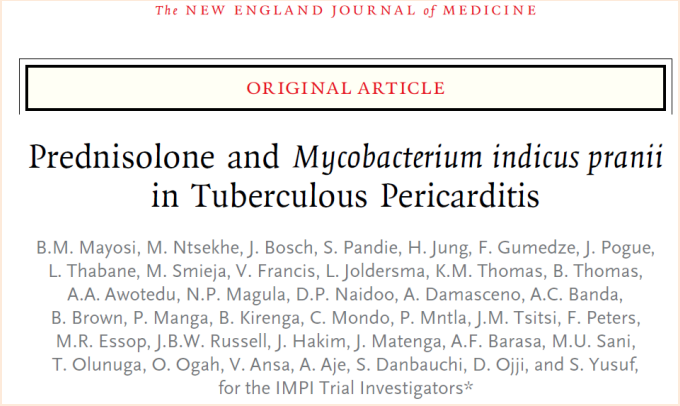
PICO 7. Does the use of adjuvant corticosteroids in tuberculous **pericarditis** provide mortality and morbidity benefits?

Recommendation 7: We suggest initial adjunctive corticosteroid therapy not be routinely used in patients with tuberculous pericarditis *(Conditional recommendation / Very low certainty in the evidence).* "However, selective use of corticosteroids in patients who are at highest risk for inflammatory conditions might be appropriate. Such patients might include those with large pericardial effusions, those with high levels of inflammatory cells or markers in pericardial fluid, or those with early signs of constriction."



NEJM 2014;371:1121

What do the guidelines have to say about fluoroquinolones for DS-TB?

- “In scenarios in which EMB or INH cannot be used, the role of moxifloxacin or levofloxacin has not been established through clinical trials. Experts on occasion use moxifloxacin or levofloxacin in place of EMB during IP in adults in whom EMB cannot be used, or in place of INH throughout treatment in adults in whom INH cannot be used.”
- “There is no evidence that moxifloxacin or levofloxacin can be used in place of a rifamycin or PZA while maintaining a 6-month treatment duration.”
- “There is definitive trial evidence that 4-month daily regimens that substitute moxifloxacin or gatifloxacin for EMB, or moxifloxacin for INH, are significantly less effective [than the standard daily 6-month regimen].”

What do the guidelines have to say about fluoroquinolones for DS-TB?

- A single randomized trial showed that daily MRZE for 2 months then weekly P(1200mg)M had relapse rates similar to standard regimen given daily for 6 months. Use of this regimen (including daily moxifloxacin-containing intensive phase) may be considered. It is important to note that each dose of RPT was preceded by a meal of 2 boiled eggs and bread to increase absorption of RPT. If this regimen used, it is ideally implemented within the context of program-based operational research with suitable monitoring. Of note, there is no evidence that a once-weekly P(1200mg)M regimen after 2 months of HRZE intensive phase would achieve similar outcomes.

Thank you

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- ATS Documents Editor **Kevin Wilson** and GRADE Methodologist **Jan Brozek**
- **Reviewers:** ATS, IDSA, CDC, NTCA, ERS, ACET (>350 reviewer comments)
- **Community Research Advisors Group of the CDC-TBTC and Treatment Action Group**
- **Writing Committee Members who persisted through innumerable revisions and questions:** Narges Alipanah, Pennan Barry, Adithya Cattamanchi, Lelia Chaisson, Richard Chaisson, Charles L. Daley, Malgosia Grzemska, Julie Higashi, Christine Ho, Philip Hopewell, Salmaan Keshavjee, Christian Lienhardt, Richard Menzies, Cynthia Merrifield, Masahiro Narita, Rick O'Brien, Charles Peloquin, Ann Raftery, Jussi Saukkonen, Simon Schaaf, Giovanni Sotgiu, Jeffrey Starke.
- **Pahim Nahid (ATS), Susan Dorman (IDSA), GB Migliori (ERS), Andrew Vernon (CDC)**

Extra Slides

Treatment of Drug-Susceptible Tuberculosis Guideline Contents

1. **ORGANIZATION AND SUPERVISION OF TREATMENT**
   - Patient-Centered Care and Case Management
   - Ensuring Adherence and Treatment Success
2. **RECOMMENDED TREATMENT REGIMENS**
   - Deciding to initiate treatment
   - Preferred Regimens
   - Alternative regimens
   - patients at increased risk of relapse
   - Interruptions in therapy

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Treatment of Drug-Susceptible Tuberculosis
Guideline Contents

3. TREATMENT IN SPECIAL SITUATIONS

- HIV infection
- Children
- Pregnancy and breastfeeding
- Renal Disease
- Hepatic disease
- Anti-TNF drugs
- diabetes
- Advanced age
- Lymph node tuberculosis
- Bone, joint and spinal tuberculosis
- Pericardial tuberculosis
- Pleural tuberculosis
- Tuberculous meningitis
- Disseminated tuberculosis
- Genitourinary tuberculosis
- Abdominal tuberculosis
- Culture-negative pulmonary tuberculosis

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4. PRACTICAL ASPECTS OF TREATMENT

- Management of Common Adverse Effects
- Drug-Drug Interactions
- Therapeutic drug monitoring

4. RECURRENT TUBERCULOSIS, TREATMENT FAILURE, AND DRUG RESISTANCE

- Recurrent Tuberculosis
- Poor Treatment Response and Treatment Failure, including brief overview of drug resistance.

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Treatment of Drug-Susceptible Tuberculosis
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6. RESEARCH AGENDA FOR TUBERCULOSIS TREATMENT

- New antituberculosis drugs and regimens
- Biomarkers of treatment effect and individualization of therapy
- Treatment of tuberculosis in special situations
- Implementation research

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2. Does self administration (SAT) of medications have similar outcomes compared to directly observed therapy (DOT) in patients tuberculosis?

Quality assessment							Events / № of patients Pooled estimate		Effect		Certainty in the Evidence	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SAT	DOT	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: range 6-9 months)												
4 [a,b,c,d]	randomized trials	serious [1]	not serious	not serious	very serious [2]	none	25/689 (3.6%)	42/914 (4.6%)	**RR 0.73 (0.45 to 1.19)**	12 fewer per 1000 (from 9 more to 25 fewer)	⨁◯◯◯ VERY LOW	CRITICAL
Treatment success (follow up: range 6-9 months)												
5 [a,b,c,d,e]	randomized trials	serious [3]	not serious	not serious	not serious	none	566/775 (73.0%)	747/1001 (74.6%)	**RR 0.94 (0.89 to 0.98)**	45 fewer per 1000 (from 15 fewer to 82 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Treatment completion (follow up: range 6-9 months)												
4 [a,b,c,d]	randomized trials	serious [1]	not serious	not serious	not serious [2]	none	56/689 (8.1%)	76/914 (8.3%)	**RR 0.97 (0.69 to 1.36)**	2 fewer per 1000 (from 26 fewer to 30 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Relapse (follow up: 24 months; assessed with: two or > cultures + in a 2-month period)												
1 [f]	randomized trials	serious [4]	not serious	not serious	very serious [2]	none	15/290 (5.2%)	23/259 (8.9%)	**RR 0.58 (0.31 to 1.09)**	37 fewer per 1000 (from 8 more to 61 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
Adherence (follow up: range 6 or more months)												
1 [e]	randomized trials	serious [5]	not serious	not serious	serious [2]	none	78/86 (90.7%)	84/87 (96.6%)	**RR 0.94 (0.87 to 1.02)**	58 fewer per 1000 (from 19 more to 126 fewer)	⨁⨁◯◯ LOW	IMPORTANT
Time to smear conversion (follow up: mean 6 months) [r]												

2. Does self administration (SAT) of medications have similar outcomes compared to directly observed therapy (DOT) in patients tuberculosis?

Recommendation 2: We suggest using DOT rather than SAT for routine treatment of patients with all forms of tuberculosis. (Conditional recommendation/low certainty in the evidence)

5. Does initiation of anti-retroviral therapy during tuberculosis treatment compared to at the end of tuberculosis treatment improve outcomes among tuberculosis patients co-infected with HIV?

Quality assessment							Summary of Findings				Certainty in the evidence	Importance
							Events/No patients Pooled estimate 95% CI		Estimate			
No of Treatment arms	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	6 months	>8 months	Relative (95% CI)	Absolute (95% CI)		
Failure												
47 [a]	randomized trials & observational	serious [1,2]	serious [3]	not serious	not serious	Possible reporting bias.	55/1620 2.6% (1.2 to 4.0)	29/658 2.7% (0.5 to 5.0)	**RR 0.8** (0.4 to 1.5)	1 fewer per 1000 (from 38 fewer to 25 more)	⨁ VERY LOW	CRITICAL
Relapse												
27 [a]	randomized trials & observational	serious [1,2]	serious [3]	not serious	not serious	Possible reporting bias. Dose response [4]	119/830 9.1% (0.4 to 17.8)	29/425 4.7% (0 to 11.2)	**RR 2.4** (1.2 to 5.0)	44 more per 1000 (from 15 more to 170 more)	⨁ VERY LOW	CRITICAL
Relapse – in patients NOT taking ART (anti-retroviral therapy)												
8 [a]	randomized trials & observational	serious [1,2]	serious [3]	not serious	not serious	Possible reporting and selection bias.	158 / 872 18%	15 / 328 5%	**aOR 3.1** (1.4 to 6.7)	130 more per 1000 (from 50 more to 260 more)	⨁ VERY LOW	CRITICAL
Death												
47 [a]	randomized trials & observational	serious [1,2]	serious [3]	not serious	not serious	Possible reporting bias.	209/1829 9.6% (5.9 to 12.5)	107/765 13.9% (7.3 to 20.4)	**RR 0.9** (0.5 to 1.6)	43 fewer per 1000 (from 145 fewer to 52 more)	⨁ VERY LOW	CRITICAL

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

Recommendation 8: We recommend initial adjunctive corticosteroid therapy with dexamethasone or prednisolone given for six weeks for patients with tuberculous meningitis (Strong recommendation / Moderate certainty in the evidence).

9. Among HIV-negative patients (adults and children) with paucibacillary TB (i.e., **confirmed** to be smear negative, culture negative), does a shorter duration of treatment have similar outcomes compared to the standard 6-month treatment duration?

Recommendation 9: We suggest that a 4-month treatment regimen is adequate for treatment of HIV-negative adult patients with AFB smear- and culture-negative pulmonary tuberculosis (Conditional recommendation / Very low certainty in the evidence).

Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

	Intensive Phase		Continuation Phase				
Regimen	Drug[a]	Interval and Dose[b] (Minimum Duration)	Drugs	Interval and Dose[b,c] (Minimum Duration)	Range of Total Doses	Comments[c,d]	Regimen Effectiveness
1	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	7 d/wk for 126 doses (18 wk), or 5 d/wk for 90 doses (18 wk)	182–130	This is the preferred regimen for patients with newly diagnosed pulmonary tuberculosis.	Greater
2	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	110–94	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.	
3	INH RIF PZA EMB	3 times weekly for 24 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	78	Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance.	
4	INH RIF PZA EMB	7 d/wk for 14 doses then twice weekly for 12 doses[e]	INH RIF	Twice weekly for 36 doses (18 wk)	62	Do not use twice-weekly regimens in HIV-infected patients or patients with smear-positive and/or cavitary disease. If doses are missed, then therapy is equivalent to once weekly, which is inferior.	Lesser