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

Treatment of Drug-Susceptible Tuberculosis

On behalf of the writing committee
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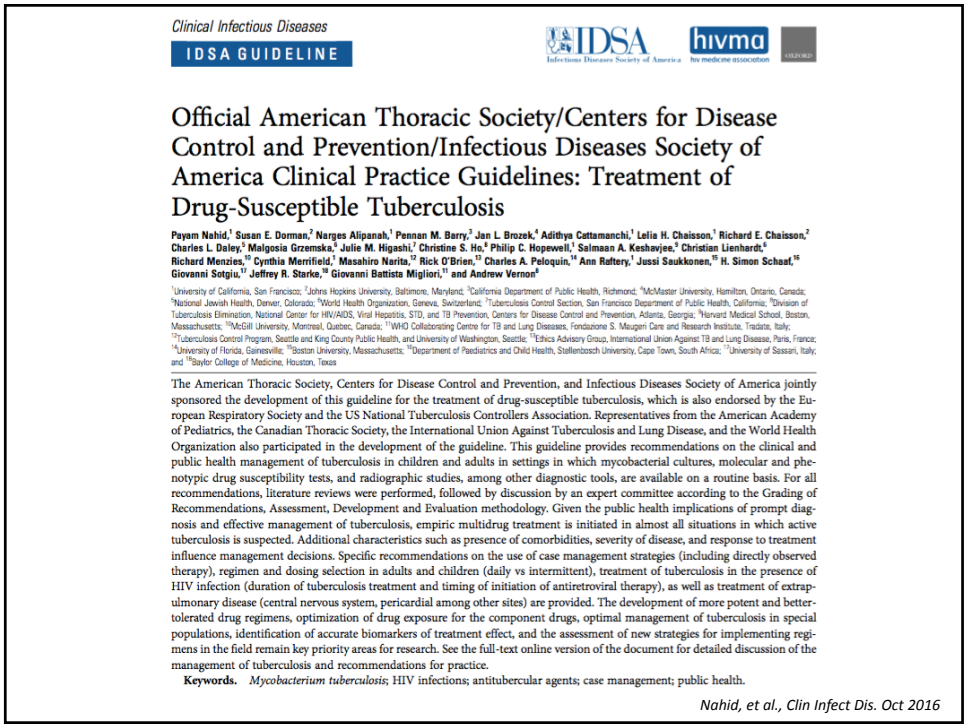

Clinical Infectious Diseases

IDSA GUIDELINE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

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

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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.**

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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Treatment of Drug-Susceptible Tuberculosis
Guideline Contents

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
Guideline Contents

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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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].

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

Nine PICOs addressed:

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

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

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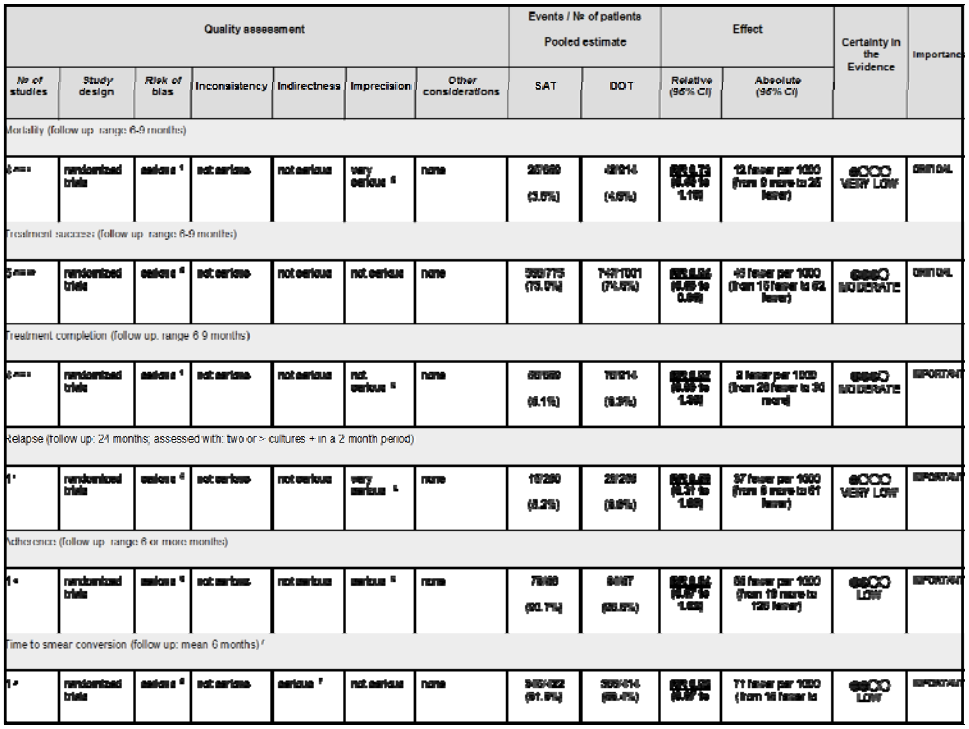

Quality assessment							Events / № of patients Pooled estimate		Effect		Certainty in the Evidence	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SAT	DOT	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: range 6-9 months)												
3	randomized trials	serious [1]	not serious	not serious	very serious [2]	none	20/689 (3.0%)	42/914 (4.6%)	[illegible] 1.19)	12 fewer per 1000 (from 9 more to 25 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Treatment success: (follow up: range 6-9 months)												
5	randomized trials	serious [2]	not serious	not serious	not serious	none	559/775 (72.0%)	747/1001 (74.6%)	[illegible] 0.99)	45 fewer per 1000 (from 151 fewer to 62 fewer)	⊕⊕◯◯ MODERATE	CRITICAL
Treatment completion (follow up: range 6 9 months)												
3	randomized trials	serious [1]	not serious	not serious	not serious [3]	none	69/599 (6.1%)	76/914 (8.3%)	[illegible] 1.39)	3 fewer per 1000 (from 28 fewer to 30 more)	⊕⊕◯◯ MODERATE	IMPORTANT
Relapse (follow up: 24 months; assessed with: two or > cultures + in a 2 month period)												
1	randomized trials	serious [2]	not serious	not serious	very serious [4]	none	10/280 (3.2%)	28/289 (9.6%)	[illegible] 1.09)	37 fewer per 1000 (from 6 more to 61 fewer)	⊕◯◯◯ VERY LOW	IMPORTANT
Adherence: (follow up: range 6 or more months)												
1	randomized trials	serious [5]	not serious	not serious	serious [6]	none	75/89 (80.7%)	84/87 (96.6%)	[illegible] 1.03)	66 fewer per 1000 (from 19 more to 126 fewer)	⊕◯◯◯ LOW	IMPORTANT
Time to smear conversion (follow up: mean 6 months) [7]												
1	randomized trials	serious [2]	not serious	serious [7]	not serious	none	345/422 (81.8%)	399/414 (96.4%)	[illegible] 0.97)	77 fewer per 1000 (from 16 fewer to	⊕◯◯◯ LOW	IMPORTANT

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)

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3. 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).

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4. 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).

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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?

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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												
[illegible]	[illegible]	[illegible]	serious [1]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	⨁⨁◯◯ MODERATE	CRITICAL
Mortality												
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	⨁⨁⨁⨁ HIGH	CRITICAL
AIDS-defining illness or death												
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	⨁⨁⨁⨁ HIGH	CRITICAL
Treatment success												
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	⨁⨁⨁⨁ HIGH	CRITICAL
Grade 3-4 adverse event												
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	⨁⨁⨁⨁ HIGH	CRITICAL
Relapse												
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	very serious [1]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	⨁⨁◯◯ LOW	IMPORTANT
Treatment completion												
[illegible]	[illegible]	[illegible]	not serious	not serious	serious [2]	none	232/961 (24.1%)	164/763 (24.4%)	[illegible]	16 more per 1000 (from 24 fewer to 57 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

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?

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

Recommendation 5a: For **HIV-infected patients receiving antiretroviral therapy**, we suggest using the standard 6-month daily regimen

Recommendation 5b: 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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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												
17[1]	randomized trials & observational	serious [1,3]	serious [3]	not serious	not serious	Possible reporting bias.	66/1620 2.6% (1.2 to 4.0)	29/986 2.7% (0.6 to 5.0)	RR 0.8 (0.4 to 1.6)	1 fewer per 1000 (from 36 fewer to 28 more)	⊕◯◯◯ VERY LOW	CRITICAL
Relapse												
27[1]	randomized trials & observational	serious [1,3]	serious [3]	not serious	not serious	Possible reporting bias. Dose response [4]	119/630 9.1% (0.4 to 17.8)	29/426 4.7% (0 to 11.2)	RR 2.4 (1.2 to 5.0)	44 more per 1000 (from 16 more to 170 more)	⊕◯◯◯ VERY LOW	CRITICAL
Relapse – in patients NOT taking ART (anti-retroviral therapy)												
3[1]	randomized trials & observational	serious [1,3]	serious [3]	not serious	not serious	Possible reporting and selection bias.	108 / 672 16%	16 / 328 5%	aOR 3.1 (1.4 to 6.7)	130 more per 1000 (from 60 more to 260 more)	⊕◯◯◯ VERY LOW	CRITICAL
Death												
17[1]	randomized trials & observational	serious [1,3]	serious [3]	not serious	not serious	Possible reporting bias.	208/1620 6.6% (5.6 to 12.6)	107/755 13.6% (7.3 to 20.4)	RR 0.9 (0.5 to 1.6)	43 fewer per 1000 (from 145 fewer to 82 more)	⊕◯◯◯ VERY LOW	CRITICAL

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).

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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).

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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).

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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

2016 ATS/CDC/IDSA TB Treatment Guidelines
Nahid, et al., Clin Infect Dis. Oct 2016

Thank you

- **Strong commitment and leadership from ATS/CDC/ERS/IDSA**
- 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.
- **Susan Dorman (IDSA), GB Migliori (ERS), Andrew Vernon (CDC)**

Evidence review for Intermittent therapy for drug-susceptible TB:

Dr. Dick Menzies
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McGill University
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Questions addressed: intermittent therapy

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

2: Does intermittent dosing in the continuation phase have similar outcomes compared to daily dosing in the continuation phase in patients with drug susceptible pulmonary tuberculosis?

Evidence review for Intermittent therapy

Summary of evidence available

- Review of 'Head-to-Head' RCTs 1970-2009; Mwandumba, Cochrane 2001
- Review of RCTs and Cohorts: Chang AJRCCM 2006
- Review of 57 RCTs 1970-2008: Menzies, PLOS Med 2009
- Review of 4 pediatric studies: Menon Ind J Ped 2009
- HIV-TB review: Khan CID 2010 & 2012
- Updated review of RCTs: Johnston, Campbell & Menzies: 1970 – 2016 (not yet published)

Head-to-Head RCTs of Intermittent vs daily therapy for TB in adults – meta-analysis. *(Mwandumba & Squires. Cochrane; 2001)*

Systematic review and meta-analysis – adults older than 16.
Only one trial with 299 pulmonary TB. Daily vs 3X weekly. INH/RIF/PZA/EMB for 6 months

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

In Total: Intermittent had fail/relapse more than 4 times higher, but very low power as few events

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Dosing schedules of 6-month regimens and relapse.

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

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

Daily through-out – Lowest: **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 2 month culture positive
- Also greater if followed by 1X weekly Rifapentine

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Evidence review for Intermittent therapy

Menzies PLOS Med review - Search Strategy

- First review: Jan 1 1970 to June 30 2008
- English, French, Spanish
- Embase, Medline, Cochrane databases
- Searched references, prior reviews, guidelines

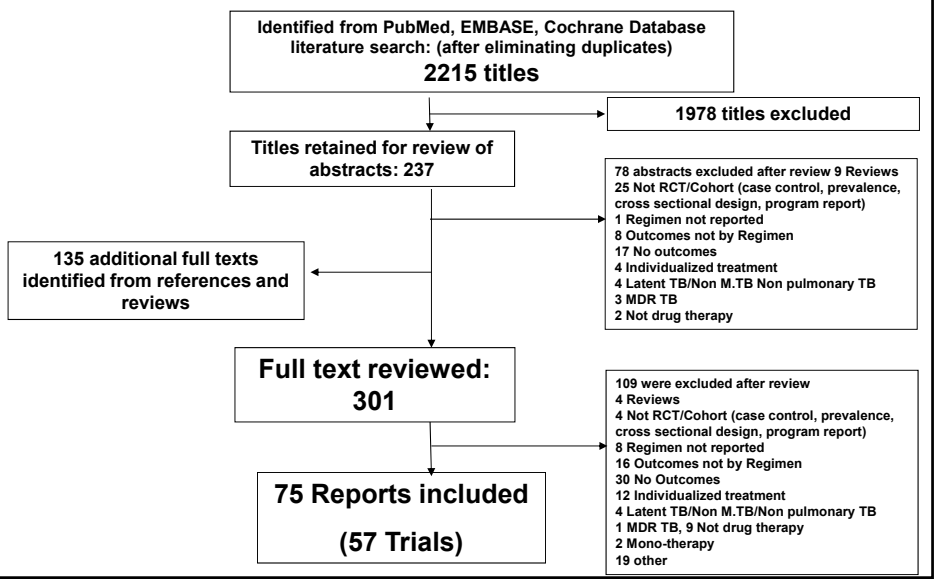
Evidence review for Intermittent therapy –

Menzies PLOS Med review - Study inclusion criteria:

- RCTs that reported treatment outcomes of new bacteriologically-confirmed pulm. TB
- Reported microbiologically confirmed outcomes of failure, or relapse.
- Acquired drug resistance – if DST done initially plus DST with fail/relapse
- Arms using ≥6 months INH & Rifampin (if rifapentine, or rifabutin, or monotherapy at any point – excluded)
- Drug sensitive patients only (or New cases but no DST done)

Evidence review for Intermittent therapy

Menzies PLOS Med review: Summary of study selection



Menzies PLOS Med review - Intermittent therapy and outcomes – from Meta-regression
(RCT in New cases and no HIV)

Intermittent schedule	Failure IRR (95% CI)	Relapse IRR (95% CI)	ADR IRR (95% CI)
Daily throughout	1.0 (reference)	1.0 (reference)	1.0 (reference)
Daily then thrice weekly	0.8 (0.5, 1.3)	1.0 (0.7, 1.3)	0.9 (0.4, 1.8)
Daily then twice weekly	1.3 (0.9, 1.8)	0.8 (0.7, 1.1)	0.7 (0.4, 1.1)
Thrice weekly throughout	1.3 (1.0, 1.7)	1.1 (0.9, 1.3)	4.9 (3.3, 7.4)

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Intermittent or daily therapy for TB in children – meta-analysis. *(Ramesh Menon et al, Indian Pediatrics. 2009; May 20)*

Systematic review and meta-analysis – children less than 16. Four trials with 466 children

Odds of cure: Daily: **1.0 (reference)**
Twice weekly: Per protocol: **0.27 (0.15, 0.51)**
Intention to treat: **0.66 (0.23, 1.84)**

Daily therapy had significantly higher cure rates - in children who were adherent

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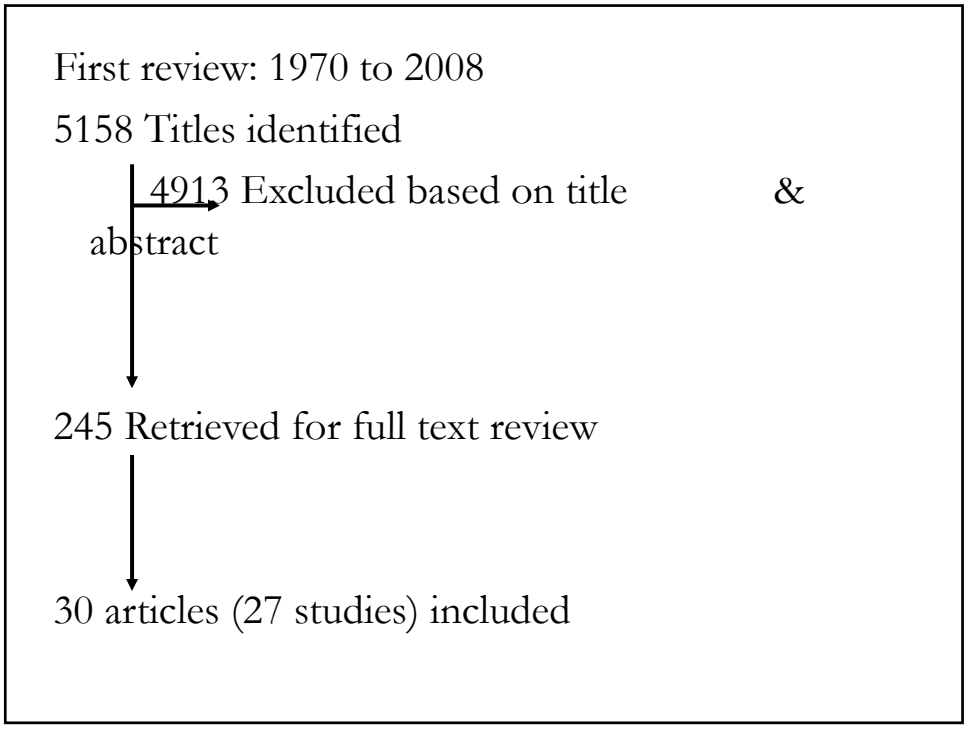
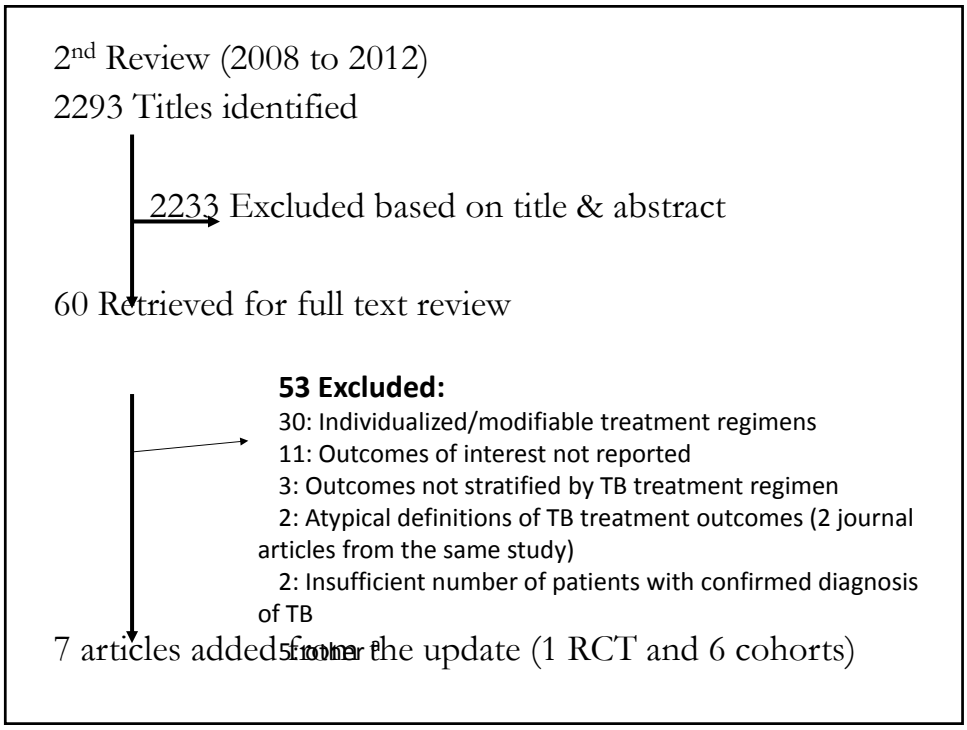
Treatment of active tuberculosis in HIV co-infected patients:

Faiz A. Khan MD, Dick Menzies MD MSc.

Methods- Inclusion criteria

- Randomized controlled trials or cohort studies
- Standardized regimens that contained rifampin or rifabutin
- Serologically confirmed HIV status
- Microbiologically confirmed active TB
- Failure or relapse microbiologically confirmed
- Patients with pre-treatment MDR-TB were excluded from all analyses (if separable)


First review: 1970 to 2008
5158 Titles identified
4913 Excluded based on title & abstract
245 Retrieved for full text review
30 articles (27 studies) included


2nd Review (2008 to 2012)
2293 Titles identified
2233 Excluded based on title & abstract
60 Retrieved for full text review
53 Excluded:
30: Individualized/modifiable treatment regimens
11: Outcomes of interest not reported
3: Outcomes not stratified by TB treatment regimen
2: Atypical definitions of TB treatment outcomes (2 journal articles from the same study)
2: Insufficient number of patients with confirmed diagnosis of TB
7 articles added from the update (1 RCT and 6 cohorts)

Intermittency and Pooled treatment outcomes – all studies

	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) 99/2813	6.3% (1.2, 11.4) 142/1267	11.8% (8.5, 15.0) 480/3293	4.2% (0, 12.9) 2/60
Thrice weekly	**5.2%** (1.5, 8.8) 32/464	**18.2%** (0, 39) 44/210	10.1% (4.3, 16) 52/516	**11.4%** (0, 66) 18/188

Intermittency and Adjusted odds of treatment outcomes – all studies

	Failure: aOR (95% CI)[a]	Relapse aOR (95% CI)[a]	Death: aOR (95% CI)[a]	ADR aOR (95% CI)[b]
Daily (reference)	**1.0**	**1.0**	**1.0**	**1.0**
Thrice weekly	**2.0 (0.8, 5.0)**	**2.2 (0.7, 7.3)**	**0.7 (0.3, 1.4)**	**3.7 (0.7, 18.9)**
p value for difference	**0.13**	**0.18**	**0.33**	**0.11**

Intermittency and Adjusted odds of outcomes – stratified by ART use

Dosing Schedule	Failure: aOR (95% CI)[a]		Relapse: aOR (95% CI)[a]		Death: aOR (95% CI)[a]	
	ART		ART		ART	
	None / NR[b]	All / Some[c]	**None** / NR[b]	All / Some[c]	**None** / NR[b]	All / Some[c]
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)

Intermittent therapy for drug-susceptible TB: Update review

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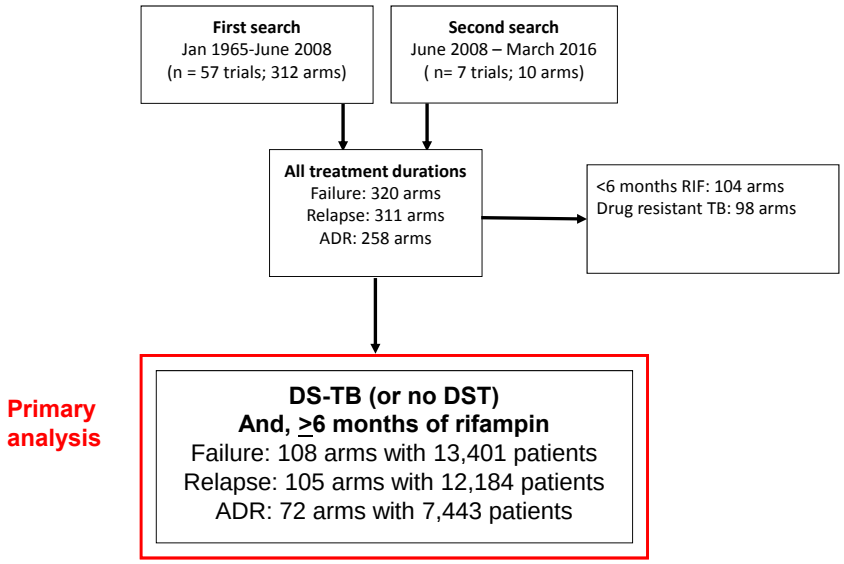
Evidence review for Intermittent therapy

Search Strategy - update

- First review: Jan 1 1970 to June 30 2008
- 2nd review: June 1, 2008 – March 15, 2016

Evidence review for Intermittent therapy *(from Johnston 2016, do not cite, show or copy*

Studies included in updated analysis



Evidence review for Intermittent therapy

Primary analysis

- Population with DS-TB or no DST
- Patients at least 6 months Rifampin
- Proportion treatment failure, relapse, ADR with the following treatment schedules:
  1. Daily (≥5 days per week) throughout
  2. Daily intensive phase then twice weekly
  3. Daily intensive phase then thrice weekly
  4. Thrice weekly throughout

Note: No trials found with Twice weekly through-out (Initial & Continuation phase – the "Denver regimen")

Evidence review for Intermittent therapy *(from Johnston 2016, do not cite, show or copy*

Initial Phase: Daily vs Intermittent

Initial Phase Schedule	*Arms (N)*	*Events/Participants (N)*	*Point Estimate 95% CI*
Failure			
Daily	62	112/8223	0.2% (0 - 0.4)
3x per week	19	28/2310	0.6% (0 - 1.4)
Relapse			
Daily	59	254/7475	2.5% (1.8 - 3.2)
3x per week	19	128/2130	**6.8% (3.8 - 9.9)**
Acquired Drug Resistance			
Daily	43	11/4700	0.1% (0 - 0.2)
3x per week	15	16/1778	0.3% (0 - 0.8)

Note: No trials found with Twice weekly through-out (Initial & Continuation phase – the "Denver regimen")

Evidence review for Intermittent therapy *(from Johnston 2016, do not cite, show or copy*

Continuation Phase

Factor	*Arms (N)*	*Failure Events/Participants (N)*	*Point Estimate*
Daily throughout	62	112/8223	0.2% (0.1 - 0.4)
Daily then 3x per week	18	19/2075	0.4% (0 - 1.1)
Daily then 2x per week	9	21/793	1.3% (0 - 2.9)
Relapse			
Daily throughout	59	254/7475	2.5% (1.8 - 3.2)
Daily then 3x per week	18	72/2007	3.0% (1.0 - 5.1)
Daily then 2x per week	9	49/572	**7.3% (3.5 - 11.1)**
Acquired Drug Resistance			
Daily throughout	43	11/4700	0.1% (0 - 0.2)
Daily then 3x per week	9	1/588	0.1%(0 - 0.3)
Daily then 2x per week	5	2/377	0.2% (0 - 0.6)

Evidence review for Intermittent therapy *(from Johnston 2016, do not cite, show or copy*

Adjusted analyses (meta-regression)

DS-TB, or no DST, Rif duration ≥6 months

Factor	*Failure IRR*	*Relapse IRR*	*ADR IRR*
Daily throughout	1.0	1.0	1.0
Daily then 3x per week	1.5 (0.4-5.4)	1.2 (0.6-2.3)	0.6 (0.1-5.7)
Daily then 2x per week	**3.0 (1.0-8.8)**	1.8 (0.98-3.3)	0.96 (0.2-5.0)
3x per week throughout	**3.7 (1.1-12.6)**	**2.2 (1.2-3.9)**	**10.0 (2.1-47)**

Negative binomial regression performed in Stata, Variables in model: Rifampin duration, Use of pyrazinamide, Use of streptomycin, Administration schedule, Number of drugs in initial and continuation phases, Use of DOT

Evidence review for Intermittent therapy

Sensitivity Analysis

- We examined the following:

1. Drug sensitive TB only (No DST dropped)
2. All studies (i.e. like Menzies *PLOS Med.* 2009)
3. Streptomycin-based regimens removed
4. Streptomycin resistant strains included
5. Drug resistant strains only
6. Regimen of 2HRZ(E), 4HR(E) only
7. Removed arms with only HIV infected patients

Findings essentially **unchanged** with all these

Evidence review for Intermittent therapy

FAQS (Frequently asked questions)

- How many studies used DOT
  - Used DOT throughout therapy: 57% (most of intermittent)
  - Used DOT in part of therapy : 14%
  - Did not use DOT: 29% (mostly daily)
- How many studies had <10% total of loss to follow-up & default & transfer & unknown?
  - <10% loss: 66% of studies
  - >10% loss: 33% of studies

Evidence review for Intermittent therapy

FAQS (Frequently asked questions)

- How many HIV infected patients were included in these studies?
  - 1509 Patients were HIV positive (11% of all patients)
  - In 67% of the studies 0 (zero) patients had HIV
- How many studies were published since 1990 and how many since 2000?
  - Prior to 1990: 69%,
  - 1990 – 2000: 19%
  - Post 2000: 12%

Evidence review for Intermittent therapy

Conclusions

- **Intermittent treatment Three times/week - from beginning** (or after 2 weeks) has higher rates of failure and relapse, and ADR in multiple reviews :
  - In a 2001 Cochrane review of Direct head-to-head studies
  - In a 2006 review of RCTs and Cohorts – (Relapse)
  - In a 2009 review children (Failure)
  - In a 2009 review of adults (Failure and ADR)
  - In 2012 review of treatment of HIV-TB (Failure & Relapse - but significant only if ARV NOT given)
  - In a 2016 updated review (Failure, Relapse and ADR)
- Note: there is VERY little published evidence for twice weekly from beginning ("Denver regimen"). No RCTs

Evidence review for Intermittent therapy

Conclusions

- **Daily initially then Twice weekly intermittent in continuation** phase (after first 2 months) has higher rates of relapse:
  - In a 2016 updated review
- **Daily initially, followed by Thrice weekly therapy** has very good results:
  - In a 2009 review of adults
  - In 2012 review in HIV-infected
  - In a 2016 updated review

Evidence review for Intermittent therapy

Discussion - Limitations

- Very few large scale randomized trials with direct comparison of Intermittent vs Daily. Could not pool data from Head-to-Head comparisons
- Most studies conducted in Low and Middle income countries. But drop-out rates and non-adherence low in most studies. Quality of care could be considered similar to US programme standards
- Some studies/regimens did not use PZA
  - But sensitivity analyses – Arms with PZA only = same findings
- Even though differences are significant, and odds ratios are high, the **absolute effect size is small** – difference in relapse rates of 4%, and of acquired drug resistance of 1%

Evidence review for Intermittent therapy

Discussion - Strengths

- Large number of trials identified. Only studies with bacteriologically confirmed diagnoses & outcomes (fail and relapse were confirmed) were included.
- Consistent results from multiple reviews in different populations (adults, children, HIV infected). Even if not always significant, consistent trends seen.
- In 3 reviews multivariate analysis used – to adjust for confounding factors (eg use of PZA). Findings stronger
- Studies from many countries, including resource-poor, "real-life" settings - more applicable/generalizable

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HIV-TB review

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HIV-TB: Other questions
Use of ART, and Duration of therapy:

Questions addressed: HIV-TB

In patients with HIV-TB:

1: Is it necessary to prolong therapy – past usual 6 months?

2. Does ART modify these two answers?

Use of ART and Pooled treatment outcomes – all studies

	Failure Rate (95%CI) events/subjects	Relapse Rate (95%CI) events/subjects	Death Rate (95%CI) events/subjects	ADR Rate (95%CI) events/subjects
No ART // NR	3.2% (1.8, 4.6) 98/2481	**14.4% (4.9, 23.9) 178/1194**	12.4% (8.7, 16.1) 407/2888	**16.6% (10.7, 22.4) 19/157**
Some or All on ART	2.0% (0.5, 3.5) 33/796	**1.1% (0, 2.8) 8/283**	9.8% (5.2, 14.3) 125/921	**3.3% (0, 7.0) 1/91**

Use of ART and Adjusted odds of treatment outcomes – all studies

	Failure: aOR (95% CI)[a]	Relapse aOR (95% CI)[a]	Death: aOR (95% CI)[a]	ADR aOR (95% CI)[b]
None // NR	1.7 (0.7, 4.0)	**14.3 (2.1, 98)**	1.4 (0.7, 2.8)	2.0 (0.5, 7.9)
Some or All	1.0	**1.0**	1.0	1.0
p value for differences	0.22	**<0.01**	0.33	0.33

Duration of Rifampin and Pooled treatment outcomes – all studies

	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
2 Months	3.5% (1.3, 5.8) 47/999	10.8% (0, 28) 38/222	13.4% (7.9, 20) 216/1215	No studies.
6 Months	2.6% (1.2, 4.0) 55/1620	9.1% (0.4, 18) 119/830	9.2% (5.9, 12.5) 209/1829	10.4% (0, 21) 209/1829
8+ Months	2.7% (0.5, 5.0) 29/658	4.7% (0, 11.2) 29/425	13.9% (7.3, 20) 107/765	9.7% (1.6, 18) 13/146

Duration of Rifampin and Adjusted odds of treatment outcomes – all studies

	Failure: aOR (95% CI)[a]	Relapse aOR (95% CI)[a]	Death: aOR (95% CI)[a]	ADR aOR (95% CI)[b]
2 Months	1.4 (0.6, 3.2)	**5.0 (1.9, 13)**	0.9 (0.5, 1.6)	No studies
6 Months	0.8 (0.4, 1.5)	**2.4 (1.2, 5.0)**	0.7 (0.5, 1.1)	0.8(0.3, 1.9)
≥ 8 Months (ref)	1.0	1.0	1.0	1.0
Overall p value	0.34	<0.01	0.24	0.55

Duration of Rifampin and Adjusted odds of outcomes –stratified by ART use

Duration of Rifampin	Failure: aOR (95% CI)[a]		Relapse: aOR (95% CI)[a]		Death: aOR (95% CI)[a]	
	ART		ART		ART	
	None / NR[b]	All / Some[c]	None / NR[b]	All / Some[c]	None / NR[b]	All / Some
2 Months	**0.9 (0.4, 2.0)**	**3.8 (0.7, 21.2)**	**6.7 (2.4, 19)**	**.01 (0, 0.2)**	**1.7 (1.0, 2.8)**	**0.2 (0.1, 1.3**
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**	**0.005**	**0.12**

Adjusted incidence rate ratios (aIRR) of failure and relapse in HIVTB cases by dosing schedule (Source – 2010 review)

Dosing schedule	Failure: aIRR* (95% CI)	Relapse: aIRR* (95% CI)	Death during Treatment: aIRR* (95% CI)
Initial phase daily	1.0 (reference)	1.0 (reference)	1.0 (reference)
Initial phase thrice weekly	4.0 (1.5, 10.4)	4.8 (1.8, 12.8)	1.3 (0.7, 2.3)
Overall p value	(.02)	(.002)	(0.42)

Conclusions

- In this review outcomes of treatment of HIV-TB better if:
  - At least 8months duration of rifampin therapy - IF NO ARV GIVEN
  - daily dosing (but significant only if ARV NOT given)
  - ARV given – most important effect detected