TB Intensive
San Antonio, Texas
November 29-December 2, 2011

TB Disease: ATS/CDC/IDSA Treatment Guidelines
Barbara Seaworth, MD, FIDSA, FACP
November 30, 2011

Barbara Seaworth, MD, FIDSA, FACP has the following disclosures to make:

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- No other relevant financial relationships with any commercial companies pertaining to this educational activity
Treatment of Tuberculosis

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Heartland National TB Center

Objectives

• Identify standard regimens for treatment of drug susceptible TB
• Discuss strategies resulting in improved patient outcomes
  – Intensity of dosing
  – Prolongation of therapy
• Recognize those at risk of poor outcomes
• Manage a TB suspect
Purpose

What’s New In this Document

CONTENTS OF

1. Introduction and Background

2. Organization and Supervision of Treatment

3. Drugs in Current Use

4. Principles of Antituberculosis Chemotherapy

5. Recommended Treatment Regimens

6. Practical Aspects of Treatment

7. Drug Interactions

8. Treatment in Special Situations

9. Management of Relapse, Treatment Failure, and Drug Resistance

10. Treatment of Tuberculosis in Low Income Countries: Recommendations and Guidelines of the WHO and the IUATLD

11. Research Agenda for Tuberculosis Treatment

USPHS/IDSA

Evidenced-based Rating Scale

- Strength of the Recommendation
  - A = Preferred
  - B = Acceptable alternative
  - C = Offer when unable to give A or B
  - D = Should generally NOT be offered
  - E = Should NEVER be offered

- Quality of Supporting Evidence
  - I = Randomized clinical trial
  - II = Clinical trial, not randomized
  - III = Expert opinion
Strategies Stressed in Guidelines

• **Identification of patients at increased risk of relapse**
  – Obtain sputum smear and culture at end of initial phase of treatment (2 months)

• **Extended therapy** for patients with drug-susceptible pulmonary TB
  – Who have **cavitation** on initial CXR
  – Who have a **positive sputum culture at 2 months**

• **Counting Doses**
  – Define treatment completion by number of doses taken as well as duration of treatment

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Strategies Stressed in Guidelines

• **RIFABUTIN** (RBT): May be used as a primary drug for patients (especially HIV+) receiving medications having unacceptable interactions with rifampin (e.g. Protease Inhibitors, methadone)

• **Fluoroquinolones** (Levofloxacin or Moxifloxacin) may be used when first line drugs are not tolerated or the organism is resistant
Treatment of Culture-Positive Drug Susceptible Pulmonary TB

• General conclusions from the literature:
  – 6 mo (26 wk) is the \textit{MINIMUM} duration of RX
  – 6 mo regimens require rifampin and INH throughout and PZA for the first 2 months
  – 6 – 9 mo regimens are effective without INH if PZA given throughout
  – Intermittent regimens (2-3x/wk): DOT ONLY!
    • Drug susceptible isolate

Treatment of Culture-Positive Drug Susceptible Pulmonary TB

• General conclusions from the literature:
  – Without PZA - minimum duration is 9 months
  – Without rifampin - minimum duration is 12 months (up to 18 months)
  – Streptomycin and ethambutol (EMB) are approximately equivalent in effect
    • Because of high incidence of Streptomycin resistance ethambutol is preferred for initial therapy
      – Use streptomycin only if isolate is proven susceptible
Treatment Regimens for TB Disease

- **Initiation phase** of therapy
  - 8 weeks
  - INH, Rifampin and PZA +/- EMB
- **Continuation phase** of therapy
  - 16 weeks
  - INH and Rifampin

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Treatment of Culture Positive Pulmonary Tuberculosis

Regimens Rated **A-1 (HIV Uninfected)**

**INITIAL PHASE**
- 2 mo I,R,Z,E daily (56 doses, 8wks) or
- 2 mo I,R,Z,E 5x/wk (40 doses, 8wks) then

**CONTINUATION PHASE**
- 4 mo - I,R daily (126 doses, 18 wks) or
- 4 mo – I,R 5x/wk (90 doses, 18 wks) or
- 4 mo – I,R, 2x/wk (36 doses, 18 wks)
Treatment of Culture Positive Pulmonary Tuberculosis

– **Regimens Rated A-II (HIV Uninfected)**
  - 2 weeks – I,R,Z,E daily (14 doses) **then**
  - 6 weeks – I,R,Z,E **twice** weekly (12 doses)

  • PLUS (DOT only)
  • -4mo – I,R Twice weekly (36 doses, 18 weeks) **or**

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Treatment of Culture Positive Pulmonary Tuberculosis

– **Regimens Rated A-III (HIV Uninfected)**
  - 2 weeks – I,R,Z,E **5x/week** (10 doses) **then**
  - 6 weeks – I,R,Z,E **twice** weekly (12 doses)

  – PLUS (DOT only)
  • -4mo – I,R Twice weekly (36 doses, 18 weeks) **or**
Treatment of Culture Positive Pulmonary TB

– THRICE WEEKLY – “HONG KONG” REGIMEN
  » Regimen Rated BI (HIV uninfected)

– Initial phase
  • 2mo – I,R,Z,E 3x/week (24 doses, 8weeks)

PLUS

– Continuation phase
  • 4mo – I,R 3x/wk (54 doses, 18 weeks)

Nucleic Acid Amplification NAAT

• FDA cleared for respiratory specimens
  – M.tb Direct Test® (MDT) (Gen-Probe®)
    – also referred to as PCR tests

• DNA probe detects M TB complex RNA directly in the sputum
  – >95% sensitive for AFB smear + TB
  – 55 – 75% of AFB smear – (culture +) patients detected

• Does not distinguish live and dead bacilli
CDC Recommendations for NAAT

• “NAAT should be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities.”

Why Use A NAAT?

• Confirms AFB + case as M TB

• If AFB + case is NAAT negative on 2 specimens
  – Suspect this is not M TB
    • Suspend Contact investigation and
    • Hold TB treatment unless TB strongly suspected.

• If patient is not strongly suspected as M TB and is NAAT negative x 2,
  – Remove from isolation.
Case Management

• Monthly clinical visit
  – check response to therapy,
  – evaluate for toxicity:
    • hepatitis, visual acuity, Ishihara Plates
  – repeat education (document!)

• Monthly laboratory to check liver enzymes, CBC

• Document susceptibility of isolate prior to stopping ethambutol

Pt educated regarding:
  signs/symptoms of visual and liver toxicity & need
to report these to provider

Case Management

• For pulmonary TB – Monthly sputum until two consecutive cultures are negative
  – -2 month sputum is crucial
  – 80% should convert by 2 months, 95% by 3 months
Drug Susceptibility Tests

- INH, Rifampin, Ethambutol, and PZA are recommended for *each initial* isolate
- Expect results by day 28
- If the private lab does not do susceptibilities, referral may lead to unnecessary delays
  - Positive culture should be sent for DST within 24 hrs, lab should not wait for culture to grow on solid media

When should I consider my specimen delayed?

<table>
<thead>
<tr>
<th>Day</th>
<th>Specimen received in the lab</th>
<th>At 24 hours, expect smear results</th>
<th>At 48 hours, expect results of NAAT or Molecular DST</th>
<th>At 72 hours, expect results of IGRA</th>
<th>At 21 days, expect a culture ID (TB or not)</th>
<th>At 28 days, expect 1st line susceptibility results, expect 2nd line 4 weeks after requested</th>
<th>At 6-8 weeks, expect the culture to be finalized if negative</th>
</tr>
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When Should You Expect the Culture to Turn Positive?

Time to Culture Positive by Presence of Cavitary Lesions

Figure 1 Pre-treatment TTP (in days) and absence or presence of single or multiple cavities. There is a significant trend in TTP on the log scale (P < 0.001). Figures represent median TTP. Dots represent outliers more than 1.5 times the interquartile range beyond the upper quartile on the log scale. TTP = time to positivity.

Perrin Int J TB Lung Dis, Dec 2010

Figure 2 Pre-treatment TTP (in days) and radiological extent of disease defined by Simon. There is a significant trend in TTP on the log scale (P < 0.001). Figures represent median TTP. Dots represent outliers more than 1.5 times the interquartile range beyond the upper quartile on the log scale. TTP = time to positivity.

Perrin Int J TB Lung Dis, Dec 2010
What About Ethambutol?

• A four drug regimen is recommended until susceptibility tests are reported

• If treatment is being initiated after drug susceptibility tests are known and the organisms are susceptible, ethambutol is not necessary if patient is given both INH and rifampin

• Ethambutol can be stopped as soon as the lab reports an isolate susceptible to INH & rifampin.

TBTC STUDY 22: RATE OF FAILURE or RELAPSE, BY REGIMEN, SPUTUM CULTURE, AND CHEST RADIOGRAPH

<table>
<thead>
<tr>
<th>Rate of Failure/Relapse (%)</th>
<th>Positive</th>
<th>Negative</th>
<th>Cavitary</th>
<th>Non-Cavitary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive culture at 2 mo</td>
<td>26.7%</td>
<td>3.8%</td>
<td>8.9%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Chest radiograph at study entry</td>
<td>20%</td>
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</tbody>
</table>

Prolongation of Continuation Phase

Continuation phase increased to 7 mo if initial CXR is cavitary & culture is positive at 2 mo

- Rational for Extending Therapy
  - Continuation of PZA for an additional 2 months was not helpful in drug susceptible disease
  - Prolongation of continuation phase by 2 months decreased relapses in silico-tuberculosis from 20% to 2%

Effect of Prolonging Therapy on Treatment Failure or Relapse

Treatment of Silico-tuberculosis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>SHRZ - 6mo*</th>
<th>SHRZ – 8mo*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=49)</td>
<td>(n=50)</td>
</tr>
<tr>
<td>Relapse</td>
<td>20%</td>
<td>2%</td>
</tr>
</tbody>
</table>

* Three times weekly therapy

Am Rev Respir Dis 1991;143:262-267
End of Therapy (EOT) Cavity: A Risk Factor for Relapse

![Graph showing proportion of subjects with tuberculosis relapse by findings on early and EOT CXR. EOT = end of treatment; CXR = chest radiograph.]

Hamilton; Int J Tuber Lung Dis 2008

New Treatment Guidelines Tailoring Treatment Regimens

- Prolongation of continuation phase
  - Positive 2 month culture with cavitary disease
  - Extrapulmonary disease
    - Meningitis
    - Disseminated disease in children
  - HIV TB in children and adolescents

ATS, CDC, IDSA: Treatment of Tuberculosis 2003
Additional New Treatment Guidelines
Tailoring Treatment Regimens

• **Consider** - Prolongation of continuation phase when patient:
  – Slow to clinically or radiographically respond
  
  – Positive 2 month culture OR cavitary disease?
  
  – End of therapy (EOT) cavity present
  
  – <10% ideal body weight?

Relapse

• Circumstance in which a patient becomes and remains culture-negative while receiving antituberculosis drugs but at some point after completion of therapy, either becomes culture-positive again or experiences clinical and radiographic deterioration consistent with active tuberculosis

• Try to identify “WHY” your patient relapsed so you can do it right this time!
Treatment Guidelines 2003

• “Microbiological Confirmation of Relapse Should be Pursued Vigorously”
  – Confirm relapse bacteriologically
  – Use DNA fingerprinting to identify new infection causing the disease versus relapse
  – Identify drug susceptibility pattern of isolate

Relapsed Tuberculosis

• Most relapses occur within the first 6 – 12 months after stopping therapy but some occur 5 or more years later

  • Nearly all drug susceptible patients who were treated with a rifamycin and received DOT will relapse with drug susceptible organisms

  – Treat with standard RIPE regimen
Relapsed Tuberculosis Management Strategies

• If culture & susceptibility studies (those treated in other countries) were not done but treatment given by DOT
  
  – Usual treatment with RIPE
    • Watch carefully for clinical deterioration -
      – Consider expanding the regimen by adding at least 2 drugs
  
  – Consider an expanded regimen if immune suppressed, significantly ill, or extensive disease

Relapsed Tuberculosis Management Strategies

• Suspect drug resistance if
  
  – Patients treated with self administered therapy
  – Patient was poorly adherent
  – Patient deteriorates clinically or radiographically during initial weeks of treatment
  
  – Consider expanded regimen, especially if immune suppressed
    • RIPE plus a fluoroquinolone and an injectable
Patients at Risk of Relapse

• Who Should We Suspect?

• What Can We Do Differently to Decrease the Risk?

Treatment Related Risk Factors for Early Relapse of TB

• Evaluation of 113 cases of relapsed TB when matched with case controls
  – Non-cavitary TB, relapse rate: 1.1%
  – Cavitary TB relapse rates:
    • Thrice weekly Rx: 7.8%
    • Daily Rx: 3.3%
    • Extended thrice weekly: 0.5%
    • Extended daily 0.4%
  – Either intensive phase or both was beneficial

» Chang, Am J Respir Crit Care Med. 2004; 170: 1124-30
Treatment Related Risk Factors for Early Relapse-Dosing Intensity

- Review of trials, 200 cases of relapse, 6 month Rx

- Relapse rates higher when intermittent therapy used especially in initiation phase
  - Daily IP, 3 x/wk CP: 1.6%
  - Daily IP 2x/wk CP: 2.8%
  - 3/wk IP and CP: 5.0%

- Relapse higher especially with cavitary disease and positive 2 month cultures
  - Only 6 month daily or 6 month daily IP and 3/wk CP had relapse rates <5%

Chang Am J Respir Crit Care Med 2006; Vol 174 p 1153

In the Treatment of TB, You Get What You Pay For…

- “A consistent theme has begun to appear: more extensive disease requires more treatment, and the fewer total doses, the higher the risk that treatment will prove inadequate”

  - What should we conclude?
    - First: **More treatment means more cures**
    - Second: Programs need to consider some individualization of therapy
    - Third: Should not deter us from intermittent therapy but should remind us of need for sophisticated management based on case-specific circumstances
      - Should not be surprised that individuals differ in their response.

Medical Factors Associated With Relapse-Dosing Intensity

- Cavitary TB
- Extensive disease on CXR; bilateral infiltrates
- Positive 2 month culture
- Associated medical conditions
  - Diabetes
  - HIV
  - Malabsorption of TB drugs
- Tuberculous lymphadenitis
- Underweight at diagnosis and failure to gain
- Drug resistant disease
- Prior treatment for tuberculosis

Treatment Factors Associated with Relapse of Tuberculosis

- DOT
- Adherence
- Dosing intensity (Dose itself)
- Duration of therapy
  - Intensive phase
  - Continuation phase
  - Both
- Rifampin containing regimen
HIV neg, 2 mo culture neg, Non-Cavitary TB in Uganda.

Treatment of TB and Optimal Dosing Schedules

Kwok Chiu Chang, Chi Chiu Leung, Jacques Grosset, Wing Wai Yew
Thorax December, 2010

Systematic Review of 17 analytic studies – 9 systematic reviews, 8 controlled studies and 2 case-control studies.

Levels of evidence and grades of recommendations assigned according to clinical evidence with reference to Scottish Intercollegiate Guidelines.
Non HIV related TB (11 studies)

- Suggests that intermittent Rx reduces TB treatment efficacy as shown by a higher risk of relapse or failure

- Negative impact most prominent in presence of cavities

- Review suggests with standard 6 mo Rx - no significant difference between daily throughout & daily in initial phase

Level of evidence: 1+
Grade of recommendation: “A”
- Avoid intermittent doses, especially in initial phase and in presence of cavities

TB With INH Resistance (2 studies)

- Suggests that dosing intermittency reduces TB treatment efficacy as shown by:
  - Higher risk of treatment failure, relapse or acquired drug resistance

Level of evidence 1+
Grade of evidence: “A”
- Avoid dosing intermittency, especially in the initial phase in the presence of INH resistance
HIV related TB (3 studies)

- Suggests intermittent Rx, especially in initial phase reduces treatment efficacy as shown by
  - a higher risk of treatment failure, relapse, or acquired Rifampin resistance

**Level of evidence 1+**
**Grade of recommendation “A”**
- Avoid intermittency, especially in the initial phase in HIV TB

Why is the Initial Phase of Therapy So Important?
Importance of the Initiation Phase

• Evidence suggests
  – Effect of dosing schedules on treatment efficacy is best harnessed in the initial phase

• Evidence has existed in vitro for several decades that:
  – the more rapid the anti-bacterial effect –
    • the less likely is the emergence of persisters
    • and the lower is the risk of relapse.

Importance of Rifampin Especially in the Initiation Phase

• **Rifampin** is the only first line TB drug with putative activity against persisters

• Persisting bacilli are the source of relapses
Populations of Mycobacteria

- INH
- Rifampin
- EMB
- Rifampin
- PZA

Importance of the Initiation Phase

- Rifampin is the only first line TB drug with putative activity against persisters
- Persisters may revert back and forth to other subpopulations of bacilli
  - Optimizing bactericidal and sterilizing activity early will minimize overall bacterial load present during continuation phase
Relapsed Tuberculosis - Case Study

Case Study

• 47 yr old male, recurrence of TB
  – Weight at Diagnosis 117 pounds (<10% IBW)
  – Two months, 114 pounds
  – Three months, 114 pounds
  – Four months, 115 pounds

• Extensive cavitary disease on CXR

• Sputum smear + 5 ½ months

• Sputum culture + 3 ½ months
Lack of Weight Gain and Relapse Risk, TBTC Study 22

• Relapse risk high in those underweight at diagnosis 19.1% versus 4.8%

• Among pts underweight at diagnosis, if weight gain ≤ 5% after 2 months of treatment:
  – Relapse risk 18.4% vs. 10.3%
  – If also cavitary disease: 18.9%
  – If cavitary and + 2 month culture: 50.5%


Nutrition Risk Score (NRS): Relation to Respiratory Failure & Death

• Miliary TB (MTB) develops in 1 – 2% of patients and is associated with acute respiratory failure (ARF) and death

• NRS ≥ 3 is an independent predictor of acute respiratory failure (ARF) and death
  – Lower BMI, fewer lymphocytes, lower cholesterol, & albumin in those who died
  – 14/56 (25%) patients with Miliary TB developed ARF

  Kim, Europ Resp Society 2008
Treatment in Special Situations

Active TB During Pregnancy

• Diagnosis may be difficult
  – Respiratory symptoms common in late pregnancy
  – Reluctance to do a CXR
  – Extra-pulmonary disease is even more difficult

• Outcomes for BOTH mom and baby are improved with treatment during pregnancy

• Infection control is important at time of delivery if mom is still infectious
Active TB During Pregnancy

- Treatment:
  - INH, Rifampin, Ethambutol x 9 months
    - Stop ethambutol if susceptible to INH and rifampin
  - PZA only if drug resistance is present
    - PZA regarded as safe by most countries in world
- Follow carefully for hepatotoxicity- risk is increased
  - During pregnancy
  - Three months postpartum

Delayed Response
Culture Positive at 3 Months

- TB lab should automatically repeat susceptibility studies on last positive culture check to be sure
- Assess adherence
- Consider serum drug levels
- Evaluate response to therapy
  - Clinically and radiographically

By the time you know this it is 4 months into therapy!
“Treatment Failure”
Culture Positive at 4 Months

Repeat susceptibility studies
• On last positive culture
• And request on a “new sputum culture” now
  – Serum drug levels if not previously done
  – Clinical evaluation

Augment therapy
• Add at least two and preferably three new drugs to which the isolate is likely to be susceptible
• Even if no clinical or radiographic evidence of failure

MMWR Treatment of Tuberculosis 2003; 52

Tuberculosis Drug Serum Level Monitoring Recommended

• Delayed response to therapy
• Advanced AIDS with evidence of malabsorption
• Seriously ill patient to maximize therapy
• ? Diabetics
• Toxicity evaluation
• Use of second line drugs
• Acquired drug resistance
• Relapse
• Potential for drug-drug interactions
• Renal and hepatic insufficiency
Management of TST + Persons With an Abnormal CXR

- Isolated CXR with nodules and/or fibrotic lesions:
  - If no symptoms - wait
    - Collect sputum culture
    - Evaluate for symptoms
    - Repeat CXR
  - If CXR stable at 2 – 3 months and cultures are negative, treat as LTBI

- Isolated CXR with nodules and/or fibrotic lesions:
  - If patient has any signs or symptoms of TB disease: the patient is a TB suspect
    - Start 4 drugs
  - Never start a single drug in a patient with possible active TB

Culture Negative TB

- TB suspect with positive TST or IGRA
  - Risk factors for TB
  - Abnormal CXR
  - Usually – clinical symptoms

- All cultures are negative

- Classify based on clinical and/or radiograph response to treatment at 2 months
  - **Clinical or CXR improvement** – Culture Negative TB
    - Treat for 4 months (children and HIV + 6 months)
    - RIPE for 2 months, then RIE +/- PZA dependent on INH resistance
Why Do Doctors Give Patients Moxifloxacin for a Lower Respiratory Illness?

- LRTIs: A Leading Cause of Disease Burden Globally: All Ages, 2004
- In 2006, pneumonia was the leading cause of death from infectious disease in the United States
- From Reuters Health Information:
  - Moxifloxacin Improves Outcomes in Hospitalized Pneumonia Patients
  Ott, Europ Resp J , Sept 2011

Prolonged Positive Smears

- 51 year old male
- Slow clinical and CXR improvement
- Prolonged conversion of cultures (10 weeks)
- Prolonged conversion of smears (7½ months)
Significance of Persistent + AFB Smears

- Review of lab data of 428 patients, 30 with smear persistently + >20 weeks
  - 23/30 had a negative culture
  - 7/30 positive culture “treatment failure”

- Of those with negative cultures - none relapsed

- Most received standard therapy for 12 months
  - PZA was continued for 2-3 months

> Al-Moamary Chest 1999; 116:726-731

Prolonged Positive Smears

- 12 months of RX

- Culture and smear – 20 months after stopping TB meds

- CXR still extensive cavitary infiltrates

W. C. 12-11-2002
**Mycobacterium bovis**

- A member of the M TB complex which is what is identified by all TB labs or PCR
- Similar to other members but is resistant to PZA
- Is associated with extra pulmonary disease and increased mortality
- Is common in children (> 1 year) along U.S. Mexico border
  - Non-pasturized milk and cheese – a food borne disease as well as respiratory

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**M bovis & Genotyping - Texas**

All *M. bovis* are resistant to PZA and need treatment for 9 months with INH and Rifampin +/- EMB
Management of Treatment Interruptions

• Initial phase of therapy
  – <14 days – complete standard # of doses
  – >14 days – restart from the beginning

• Continuation phase
  – >80% doses by DOT – if initial smear –, may stop
  – < 80% doses by DOT and/or initial smear +
    • Repeat culture
      – Management based on clinical and bacteriological factors.

TB Research

Impact on Future TB Treatment
Rifampin Dose - High is Better

• Higher peak serum concentrations were linked to
  – Improved killing of MTB,
  – Suppression of resistance
  – Post antibiotic effect

• Short half life not important but peak concentration was

  Gumbo; Antimicrob Agents Chemother, 2007

TB Trial Consortium Study 29

• Part I compare standard therapy (rifampin 10mg/kg) to:
  – 3 x/wk rifapentine 15mg/kg + Moxi/PZA/EMB
  – Daily rifampin 15mg/kg + Moxi/PZA/EMB
  – Daily rifapentine 7.5mg/kg + Moxi/PZA/EMB

• Part II
  – Increase to rifapentine 20mg/kg 3x/wk,
  – Daily rifampin 20mg/kg
  – Rifapentine 10mg/kg
TBTC Study 27
Moxifloxin Substituted for Ethambutol

![Chart showing the percentage of cases with negative sputum cultures over weeks of treatment for Moxifloxacin and Ethambutol.](chart)

*Burman; Am J Resp Crit Care Med 2006*

### Where to Get More Information

- HEARTLAND NATIONAL TB CENTER
  - 1-800-TEX LUNG: Medical Consultation and Technical Assistance Line
  - Future training courses

- CDC

- TB Educate

- TBresources.com