Tuberculosis: update 2013

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Question 1
A TB speaker at a major conference announces from the podium:

“2012 was the year that saw more TB cases and deaths than any previous year in history”

This statement is:

A. True
B. False

• Correct answer: B
Global Burden of TB

- Plateauing—for the first time in recorded history

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>8.8 M</td>
<td>1.4 M</td>
</tr>
<tr>
<td></td>
<td>(128/100,000)</td>
<td>(20/100,000)</td>
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<tr>
<td>2011</td>
<td>8.7 M</td>
<td>1.4 M</td>
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<tr>
<td></td>
<td>(125/100,000)</td>
<td>(20/100,000)</td>
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</tbody>
</table>

TB Incidence

- Millions

TB Deaths

- HIV negative
- HIV positive

Years: 1990, 2000, 2011
Question 2
There have been major new products for TB within the last 3 years for the following tools:

A. Diagnostics, Drugs, and Vaccines
B. Diagnostics and Drugs
C. Diagnostics and Vaccines
D. Drugs and Vaccines
E. None of the above

Correct answer: B
GeneXpert: 90 min, POC test for TB, Rif-R TB

TB culture-positive patients (n = 732):

- Sensitivity: Smear-positive TB, single test: 98.2%
- Smear-negative TB, 3 tests: 90.2%
- Specificity: 99.2%

Rifampin DST:
- Sensitivity 97.6%
- Specificity 98.1%

Boehme et al. NEJM 2010; 363: 1005
Bedaquiline (TMC 207): the first new TB drug class since 1967

A Diarylquinoline Drug Active on the ATP Synthase of *Mycobacterium tuberculosis*

Koen Andries,¹* Peter Verhasselt,¹ Jerome Guillemont,²


- Fast-track FDA approval, surrogate endpoint (time to Cx conversion)
- Study 208, 161 patients, 79% vs. 58% culture conversion at 24 weeks
Case 1:

- 22 yo S. African man
- Finished medical school Dec 2012. Started internship Jan 2013
- Jan 2013: dyspnea and cough
- Seen by LMD. CXR with RLL infiltrate. Sputum no PMN.
- Started on ofloxacin
Use of FQs with possible TB

If this patient has TB:

- may improve transiently with Ofloxacin
- Use of a FQ may *delay* the diagnosis of TB
- FQ monotherapy is associated with an increased risk of FQ-Resistant TB
- Ofloxacin is less potent vs. *M. tb.* than Moxifloxacin
Case 1, continued

- Feb 2013: pleuritic chest pain with jogging, 12 kg weight loss
- CXR: large R pleural effusion. Straw colored fluid. Smear NEG
- HIV positive. CD4 count 75.
- Presumptive diagnosis: TB HIV coinfection
Question 3
The optimal next step is:

A. Start TB therapy and HAART simultaneously
B. Start TB therapy now; plan to start HAART in 2 weeks
C. Start TB Rx only; defer HAART until post TB treatment
D. Start HIV therapy with multidrug HAART only

Correct answer: B
Timing of ART in Patients with HIV-Related TB

• If on ART at diagnosis, continue... but consider drug holiday

• CD4 may rebound with TB treatment

• If not on ART...
  – CD4 <100: Start after 2 weeks
  – CD4 100-200: After 2 months
  – CD4 > 200: During maintenance phase
  – CD4 >350: Delay until post-TB treatment

Kaplan et al. MMWR March 24, 2009 / 58(Early Release);1-198
Case 1, continued

• Started INH, RIF, PZA, EMB
• Admitted for loculated empyema. Drain placed.
• Pleural biopsy non-diagnostic
• Apr 2008: pleural Cx POS for MDR-TB resistant to INH, RIF, EMB, STR
Question 4
Which of the following drugs is not indicated:

A. Pyrazinamide
B. Ethionamide
C. Cycloserine
D. Moxifloxacin
E. IV Amikacin
F. Pyridoxine
G. Bedaquiline

Correct answer: G
Bedaquiline (BDQ, Sirturo™)

- Roll out in high burden countries, 2013
- Study 208: Control group 2/81 deaths
  Bedaquiline group 10/79 deaths (no single cause)
- Black-box warning due to QT prolongation

**ONLINE FIRST**

**Approval of a Tuberculosis Drug Based on a Paradoxical Surrogate Measure**

Jerry Avorn, MD

Avorn, JAMA 2013; 309: 1349.

- WHO Expert Guideline: Reserve BDQ for MDR TB patients who have failed standard MDR TB regimens
Case 2

- A 40 year old South African miner presents for health screening
- He is asymptomatic. The screen reveals that he is:
  - HIV seropositive; CD4 26
  - CXR negative
  - TST negative
- He is started on Atripla and Isoniazid preventive therapy as per South African guidelines
Question 5
In the United States, which of the following individuals should receive screening for latent TB infection by TST or IGRA?

A. Schoolchildren whose parents are foreign-born
B. Individuals who request TST
C. BCG vaccinated healthcare worker not previously tested
D. Pre-employment food-service worker from Guatemala

Correct answer: C
Who **SHOULD** be Screened for Latent TB?

1. At risk for recent infection
   - TB contacts, health care workers, prisoners

2. Those from high prevalence areas
   - Immigrants from endemic areas (≤5 years) even if BCG vaccinated
   - Residents of inner cities or other high-risk areas

3. Medical conditions with increased risk of reactivation of LTBI
   - HIV infection
   - Steroid use (>15 mg daily for > 2 months)
   - Use of biologics including TNF-inhibitors (infliximab, etanercept, adalimumab)
   - Renal failure, diabetes or silicosis
   - Injection drug use

*Cohn et al. MMWR June 09, 2000 / 49(RR06);1-54*
Who Should **NOT** be Screened for Latent TB?

People with no risk factors for TB

– Food industry workers
– Public employees
– Schoolchildren
– Healthy adults
Case 2, continued

- Two months later he reports to the infirmary with stridor
- CXR reveals a R paratracheal mass and several cervical and supraclavicular lymph nodes
Case 2, continued
Case 2, continued

- Two months later he reports to the infirmary with stridor
- CXR reveals a R paratracheal mass and several cervical and supraclavicular lymph nodes
- A cervical lymph node fine needle aspirate shows:
  - AFB smear NEGATIVE
  - GeneXpert POSITIVE for *M. tb*. with Rif-susceptibility
  - reactive lymphocytes and mononuclear cells
Question 6
The most likely diagnosis is:

A. Lymphoma
B. Unmasking IRIS
C. Paradoxical IRIS
D. Isoniazid monoresistant active TB

*IRIS: Immune Reconstitution Inflammatory Syndrome

Correct answer: B
Immune Reconstitution Inflammatory Syndrome, IRIS

- **Unmasking IRIS:** Addition of ARVs precipitates active TB
  - Continue antimicrobials
  - Add steroids
  - Stop ARVs if life-threatening

- **Paradoxical IRIS:** Addition of ARVs precipitates sterile inflammatory lesions
  - Add steroids
  - Stop ARVs if life-threatening
Isoniazid Preventive Therapy

• Now recommended for **all** HIV seropositive individuals in some high burden countries
  – South Africa:

<table>
<thead>
<tr>
<th>Summary Recommendations</th>
<th>Pre-ART (CD4&gt;350)</th>
<th>On ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST not done*</td>
<td>IPT for 6 months</td>
<td>IPT for 6 months</td>
</tr>
<tr>
<td>TST negative</td>
<td>IPT for 6 months</td>
<td>IPT for 12 months</td>
</tr>
<tr>
<td>TST positive</td>
<td>IPT for at least 36 months</td>
<td>IPT for at least 36 months</td>
</tr>
</tbody>
</table>

• Meta-analyses and prospective studies: no clear increased risk for INH-R active TB
Case 2, continued

• Sputum sent for M. tb. culture and sensitivity

• LN biopsy sent for M. tb. culture and sensitivity

Management questions:

1. Expand TB treatment to INH + RIF + EMB + PZA?   YES

2. Add Prednisone?  YES

3. Continue the Atripla:   NO
Case 3

- 72 year old white female from suburban Maryland
- Referred by rheumatologist
- Developed progressive L hand stiffness, then bilateral shoulder and knee pain
- NSAIDs, pulse dose steroids, ineffective
- Safe to use anti-TNF agent?
Case 3, continued

• At age 21, treated for pulmonary tuberculosis (1955)
• Referred to Sanitorium, stopped college studies
• 9 months of rest therapy
• Took isoniazid, streptomycin, &
  • para-amino salicylic acid
• Persistently positive sputum cultures
Case 3, continued

- Failed 9 months of rest and 3-drug therapy
- Right upper lobectomy
- Improved. Went off antibiotics
- Married, 4 children. Healthy except for CAD and arthritis
- On exam at present her TST is 3 mm
Question 7
With TNF inhibitor planned, should she receive further TB therapy?

A. Yes
B. No

Correct answer: A
Case 3

- Her TB in 1955 was not an antibiotic treatment success
- Unknown if she had treatment failure due to drug-resistant *M. tb.* in 1955
- Possible that she has continued latent *M.tb.* or latent drug-resistant *M. tb.*
- Therefore, recommend preventive therapy prior to TNF inhibitor
Question 8
Now that a decision has been taken to treat Mrs. H for Latent Infection prior to use of TNF-inhibitor, which of the following regimens is optimal for this patient?

A. INH 9 months
B. INH 6 months
C. RIF 4 months
D. RIF + PZA 2 months

Correct answer C
# Regimens for Treatment of Latent TB

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration</th>
<th>Freq</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>INH</td>
<td>6-9 mo</td>
<td>daily</td>
<td>well-studied; 30-60% completion</td>
</tr>
<tr>
<td>RIF daily</td>
<td>4 mo</td>
<td>daily</td>
<td>Never studied. When possible INH-R or intolerance. Not for HIV+</td>
</tr>
<tr>
<td>INH + RIF</td>
<td>3 mo</td>
<td>daily</td>
<td>Not ATS endorsed An alternative</td>
</tr>
<tr>
<td>INH + Rifapentine</td>
<td>12 weeks</td>
<td>weekly</td>
<td>New, only 12 doses</td>
</tr>
<tr>
<td>RIF/PZA</td>
<td>2 mo</td>
<td>daily</td>
<td><strong>No longer recommended</strong></td>
</tr>
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</table>
Chronology of TB Drugs

- 1945 Streptomycin
- 1946 PAS
- 1946 Thiacetazone
- 1952 Isoniazid
- 1952 Pyrazinamide
- 1955 Cycloserine
- 1958 Ethionamide
- 1960 Capreomycin
- 1963 Ethambutol
- 1967 Rifampin
The patient is eager for arthritis treatment

Can I start the TNF-I immediately?  NO

Can you offer me a TNF-I which does not require treatment for LTBI?  NO
Current American College of Rheumatology Guidelines

- Initial TST or IGRA if TB risk factors are present
- If TST/IGRA positive, rule out active TB with CXR
- **Complete at least 1 month** of treatment for latent TB before starting biologic
- **Applies for all biologics** except anakinra
  - TNF biologics: adalimumab, certolizumab pegol, etanercept, infliximab, or golimumab,
  - Non-TNF biologics: abatacept, rituximab, or tocilizumab

*Singh et al. Arth Care & Res. 2012; 64: 625*
Important Clinical Issues in Tuberculosis in 2013

- Drug resistant TB ± HIV
- IRIS with TB-HIV coinfection
- Latent TB and Prevention of TB
Thank you