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

Treatment of Drug-Susceptible Tuberculosis: perspective from the life of a TB doctor in the trenches

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Treatment of Tuberculosis

American Thoracic Society, CDC, and Infectious Diseases Society of America

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.

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.

2016 ATS/CDC/IDSA TB treatment Guidelines

Guideline Contents

- Organization and supervision of treatment

  - Patient-Centered Care and Case Management

  - Ensuring adherence and treatment success

- Recommended treatment regimens

  - Preferred regimens

  - Alternative regimens

  - Patient at increased risk of relapse

  - Interruptions of therapy

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Guideline Contents

- Treatment in special situations

  - HIV infection

  - Children

  - Pregnancy and breastfeeding

  - Renal disease

  - Hepatic disease

  - Diabetes

  - Advance age

  - Other sites of extrapulmonary disease

- Management of adverse effects, drug-drug interactions

- Recurrent tuberculosis, treatment failure and drug resistance

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GRADE METHODOLOGY
(Grading of Recommendations)

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

- 9 PICO questions and associated recommendations were developed based on grading methodology

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

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Organization and Supervision of Treatment

- A public health agency conducts epidemiologic surveillance, access to diagnostic services, uninterrupted TB meds and supervision of treatment

- Use of Patient-Centered and case management,

- Develop an individualize case management plan

- Assign a case manager to help navigate the complex health care system

- Treating physician is responsible for treatment outcomes

- Legal measures in situations on non-adherence as a last resort

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Organization and Supervision of Treatment

- Improving treatment education using terminology that is appropriate to the culture, language, age and reading level of the patient

- Discussing infectiousness and infection control measures

- Reviewing methods of supervision and assessing response to therapy

- Field and home visits, incentives, enablers

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

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

DOT remains the standard of practice

- Evidence in support of this practice guideline showed that DOT was significantly associated with improved treatment outcomes in terms of patients cured and patients completing treatment

- However, the evidence did not find significant differences between SAT and DOT in terms of mortality, treatment completion and relapses

- DOT is not amenable to be study in conventional clinical trials

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3. Should tuberculosis medications be dosed daily or intermittently in the **intensive phase** of treatment?

Recommendation: 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).

4. Should tuberculosis medications be dosed daily or intermittently in the **continuation phase** of treatment?

Recommendation: 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).

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Intermittent versus daily therapy for TB in adults: Systematic review and meta-analysis

- **Only one trial** with 299 pulmonary TB.
- Daily vs 3X weekly, RIPE standard 6 months
- Intermittent had failure/relapses more than 4 times higher
- Intermittent had failure/relapses more than 4 times higher

Failure:	Daily:	0/200	**(0%)**
	3X weekly	1/199	(**0.5**%)
Relapse:	Daily:	1/200	(**0.5**%)
	3X weekly	5/198	(**2.5**%)

(Mwandumba & Squires. Cochrane; 2001

Dosing schedules of 6-month regimens and relapse.

- Systematic review of 17 studies with 5,208 patients, and 200 relapse events.

  - Daily through-out: RR= 1.0

  - Daily then 3X weekly: RR = 1.6

  - Daily then 2X weekly: RR = 2.8

  - 3x weekly through-out: RR = 5.0

- Greatest risk if cavitation or 2nd month culture was positive

Chang et al, Am J Resp Crit Care Med. 2006; 174: 1153-58

Intermittency and treatment outcomes: 2012, 34 studies included

	Risk of Failure (95%CI) events/subjects	Risk of Relapse (95%CI) events/subjects	Risk of Death (95%CI) events/subjects	Risk of ADR (95%CI) events/subjects
Daily	2.7% (1.6, 3.7)	6.3% (1.2, 11.4)	11.8% (8.5, 15.0)	4.2% (0, 12.9)
	99/2813	142/1267	480/3293	2/60
Thrice weekly	**5.2%** (1.5, 8.8)	**18.2%** (0, 39)	10.1% (4.3, 16)	**11.4%** (0, 66)
	32/464	44/210	52/516	18/188

Khan FA, et al. Treatment of active TB in HIV co-infected patients. CID, 2012

Intermittent therapy stratified by ART use: Updated 2012, 34 studies included

Dosing Schedule	Failure: aOR (95% CI)		Relapse: aOR (95% CI)		Death: aOR (95% CI)	
	ART		ART		ART	
	None / NR	All / Some	**None** / NR	All / Some	**None** / NR	All / Some
Daily (reference)	1.0	1.0	1.0	1.0	1.0	1.0
Thrice weekly	**4.1 (1.9, 9.1)**	0.4 (0.1, 2.7)	**2.1 (0.6, 6.9)**	**2.2 (0.2, 27.9)**	0.7 (0.4, 1.2)	2.0 (0.4, 11.5)

aOR, adjusted odds ratio; ART, antiretroviral therapy; CI, confidence interval; NR, not reported

Khan FA, et al. Treatment of active TB in HIV co-infected patients. CID, 2012

Intermittent therapy for drug-susceptible TB: Update review

- **Primary analysis:**

  – Population with DS-TB or no DST with at least 6 months Rifampin

  – Analysis of treatment failure, relapse, ADR with the following treatment schedules:

    - Daily (≥5 days per week) throughout
    - Daily intensive phase then twice weekly
    - Daily intensive phase then thrice weekly
    - Thrice weekly throughout

Updated review of RCTs: Johnston, Campbell & Menzies: 1970 – 2016 (not yet published).
Presented in a Webinar 11/4/16. Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis

Initial Phase: Daily versus intermittent

» Failures: events/patients
  - Daily   (112/8223) 0.2%
  - TIW   (28/2310) 0.6%

» Relapses
  - Daily   (254/7475) 2.5%
  - TIW   (128/2130) 6.8%

» ADR
  - Daily   (11/4700) 0.1%
  - TIW   (16/1778) 0.3%

No trials were found with the "Denver regimen" Two weeks daily then, twice weekly through-out

Continuation Phase: Daily versus intermittent

- Failures: events/patients
  - Daily   (112/8223) 0.2%
  - Daily then TIW   (19/2075) 0.4%
  - Daily then BIW   (21/793) 1.3%
- Relapses
  - Daily   (254/7475) 2.5%
  - Daily then TIW   (72/2007) 3.0%
  - Daily then BIW   (49/572) 7.3%
- ADR
  - Daily   (11/4700) 0.1%
  - Daily then TIW   (1/588) 0.1%
  - Daily then BIW   (2/377) 0.2%

Updated review of RCTs: Johnston, Campbell & Menzies: 1970 – 2016 (not yet published).
Presented in a Webinar 11/4/16. Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis

Other Regimens

- The preferred frequency is once daily for both IP and CP in this guideline

- Administration frequency of less than daily in the intensive phase of treatment is generally not preferred

- Administration of antituberculosis medications using DOT 5 days-a-week has not been compared to 7 days-a-week administration

- In this guidelines 5 days and 7 days-a-week is considered as "daily dosing"

Other Regimens

- Thrice-Weekly dosing Throughout
  - Associated with higher rates of treatment failure, relapse, and ADR
  - Risk of poor outcomes of treatment higher in HIV-infected patients, cavitary disease and baseline DR
- **This regimen may be considered when daily is not feasible or poorly tolerated in patients who are not HIV-infected, non-cavitary, smear negative, DS organisms. Recommendation 3b: <u>(Conditional recommendation; low certainty in the evidence)</u>**

Other Regimes

- Twice-Weekly Dosing Throughout or Twice-Weekly Dosing after 2-3 Weeks of Daily dosing
  - Not generally recommended because of lack of high quality evidence to support its use
- Some tuberculosis programs have reported long standing programmatic treatment success with the "Denver Regimen"
- **In situations where daily or thrice-weekly DOT can not be used this regimen may be consider in patients who are not HIV-infected, non-cavitary, smear negative, DS organisms Recommendation 3c: <u>(Conditional recommendation; very low certainty in the evidence)</u>**

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

Recommendation: For HIV-infected patients receiving antiretroviral therapy, we suggest using the standard 6-month daily regimen. 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).

Duration of treatment and adjusted odds of outcomes stratified by ART use

Duration Rifampin	Failure: OR (95% CI)		Relapse: OR (95% CI)		Death: OR (95% CI)	
	ART		ART		ART	
	None / NR	All / Some	None / NR	All / Some	None / NR	All / Some
6 Months	0.7 (0.4, 1.4)	1.8 (0.3, 12.2)	3.1 (1.4, 6.7)	0.2 (0.01, 2.2)	1.0 (0.6, 1.4)	0.5 (0.2, 1.2
≥8 Months (ref)	1.0	1.0	1.0	1.0	1.0	1.0
p value	0.63	0.30	0.001	0.40	0.3	0.12

aOR, adjusted odds ratio; ART, antiretroviral therapy; CI, confidence interval; NR, not reported.

Khan FA, et al. Treatment of active TB in HIV co-infected patients. CID, 2012

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

Recommendation: We recommend initiating ART during tuberculosis treatment. By 8-12 weeks of tuberculosis treatment initiation for patients with CD4 cell counts ≥50/mm³. Within the first 2 weeks of tuberculosis treatment for patients with CD4 cell counts <50/mm³ (<u>Strong recommendation / High certainty in the evidence*</u>).

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

Initiation of ART During Tuberculosis Treatment in HIV-Infected patient

- SAPit trial in patients with TB and HIV with CD4 <500; patients initiating ART **after two weeks (immediate) or 8 weeks (early)** compared to ART after 6 months of TB treatment (deferred) demonstrated 56% reduction in the relative risk of death

- Cambodia trial early versus late ART, showed that ART within two weeks of starting TB treatment reduced mortality by 34% compared to starting treatment after 8 weeks

- STRIDE trial showed significantly lower rates of progression of HIV disease or death with immediate therapy compared to early therapy

- In all these studies **immediate ART** associated with more IRIS

Abdool KS, et al. NEJM 2010; Blank FX, et al. NEJM 2011; Havlir DV. NEJM 2011; Abdool KS et al. NEJM, 2011.

Treatment Regimens for Pulmonary Tuberculosis Caused by DS Organisms

Regimen	Drug[a]	Intensive Phase Interval and Dose[b] (Minimum Duration)	Drugs	Continuation Phase 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

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Reduce the risk of relapse

- The continuation phase of treatment is extended for an additional 3 months for patient that have cavitation on initial or follow up CXR and in addition, are culture positive at the end of the second month of treatment

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

Recommendation: We suggest initial adjunctive corticosteroid therapy not be routinely used in patients with tuberculous pericarditis <u>(Conditional recommendation / Very low certainty in the evidence).</u>

Pericardial Tuberculosis

- Corticosteroids have previously been universally recommended as adjunctive therapy for tuberculosis pericarditis

- A RCT of 1400 patients did not find differences in mortality cardiac tamponade, or constrictive pericarditis in patients that received corticosteroids versus placebo

- A systematic review for the guidelines did not find a benefit in using corticosteroids

- Patients at higher risk of inflammatory complications such as large pericardial effusions, high levels of inflammatory markers or those with early signs of constriction can be given corticosteroids

Mayosis BM, et al. Imunotherapy for tuberculosis pericarditis. NEJM 2014.

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

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

Tuberculosis Meningitis

- Based on expert opinion repeat lumbar punctures should be considered early in the course of therapy

- In children AAP recommends treatment with INH, RIF, PZA and ethionamide or aminoglycoside for 2 months followed by 7-10 months of INH and RIF.

- In adults INH, RIF, PZA and EMB as the fourth drug is recommended

- Fluoroquinolones and high doses RIF are being evaluated in RCT

- Neurosurgery consult maybe needed for hydrocephalus or cerebral abscess

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Immune Reconstitution Inflammatory Syndrome (IRIS)

- IRIS does not worsen treatment outcomes for either tuberculosis or HIV infection

- **An exception:** The development of IRIS in patients with HIV infection with CNS tuberculosis where IRIS can cause severe or fatal neurological complications

- In a study of TB meningitis and HIV infection, early initiation of ART was associated with worst outcomes

- **Do not initiate ART in the first 8 weeks in patients with TB meningitis and HIV infection even if CD4 cell count < 50**

Torok ME, et al. Timing of initiation of ART in HIV associated TB meningitis. 2011 CID

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9. Among HIV-negative patients 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: 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 <u>(Conditional recommendation / Very low certainty in the evidence).</u>

Culture negative pulmonary tuberculosis

- Alternative diagnosis must be considered and appropriate diagnostic studies undertaken in patients who appear to have culture negative tuberculosis
- Consider errors in specimen processing
- Consider recent use of antibiotics to treat pneumonia
- Consider rapid molecular testing as part of the diagnostic evaluation
- Consider bronchoscopy with bronchoalveolar lavage and biopsy
- Of there are concerns with the adequacy of the work up a standard regimen is preferred

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Key Updates from 2003 edition in the New TB Treatment Guidelines

- Evidence base for case management (patient education, incentives, enablers, DOT) reviewed
- Evidence base for intermittent therapy reviewed
  - **Once weekly regimen NOT recommended**
  - **Daily rather than intermittent dosing in the intensive phase of therapy is recommended**
  - **Daily or three times weekly dosing in the continuation phase of therapy is recommended**
  - **Avoid the once weekly regimen of INH900/RPF 600**

Key updates from 2003 edition in the new TB treatment guidelines

- Early initiation of ART in HIV/TB patients
- Duration of TB treatment in HIV with ART, 6 months
- TB treatment extended if not on ART
- Steroids not routinely recommended for TB pericarditis
- Avoid use of ART during treatment of tuberculosis meningitis in the first 8 weeks of treatment

Conclusions

- **Intermittent treatment Three times/week** - **from beginning** has higher rates of failure and relapse, and ADR in multiple reviews
- There is no RCTs published evidence for the "Denver regimen"
- Daily initially (IP) then Twice weekly intermittent in continuation phase has higher rates of relapse
- Daily initially, followed by Thrice weekly therapy has very good results

Thank you!

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