Mayo Clinic Center for Tuberculosis

CDC/IDSDA/ATS 2016 Updated TB Treatment Guidelines: What’s new?

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Disclosure

• No financial conflicts of interest
Objectives

1. Identify where updated guidelines provide:
   A. *New recommendations* in TB mgmt.
   B. Similar recommendations as noted previously (2003 Statement)

2. Challenges and opportunities implementing new/updated 2016 TB Guidelines
Important Caveat when using updated TB Guidelines - I

• Recommendations given are **NOT** applicable across all levels of resources that are available to tuberculosis control programs worldwide.

• These guidelines are intended for (relatively well resourced) areas with routine availability of:
  • Mycobacterial cultures
  • Molecular and phenotypic drug susceptibility tests
  • Radiographic facilities are routinely available

• Underresourced TB Programs (globally) have protocol differences - via
  • WHO, PAHO, etc
Important Caveat when using updated TB Guidelines - II

How to use Medical Guidelines:

• Every medical guideline is a document with the objective of guiding decisions and outlining criteria for the diagnosis, management, and treatment in specific medical conditions

• Guidelines are designed to be ‘evidence-based’ recommendations; for relatively commonly encountered clinical situations
  • But cannot account for every type of patient, disease presentation or social context

• Thus, Guidelines are NOT directives, orders or mandates
  • Use of guidelines must be integrated within the clinical and social context of every patient and resource setting
Important Caveat when using updated TB Guidelines - III

Health providers should try to adhere to published recommendations; however, many clinical patient presentations / circumstances will require some degree of flexibility and periodic creativity in order to delivery and complete the best therapy possible.

Examples:

- My 1st patient at Mayo (July 2000): 32 yo Somali woman, 8 mo. pregnant with cavitary pulmonary MDR TB; 4 other children at home and husband with abnormal CXR.

- Sheboygan, WI public health managing older Hmong woman with MDR TB and refusing therapy (noting cultural differences).
2016 TB Guidelines Methodology

• Nine **PICO** questions were composed and addressed
  
  - Population, intervention, comparators, outcomes

• Recommendations are based on GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology to assess certainty of evidence and rate strength of recommendations:
  
  - Incorporating patient values and costs as well as judgments about trade-offs between benefits and harms
**PICO Question #1:** Does adding case management interventions to curative therapy improve outcomes compared to curative therapy alone among patients with tuberculosis?

- **Case management defined as…**
  - Patient education/counseling
  - Patient reminders
  - Field/home visits
  - Incentives/enablers
  - Integration/coordination of care with specialists and medical home

- **Recommendation 1:** “We suggest using case management interventions during treatment of patients with tuberculosis:
  - *(conditional recommendation; low certainty in the evidence)*
PICO Question #1: Does adding case management interventions to curative therapy improve outcomes compared to curative therapy alone among patients with tuberculosis?

Why only a “conditional recommendation” here?

• “The quality of evidence is variable in the few studies examining the impact of case management interventions on outcomes such as treatment success”

• “However, these studies suggest that for the most part, patient-centered case management interventions are helpful with little evidence of harm to patients”

• Discussions - Panel felt quite strongly that case management was an integral component towards successful TB patient outcomes
PICO Question 2: Does self-administered therapy (SAT) have similar outcomes compared to directly observed therapy (DOT) in patients with various forms of 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)

• Nov 2016 Panel Discussion: “OK - Got it, but why not use stronger language in recommending DOT for all patients?”
DOT remains ‘standard’ component of TB management – but a few caveats:

- Systematic reviews (high/med/low TB burden countries have not shown improvement in cure, treatment completion, mortality and disease relapse with DOT vs. SAT

- However – DOT (compared to SAT) was associated with significant improvements in:
  - Treatment success (sum of pts cured & completing treatment)
  - Increased sputum conversion during treatment
Important considerations with DOT - I

- DOT is a part of a “multi-faceted” public health strategy for TB mgmt and thus:
  - Difficult to measure specific benefit in clinical trials
  - Note: clinical trials setting not always reflective of “real world” practice – Caution with interpretation:
    - Clinical Trials typically with higher monitoring/more patient engagement
    - SAT in clinical trial setting may artifactually appear as good as DOT
Important considerations with DOT - II

• Population studies suggest DOT (compared to SAT) have been associated with:
  1. Reduction in acquisition and transmission of DR TB
  2. Increased treatment success in HIV (+) pts receiving RFB-TB regimens
  3. Shorter duration for TB tx completion
  4. Higher treatment completion rates in incarcerated pts transitioning to community setting
  5. Reduction in mortality and loss to f/u

Nov 2016 RTMCC webinar panel felt strongly that DOT remains the standard of TB care in US
Lake Tahoe

Nevada

California
**PICO Question 3:** 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?

- **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).*

- Based on systemic reviews, daily therapy was felt to be superior to intermittent therapy
  - More important during intensive phase (higher bacillary burden)
Intermittent vs. Daily Therapy

• Single trial with 399 pts (Hong Kong)
• Trial compared treatment 3x/week with daily therapy for six months (RIPE).
• Results:
  • No difference in cure rate between groups:
    • 198 out of 199 people in the 3x/wk group
    • All 200 pts in the daily group
  • However → 5 (1 in 198; 2.5%) patients relapsed in the 3x/wk group compared to 1 (1 in 200; 0.5%) in the daily tx group
Dosing schedules of 6-month regimens and relapse.


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

**Daily through-out** – Lowest: \( \text{RR} = 1.0 \)

**Daily then 3X weekly**: \( \text{RR} = 1.6 \)

**Daily then 2X weekly**: \( \text{RR} = 2.8 \)

**3x weekly through-out**: \( \text{RR} = 5.0 \)
- greatest risk if cavitation or 2 month culture positive
- Also greater if followed by 1X weekly Rifapentine
**PICO Question 3:** 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?

- **Recommendation 3b:** Use of thrice-weekly therapy in the intensive phase (with or without an initial 2 weeks of daily therapy) may be considered in patients who are **not HIV-infected** and are also at **low risk of relapse**

  Examples:
  - Pulmonary, non-cavitary and/or smear neg. TB
  - Drug susceptible disease

  *(conditional recommendation; low certainty in the evidence)*

- *Option less favored → associated with higher rates of treatment failure, relapse, drug resistance*
PICO Question 3: 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?

- **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)*.

- The “Denver regimen”
  
  - Some TB programs reported long standing treatment success with this program
  
  - Not generally recommended because of lack of high quality evidence to support its use
### Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms - 2016

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Intensive Phase</th>
<th>Continuation Phase</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Interval and Dose&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Drugs</td>
</tr>
<tr>
<td>1</td>
<td>INH RIF PZA EMB</td>
<td>7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)</td>
</tr>
<tr>
<td>2</td>
<td>INH RIF PZA EMB</td>
<td>7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)</td>
</tr>
<tr>
<td>3</td>
<td>INH RIF PZA EMB</td>
<td>3 times weekly for 24 doses (8 wk)</td>
</tr>
<tr>
<td>4</td>
<td>INH RIF PZA EMB</td>
<td>7 d/wk for 14 doses then twice weekly for 12 doses&lt;sup&gt;e&lt;/sup&gt;</td>
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</tbody>
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**Regimen Effectiveness**
- Greater

This is the preferred regimen for patients with newly diagnosed pulmonary tuberculosis.

Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.

Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance.

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.
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?

- **Recommendation 4a:** “We recommend the use of daily or 3x/weekly dosing in the continuation phase of therapy for drug-susceptible pulmonary tuberculosis”
  - *(strong recommendation; moderate certainty in the evidence)*.

- Feb 3, 2017 RTMCC Guidelines webinar:
  - Daily vs. 3x/week treatment options in continuation phase need to be *taken in context* – examples:
    - Local health department resources
    - Severity of patient’s TB disease
    - Drug susceptibility testing
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?

• **Recommendation 4b**: If intermittent therapy is to be administered in the continuation phase, then suggested use of **3x/weekly** instead 2x/weekly
  
  • *(conditional recommendation; low certainty in the evidence)*.

• Allows for the possibility of some doses being missed / more flexible compared with BIW
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?

• **Recommendation 4c**: “We recommend against the use of once-weekly therapy with INH and rifapentine in the continuation phase”
  - *(strong recommendation; high certainty in the evidence)*.

• The exception:
  - In uncommon situations where more than once-weekly DOT is difficult to achieve, once-weekly continuation phase therapy with INH 900 mg plus RPT 600 mg may be considered for use only in HIV-uninfected persons without cavitation on chest radiography.
Nevada Ghost Towns
- Comstock Load / Silver Mining
- Western migration 1850’s
**PICO Question 5:** Does extending treatment beyond 6 months improve outcomes compared to the standard 6-month treatment regimen among pulmonary tuberculosis patients coinfected with HIV?

- **Recommendation 5a:** “For HIV-infected patients receiving ART, we suggest using the standard 6-month daily regimen consisting of an intensive phase of 2 months of INH, RIF, PZA, and EMB followed by a continuation phase of 4 months of INH and RIF for the treatment of drug-susceptible pulmonary tuberculosis”
  - *(conditional recommendation; very low certainty in the evidence).*
Duration of TB therapy in HIV Co-infected patients - Background

• Retrospective reviews of HIV-TB co-infected patients do show ↓ relapse rates with both daily therapy and extended therapy (e.g. 8 mo)

• However, many studies:
  • Evaluated Non-randomized cohorts
  • Were retrospective reviews that occurred before wide implementation of HAART (effective ART) or without HIV therapy at all
  • Often using intermittent therapy (in adv AIDS pts)
Duration of TB therapy in HIV Co-infected patients - Background

• Limited data available for RCTs involving HIV-TB patients on HAART– do show fairly comparable rates of relapse in HIV and non-HIV pts treated for 6 months of standard combination TB therapy
  • Mfinanga S. et al. Lancet Inf Dis 2014;14:563-71

• Therefore: **6 months** remains standard TB therapy duration in HIV co-infected pts receiving HAART

• **Side note:** consider extending for immunologically advanced HIV pts with heavy TB disease burden (initially) and slow response to therapy
Duration of TB therapy in HIV Co-infected patients - Background

Favor longer durations in therapy for HIV co-infected pts in those who:

• Are not taking HAART (PICO #6)
• Similar as in HIV neg. pts with TB
  • Both (+) cavitary disease & (+) MTB cultures at completion of 2 months therapy
  • Consider in patients with *either* (+) cavitary disease & (+) MTB cultures at completion of 2 months therapy and with slow clinical response to TB therapy
• Drug resistant TB
• Select forms of extrapulmonary TB
  • CNS TB
  • Bone/Joint/Vertebral TB
PICO Question 5: Does extending treatment beyond 6 months improve outcomes compared to the standard 6-month treatment regimen among pulmonary tuberculosis patients coinfected with HIV?

• Recommendation 5b: In uncommon situations in which HIV-infected patients do NOT receive ART during tuberculosis treatment, we suggest extending the continuation phase with INH and RIF for an additional 3 months (9 mo total therapy) for treatment of drug-susceptible pulmonary tuberculosis

  • (conditional recommendation; very low certainty in the evidence).
PICO Question 6: Does initiation of ART during tuberculosis treatment compared to at the end of tuberculosis treatment improve outcomes among tuberculosis patients coinfected with HIV?

• **Recommendation 6:** We recommend initiating ART during tuberculosis treatment.
  
  • Antiretroviral therapy should ideally be initiated within the **first 2 weeks** of tuberculosis treatment for patients with CD4 counts <50 cells/µL and
  
  • by **8–12 weeks** of tuberculosis treatment initiation for patients with CD4 counts ≥50 cells/µL
  
  • *(strong recommendation; high certainty in the evidence)*

• Note: an exception is patients with HIV infection and tuberculous meningitis
The use of ART during TB therapy in HIV co-infected pts reduces both mortality and AIDS-assoc. conditions

• **SAPiT trial**: Randomized HIV-TB pts with CD4 < 500 cells into 3 groups:
  - Immediate group (ART start after 2-4 weeks TB therapy)
  - Early group (ART start at 8-12 weeks of TB therapy)
  - Deferred group (ART started after TB therapy – 6 mo)

  - Patients receiving immediate or early ART had **56% reduction** in relative risk of death (compared to deferred group)
  - The death rate rose from **5.4 to 12.1** per 100 person-years when initiation of ART was delayed until the completion of TB therapy

The use of ART during TB therapy in HIV co-infected pts reduces both mortality and AIDS-assoc. conditions

• **CAMELIA** (Cambodian Early versus Late Introduction of Antiretrovirals)
  • 661 pts randomly assigned to
    • Earlier ART (2 weeks after starting TB tx) or
    • Later ART (8 weeks after starting TB tx)

• **34% reduction in mortality** among pts in “Early ART” group compared with “Later ART” group

• Advanced HIV pts – with medial CD4 ~ 25

N Engl J Med 2011;365:1471-81
The use of **ART** during TB therapy in HIV co-infected pts reduces both mortality and AIDS-assoc. conditions

**ACTG A5221 STRIDE**

- Open-label, randomized study comparing earlier ART (within 2 weeks of starting TB tx) with later ART (between 8 and 12 weeks) in HIV-1 infected patients
- CD4+ T-cell counts of less than 250

- In the earlier-ART group, **12.9% of patients** had a new AIDS-defining illness or died by 48 weeks
- **16.1%** with AIDS-illness or death in the later-ART group (95% confidence interval [CI], −1.8 to 8.1; P = 0.45).

N Engl J Med 2011;365:1482-91
CDC/RTMCC Webinar Nov 2016 Take home points with HIV-TB co-Management

• Need to monitor for IRIS (immunologic reconstitution inflammatory syndrome)
  • More common in all 3 studies with patients starting ART early

• IRIS is a diagnosis of exclusion
  • Need to evaluate r/o other ddx considerations - examples:
    • Drug-resistant TB
    • Opportunistic infection (PCP, crypto, CMV, Toxoplasma, etc)
    • Malignancy
CDC/RTMCC Webinar Nov 2016 Take home points with HIV-TB co-Management

• TB with HIV and/or HBV/HCV – requires close communication and "Team Approach" with HIV and TB providers (and/or hepatitis providers)
  • Public health: the “Quarterback” of the health care team
  • Foster dialogue and ensure a commonly understood patient care “game plan”
Winters in Nevada
- Downhill Skiing!!
**PICO Question 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).*
**PICO Question 7:** Does the use of adjuvant corticosteroids in tuberculous pericarditis provide mortality and morbidity benefits?

- RCT with 1400 pts with suspected pericardial TB (with and w/o steroids given)
  - 2/3 pts enrolled were HIV (+)
  - No difference in mortality, cardiac tamponade or constrictive pericarditis
    - The incidence of constrictive pericarditis and hospitalization were both significantly lower in pts on steroids
    - However, incidence of cancer, primarily Kaposi sarcoma, was increased in pts on steroids

- Recommendation not to routinely use steroids for pericardia TB
  - Consider for pts with Lg pericardial effusions, high inflammatory exudate or with early signs of constriction

**PICO Question 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 tapered over 6–8 weeks for patients with tuberculous meningitis”
  - *(strong recommendation; moderate certainty in the evidence)*

- **Note:** Duration of steroids for CNS TB *can be variable* and occasionally prolonged
  - Weeks – to – months (based on pt response)
PICO Question 9: Does a shorter duration of treatment have similar outcomes compared to the standard 6-month treatment duration among HIV-uninfected patients with paucibacillary tuberculosis (ie, smear negative, culture negative)?

• Recommendation 9: “We suggest that a 4-month treatment regimen is adequate for treatment of HIV-uninfected adult patients with AFB smear- and culture-negative pulmonary tuberculosis”
  • (conditional recommendation; very low certainty in the evidence).
Culture-negative TB – different mgmt options can apply

- **CDC/ATS/IDSA**: 4 months total therapy
  - 2 mo (INH/RIF/PZA/EMB)
  - 2 mo (INH/RIF)

- **In Minnesota**, 12%-18% of TB cases are INH-resistant and a very large percentage of these patients are Somali
  - Concern for INH-resistant culture-neg. TB and risk of MDR TB development

- **Mayo/Olmsted Co**: Continue all 4-drug TB drugs for 4-6 months therapy
The End

• Questions??

– “Nev-AD-a,” or “Nev-a-duh”
– NOT “Nev-AH-da”