Official ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis (Nahid et al, CID 2016)

APPENDIX A: METHODS

Panel composition and meetings

We followed the procedures and methodology of the Guideline Development Checklist (available at: http://cebgrade.mcmaster.ca/guidelinechecklistonline.html) and the Guideline Development Tool (GDT), available at: http://www.gradepro.org/, to assemble a team of experts including specialists in pulmonary medicine, infectious disease, pharmacokinetics, pediatrics, primary care, and public health. The panel also included methodologists who helped in conducting systematic reviews, summarizing the evidence, formulating recommendations, and assessing the certainty in the evidence (also known as the quality of evidence) and rating the strength of the recommendations using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach [1, 2]. A face-to-face meeting was held in May 2014 and May 2015 coinciding with the ATS Conferences in San Diego and Denver. During the meetings, the guideline panel discussed specific questions, the existing research evidence, and drafted recommendations.

Disclosure of potential conflicts of interest

Guideline panel members disclosed all potential conflicts of interest according to the American Thoracic Society policies (see Financial Disclosures). The chairs (P. Nahid, S. Dorman, GB. Migliori, and A. Vernon) reviewed and managed all potential conflicts of interest of panel members. During all deliberations, panel members with potential conflicts of interest abstained from decisions about specific questions being asked and recommendations related to their potential conflict of interest. The ATS provided meeting facilities during its conference and financial support to perform systematic reviews to support recommendations. The views and interests of the ATS, as well as of any commercial entity that provided external funding for ATS, had no influence on the final recommendations.

Formulating specific clinical questions and determining outcomes of interest

We used the GDT and electronic questionnaires to brainstorm and subsequently prioritize questions related to the treatment of various forms of tuberculosis.

The following questions were prioritized and addressed in this document:

1. Does adding case management* interventions to curative therapy improve outcomes compared to curative therapy alone among patients with tuberculosis? *Case management: patient education/counseling, field/home visits, integration/coordination of care with specialists and medical home, patient reminders, incentives/enablers.
2. Does self-administered therapy (SAT) have similar outcomes compared to directly observed therapy (DOT) in patients with various forms of tuberculosis?
3. Does intermittent dosing in the intensive phase have similar outcomes compared to daily dosing in the intensive phase of treatment for drug-susceptible pulmonary tuberculosis?
4. 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 patients?
5. Does extending treatment beyond 6 months improve outcomes compared to the standard 6-month treatment regimen among pulmonary tuberculosis patients co-infected with HIV?
6. 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?
7. Does the use of adjuvant corticosteroids in tuberculous **pericarditis** provide mortality and morbidity benefits?

8. Does the use of adjuvant corticosteroids in tuberculous **meningitis** provide mortality and morbidity benefits?
9. Does a shorter duration of treatment have similar outcomes compared to the standard 6-month treatment duration among HIV-uninfected patients (adults and children) with paucibacillary TB (i.e., smear negative, culture negative)?

The writing committee selected outcomes of interest for each question following the approach suggested by the GRADE Working Group (http://www.gradeworkinggroup.org). All outcomes were identified a priori and the panel explicitly rated their relative importance for decision-making. Ranking outcomes by their relative importance can help to focus attention on those outcomes that are considered the most important and help to manage or clarify potential disagreements.

Literature search and selection of evidence

The methodologists (N. Alipanah, L. Chaisson, D. Menzies, G. Sotgui, A. Cattamanchi and P. Nahid) prepared evidence profiles (**See Appendix B**) for each question following the GRADE approach and using the GDT. The chairs (P. Nahid, A. Vernon, S. Dorman, and G.B. Migliori), and all guideline panel members, reviewed the summaries of evidence and made corrections when appropriate. The evidence profiles were based on a systematic review of the literature performed specifically for these guidelines.

Systematic review search methodologies were as follows:

PICO Question 1: Does adding case management* interventions to curative therapy improve outcomes compared to curative therapy alone among patients with tuberculosis? *Case management: patient education/counseling, field/home visits, integration/coordination of care with specialists and medical home, patient reminders, incentives/enablers.

Comparison: Incentives and enablers versus no intervention.

a) Search protocol:

Step	Search term (Medline)	Search terms (Cochrane)
1	Patient compliance[mh]	tuberculosis
2	Patient dropouts[mh]	patient compliance[mh]
3	Adherence	patient dropouts[mh]
4	Motivation[mh]	motivation[mh]
5	Social support[mh]	social support[mh]
6	Contracts[mh]	contracts[mh]
7	incentive	adherence
8	reward*	incentive*
9	voucher*	reward*
10	payment*	voucher*
11	reimbursement*	payment*
12	concordance	reimbursement*
13	cash transfer*	concordance
14	money	cash transfer*
15	token*	2-14/OR
16	1-15/OR	1 AND 15
17	tuberculosis	
18	MTB[tiab]	
19	mycobacterium TB	
20	17-19/OR	
21	16 AND 20	
Date conducted	4/9/14 (*from 1/1/2011*)[1, 2]	5/5/14
Results	792	272

1. An existing systematic review that addressed our question was identified [30].
2. If the population, intervention, comparator, outcomes, and databases used by the systematic review were the same as those that we planned to use, we simply updated the systematic review by applying the same search and selection criteria. If the population, intervention, comparator, outcomes, or databases used by the systematic

review were broader than those that we planned to use, we narrowed the search and selection criteria to address only our question.

b) Selection criteria:

Studies were selected if they (a) enrolled patients with active pulmonary TB, (b) employed a randomized controlled study or a quasi-experimental study, and (c) measured outcomes ranked as critical or important by the committee based on GRADE methodology. We planned to initially identify any existing systematic reviews and ranked these using AMSTAR. If a high quality systematic review addressing the PICO of interest existed, we sought to update the review with studies published after the review's conducted search. Where no suitable randomized trials were identified, we aimed to broaden our search to observational studies.

c) How many studies were selected:

2 articles met the inclusion criteria (see Appendix B, Evidence Profile 1).

Comparison: Reminders and tracers versus no intervention.

a) Search protocol:

Step	Search term (Medline)	Search terms (Cochrane)
1	tuberculosis	reminder systems[mh]
2	mtb[tiab]	electronic monitoring
3	mycobacterium tb	late patient tracer
4	1-3/OR	mobile applications[mh]
5	patient compliance[mh]	telecommunications[mh]
6	patient dropouts[mh]	mobile
7	cooperative behavior[mh]	text messag*
8	treatment refusal[mh]	SMS
9	medication adherence	1-8/OR
10	non-adherence	tuberculosis[kw]
11	nonadherence	TB
12	directly observed therapy	tuberculosis[mh]
13	5-12/OR	10-12/OR
14	reminder systems[mh]	9 AND 13
15	electronic monitoring	
16	late patient tracers	
17	mobile applications[mh]	
18	mobile	
19	text messag*	
20	telecommunications[mh]	
21	SMS	
22	14-21/OR	
23	4 AND 13 AND 22	
Date conducted	6/3/14 *(from 1/1/2007)*[1, 2]	6/3/14
Results	50	154

1. An existing systematic review that addressed our question was identified [531].
2. If the population, intervention, comparator, outcomes, and databases used by the systematic review were the same as those that we planned to use, we simply updated the systematic review by applying the same search and selection criteria. If the population, intervention, comparator, outcomes, or databases used by the systematic review were broader than those that we planned to use, we narrowed the search and selection criteria to address only our question.

b) Selection criteria:

Studies were selected if they (a) enrolled patients with active pulmonary TB, (b) employed a randomized controlled study or a quasi-experimental study, and (c) measured outcomes ranked as critical or important by the committee based on GRADE methodology. We planned to initially identify any existing systematic reviews and ranked these using AMSTAR. If a high quality systematic review addressing the PICO of interest existed,

we sought to update the review with studies published after the review's conducted search. Where no suitable randomized trials were identified, we aimed to broaden our search to observational studies.

c) How many studies were selected:

6 articles met the inclusion criteria (see Appendix B, Evidence Profile 2).

Comparison: Patient education and counseling versus no intervention.

a) Search protocol:

Step	Search term (Medline)	Search terms (Cochrane)
1	tuberculosis	patient compliance[mh]
2	mtb[tiab]	patient participation[mh]
3	mycobacterium tb	health education[mh]
4	1-3/OR	1-3/OR
5	patient compliance[mh]	tuberculosis[kw]
6	patient dropouts[mh]	TB
7	cooperative behavior[mh]	tuberculosis[mh]
8	treatment refusal[mh]	5-7/OR
9	medication adherence	4 AND 8
10	non-adherence	
11	nonadherence	
12	directly observed therapy	
13	5-12/OR	
14	health education[mh]	
15	counseling[mh]	
16	health promotion[mh]	
17	education	
18	counsel*	
19	14-18/OR	
20	4 AND 13 AND 19	
Date conducted	4/9/14 *(from 1/1/2011)*[1, 2]	6/3/14
Results	68	20

1. An existing systematic review that addressed our question was identified [23].
2. If the population, intervention, comparator, outcomes, and databases used by the systematic review were the same as those that we planned to use, we simply updated the systematic review by applying the same search and selection criteria. If the population, intervention, comparator, outcomes, or databases used by the systematic review were broader than those that we planned to use, we narrowed the search and selection criteria to address only our question.

b) Selection criteria:

Studies were selected if they (a) enrolled patients with active pulmonary TB, (b) employed a randomized controlled study or a quasi-experimental study, and (c) measured outcomes ranked as critical or important by the committee based on GRADE methodology. We planned to initially identify any existing systematic reviews and ranked these using AMSTAR. If a high quality systematic review addressing the PICO of interest existed, we sought to update the review with studies published after the review's conducted search. Where no suitable randomized trials were identified, we aimed to broaden our search to observational studies.

c) How many studies were selected:

3 articles met the inclusion criteria (see Appendix B, Evidence Profile 3).

PICO Question 2: Does self-administered therapy (SAT) have similar outcomes compared to directly observed therapy (DOT) in patients with various forms of tuberculosis?
Comparison: SAT versus DOT.

a) Search protocol:

Step	Search term (Medline)	Search terms (Cochrane)

1	tuberculosis	patient compliance[mh]
2	mtb[tiab]	patient participation[mh]
3	mycobacterium tb	health education[mh]
4	1-3/OR	1-3/OR
5	directly observed therapy	tuberculosis[kw]
6	supervised therapy	TB
7	directly observed treatment strategy	tuberculosis[mh]
8	DOT[tiab]	5-7/OR
9	DOTS[tiab]	4 AND 8
10	5-9/OR	
11	self administered therapy	
12	self supervised therapy	
13	unsupervised therapy	
14	11-13/OR	
15	4 AND 10 AND 14	
Date conducted	4/9/14 *(from 1/1/2006)*[1, 2]	5/15/14
Results	143	20

1. An existing systematic review that addressed our question was identified [133].
2. If the population, intervention, comparator, outcomes, and databases used by the systematic review were the same as those that we planned to use, we simply updated the systematic review by applying the same search and selection criteria. If the population, intervention, comparator, outcomes, or databases used by the systematic review were broader than those that we planned to use, we narrowed the search and selection criteria to address only our question.

b) Selection criteria:

Studies were selected if they (a) enrolled patients with active pulmonary TB, (b) employed a randomized controlled study or a quasi-experimental study, and (c) measured outcomes ranked as critical or important by the committee based on GRADE methodology. We planned to initially identify any existing systematic reviews and ranked these using AMSTAR. If a high quality systematic review addressing the PICO of interest existed, we sought to update the review with studies published after the review's conducted search. Where no suitable randomized trials were identified, we aimed to broaden our search to observational studies.

c) How many studies were selected:

6 articles met the inclusion criteria (see Appendix B, Evidence Profile 4).

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

PICO Question 4: 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 patients?

Comparison Question 3: intermittency versus daily in initial intensive phase
Comparison Question 4: intermittency versus daily in continuation phase

Search strategy

3 electronic databases were searched in Ovid; Medline,EmBase, and HealthSTAR. Search terms were tuberc* AND treat* AND intermittent. The search was limited to studies in humans, published in English since the beginning of each database. We also restricted to reviews to maximize specificity. Eligible studies were systematic reviews of treatment of tuberculosis, described methods of a systematic search, review and selection of studies, plus performed pooled analysis of intermittent regimens in the initial or continuation phase or both. Eligible reviews included randomized trials and/or cohorts but not other study designs, and did not include results from other systematic reviews (other than as part of the search).

Search results and selection of papers for the review:

In total 340 citations were identified, of which 14 full-text were selected for review. Of these 6 were not considered adequate systematic reviews (based on the criteria listed above) and 8 were included in the review.

Of these, one was a systematic review of randomized trials with head to head comparison of different intermittent schedules (this review identified only one such trial). Three systematic reviews included only randomized trials but included trials without head to head comparisons – these reviews pooled results of similar schedules, but across trials (essentially treating each arm of these RCTs as independent cohorts). Four systematic reviews included randomized trials and prospective cohort studies.

Four included adults or adults and children, and also HIV infected or uninfected. Two reviews described results in children only, two described results in HIV infected patients only (These last two were from the same group of authors with the second being an update of the first review).

PICO Question 5: Does extending treatment beyond 6 months improve outcomes compared to the standard 6-month treatment regimen among pulmonary tuberculosis patients co-infected with HIV?
Comparison: Treatment beyond 6 months versus standard 6 month treatment

A scoping review in March 2015 revealed no new RCT comparing different schedules of administration in treatment of HIV-TB. Hence no new search or review conducted. Hence all results in the GRADE tables for this PICO were taken from an existing systematic review published in 2012 [52].

PICO Question 6: 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?

Comparison: Early versus delayed antiretroviral therapy initiation

Step	Search term (Medline)	Search terms (Cochrane)
1	tuberculosis	tuberculosis[kw]
2	mtb[tiab]	TB
3	mycobacterium tb	tuberculosis[mh]
4	1-3/OR	1-3/OR
5	HIV[mh]	HIV[mh]
6	hiv	hiv
7	human immunodeficiency virus	human immunodeficiency virus
8	5-7/OR	5-7/OR
9	Antiretroviral Therapy, Highly Active[mh]	Antiretroviral Therapy, Highly Active[mh]
10	art	art
11	anti-retroviral therapy	anti-retroviral therapy
12	antiretroviral therapy	antiretroviral therapy
13	arv*	arv*
14	haart[tiab]	haart
15	9-14/OR	9-14/OR
16	drug therapy	drug therapy
17	treatment*	treatment*
18	regimen*	regimen*
19	16-18/OR	16-18/OR
20	4 AND 8 AND 15 and 19	4 AND 8 AND 15 and 19
Date conducted	5/12/14	5/12/14

Inclusion criteria:

- Randomized controlled trials evaluating early vs. delayed ART
- Enrolling HIV-infected patients with active TB (smear-positive, culture-positive, or clinical diagnosis)
- Measured outcomes determined by GRADE committee

Studies included: 9 (see Appendix B, Evidence Profile 13).

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

Comparison: Adjuvant corticosteroids versus no corticosteroids

Step	Search term (Medline)	Search terms (Cochrane)
1	tuberculosis	tuberculosis[kw]

2	mtb[tiab]	TB
3	mycobacterium tb	tuberculosis[mh]
4	1-3/OR	1-3/OR
5	pericard*	pericard*
6	steroid	steroid
7	4 AND 5 AND 6	4 AND 5 AND 6
Date conducted	9/3/14	9/3/14

Inclusion criteria:

- Randomized controlled trials steroids vs. placebo for treatment of TB pericarditis
- Enrolling patients with TB pericarditis
- Measured outcomes determined by GRADE committee

Studies included: 5 (6 were identified, but 1 excluded as an outdated regimen no longer deemed acceptable was used (Schrire V. S Afr Med J 1959); see Appendix B, Evidence Profile 14).

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

Comparison: Adjuvant corticosteroids versus no corticosteroids

Step	**Search term (Medline)**	**Search terms (Cochrane)**
1	tuberculosis	tuberculosis[kw]
2	mtb[tiab]	TB
3	mycobacterium tb	tuberculosis[mh]
4	1-3/OR	1-3/OR
5	mening*	mening*
6	steroid	steroid
7	4 AND 5 AND 6	4 AND 5 AND 6
Date conducted	8/14/14	8/14/14

Inclusion criteria:

- Randomized controlled trials steroids vs. placebo for treatment of TB meningitis
- Enrolling patients with TB meningitis
- Measured outcomes determined by GRADE committee

Studies included: 5 (9 were identified, but 3 were excluded because non-rifamycin-based regimens were used [79, 80, 82], and 1 was excluded due to insufficient data to perform analyses (Lardizabal DV, Philippines J Neurol 1998); see Appendix B, Evidence Profile 15).

PICO Question 9: Does a shorter duration of treatment have similar outcomes compared to the standard 6-month treatment duration among HIV-uninfected patients (adults and children) with paucibacillary TB (i.e., smear negative, culture negative)?

Comparison: Treatment for less than six months versus treatment for six months.

a) Search protocol:

Step	**Search term (Medline)**	**Search terms (Cochrane)**
1	tuberculosis	paucibacillary
2	mtb[tiab]	abacillary
3	mycobacterium tb	smear-negative
4	1-3/OR	culture-negative
5	smear-negative	treatment
6	culture-negative	1-4/OR
7	“sputum microbiology”	tuberculosis[kw]
8	sputum/microbiology[majr]	TB
9	paucibacillary	tuberculosis[mh]
10	pauci-bacillary	7-9/OR
11	5-10/OR	5 AND 6 AND 10

12	antitubercular agents	
13	therapeutic use[mh]	
14	isoniazid	
15	rifampin	
16	12-15/OR	
17	4 AND 11 AND 16	
Date conducted	6/19/14	10/08/14
Results	617	100

b) Selection criteria:

Studies were selected if they (a) enrolled patients with active pulmonary TB, (b) employed a randomized controlled study or a quasi-experimental study, and (c) measured outcomes ranked as critical or important by the committee based on GRADE methodology. We planned to initially identify any existing systematic reviews and ranked these using AMSTAR. If a high quality systematic review addressing the PICO of interest existed, we sought to update the review with studies published after the review's conducted search. Where no suitable randomized trials were identified, we aimed to broaden our search to observational studies.

c) How many studies were selected:

2 articles met the inclusion criteria (see Appendix B, Evidence Profile 16).

Appraisal of the guideline panel's "certainty in the evidence" for all recommendations

We followed the methods of the Cochrane Collaboration (http://handbook.cochrane.org) and assessed the risk of bias at the outcome level using the Cochrane Collaboration's risk of bias tool (Higgins JP, et al. BMJ 2011). Subsequently, we assessed the certainty in the evidence (i.e., confidence that the estimated effects are true) for each of the outcomes of interest following the GRADE approach based on the following criteria: risk of bias, precision, consistency and magnitude of the estimates of effects, directness of the evidence, risk of publications bias, presence of dose–effect relationship, and an assessment of the effect of residual, opposing confounding. Certainty in the evidence was categorized into 4 levels ranging from very low to high. We prepared the evidence-to-decision tables based on the estimates of the health effects, values and preferences and resource use.

Formulation of clinical recommendations

We prepared evidence profiles that described the summary of findings and quality of evidence assessment for each outcome, as well as evidence-to-decision tables that described the estimates of the health effects, values and preferences, and resource use. The guideline panel used the evidence summaries and the evidence-to-decision tables to formulate its recommendations.

For each recommendation, the guideline panel considered and agreed on the following: The quality of the evidence, the balance of desirable and undesirable consequences of compared management options and the assumptions about the values and preferences associated with the decision. The guideline panel also explicitly took into account possible extent of resource use associated with alternative management options. Recommendations were decided by consensus and no recommendation required voting. The panel agreed on the final wording of recommendations and remarks with further qualifications for each recommendation. The final recommendations were reviewed and approved by all members of the guideline panel.

Statements about the underlying values and preferences as well as qualifying remarks accompanying each recommendation are its integral parts and serve to facilitate more accurate interpretation; they should never be omitted when quoting or translating recommendations from these guidelines.

Rating the strength of the recommendations

We rated the recommendations as either "strong" or "weak/conditional" according to the GRADE approach. We used the words "the panel members recommend" for strong recommendations and "the panel members suggest" for weak/conditional recommendations. **Table 12** provides suggested interpretation of strong and conditional recommendations by patients, clinicians and health care policy makers. Understanding the

interpretation of these two grades of strength of recommendations is essential for health care decision-making and has explicit implications as follows:

Strong recommendation

- For patients: Most individuals in this situation would want the recommended course of action, and only a small proportion would not.
- For 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.
- For policy makers: The recommendation can be adopted as policy in most situations.

Weak/Conditional recommendation.

- For patients: The majority of individuals in this situation would want the suggested course of action, but many would not.
- For clinicians: 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.
- For policy makers: Policy-making will require substantial debate and involvement of various stakeholders.

Document review

A final draft of the guidelines was reviewed and approved by each member of the guideline panel. It was subsequently peer reviewed by experts in the field. The document was revised to incorporate the pertinent comments suggested by the peer reviewers. Once the peer reviewers were satisfied with the guidelines, the document was further reviewed and edited by the co-sponsoring societies (American Thoracic Society, Infectious Diseases Society of America, and Centers for Disease Control and Prevention) and endorsing organizations (European Respiratory Society and the US National TB Controllers Association), as well as by representatives from the Community Research Advisors Group (CRAG) of the Treatment Action Group (http://www.treatmentactiongroup.org/tb/community-engagement/crag). Once all of the co-sponsoring societies were satisfied with the quality of the document, it was formally approved and sent for publication.

References:

Please see Official ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis document for full references for citations listed in Appendix A.