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

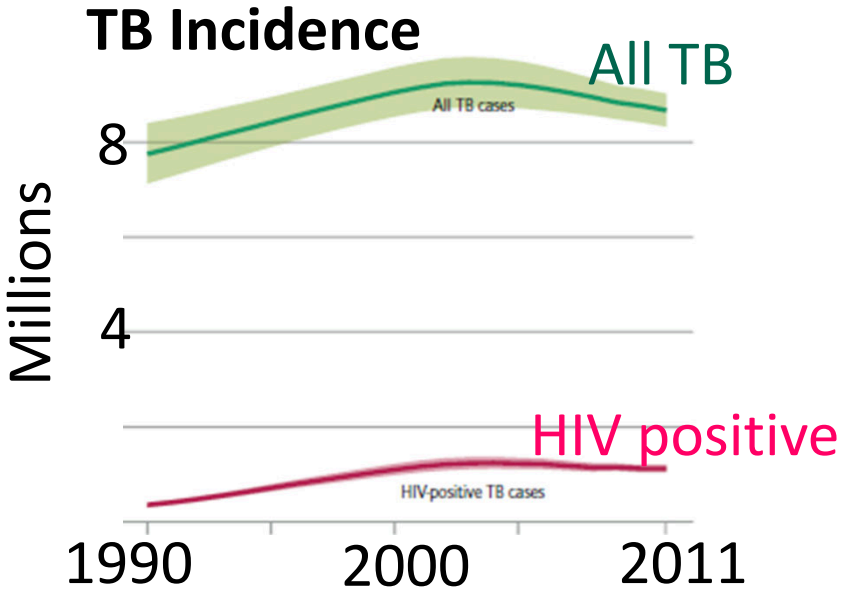
B. False

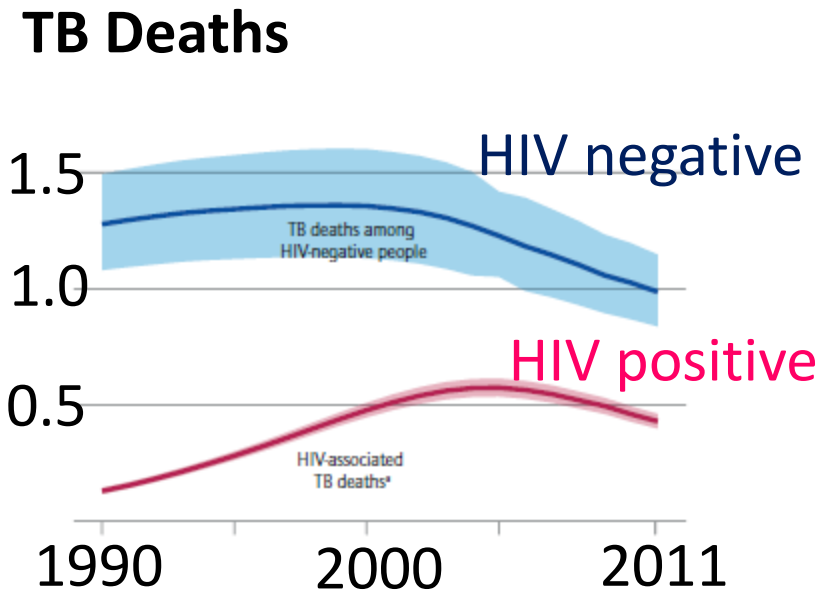
- Correct answer: B

Global Burden of TB

- Plateauing--for the first time in recorded history

Year	Cases	Deaths
2010	8.8 M (128/100,000)	1.4 M (20/100,000)
2011	8.7 M (125/100,000)	1.4 M (20/100,000)





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

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 9, 2010 VOL. 363 NO. 11

Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

Catharina C. Boehme, M.D., Pamela Nabeta, M.D., Doris Hillemann, Ph.D., Mark P. Nicol, Ph.D., Shubhada Shenai, Ph.D., Fiorella Krapp, M.D., Jenny Allen, B.Tech., Rasim Tahirli, M.D., Robert Blakemore, B.S., Roxana Rustomjee, M.D., Ph.D., Ana Milovic, M.S., Martin Jones, Ph.D., Sean M. O'Brien, Ph.D., David H. Persing, M.D., Ph.D., Sabine Ruesch-Gerdes, M.D., Eduardo Gotuzzo, M.D., Camilla Rodrigues, M.D., David Alland, M.D., and Mark D. Perkins, M.D.

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

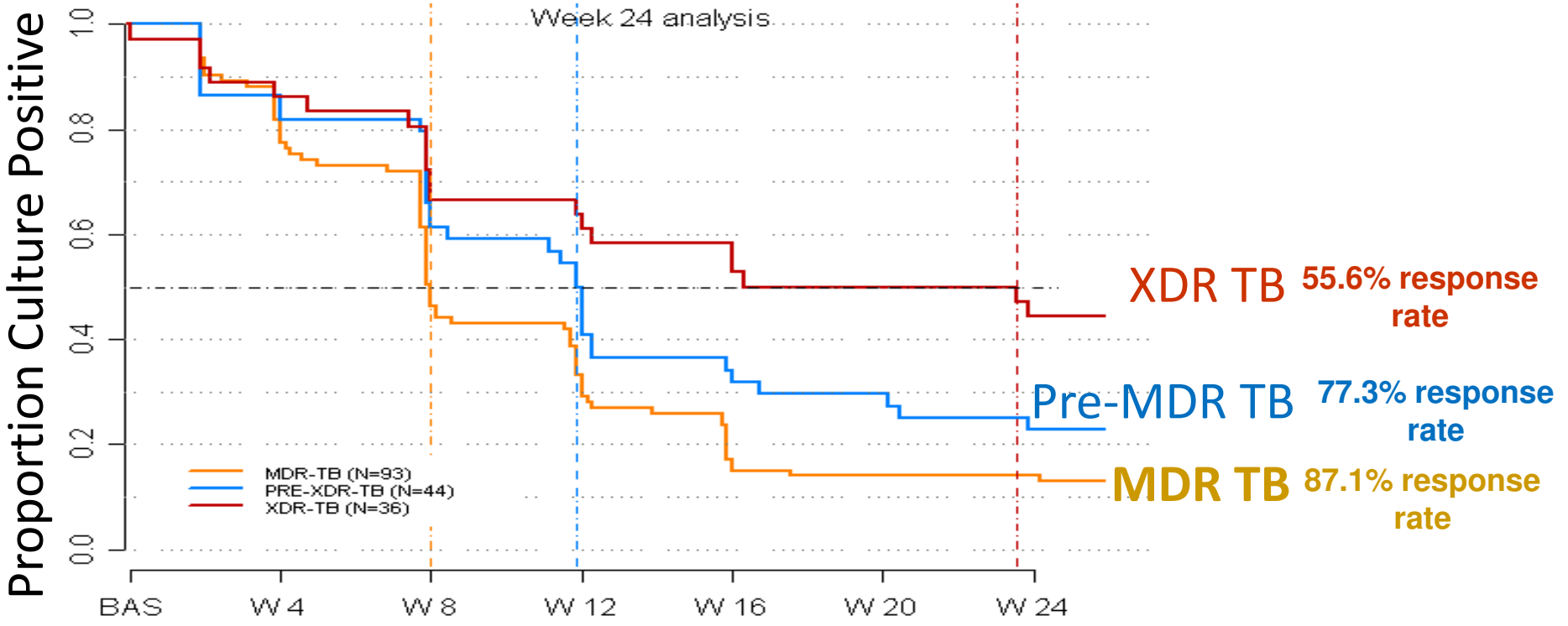
A Diarylquinoline Drug Active on the ATP Synthase of *Mycobacterium tuberculosis*

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

Science
AAAS

Andries et al. Science 2005; 307: 223

Time to Culture Conversion. 24 weeks



- 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

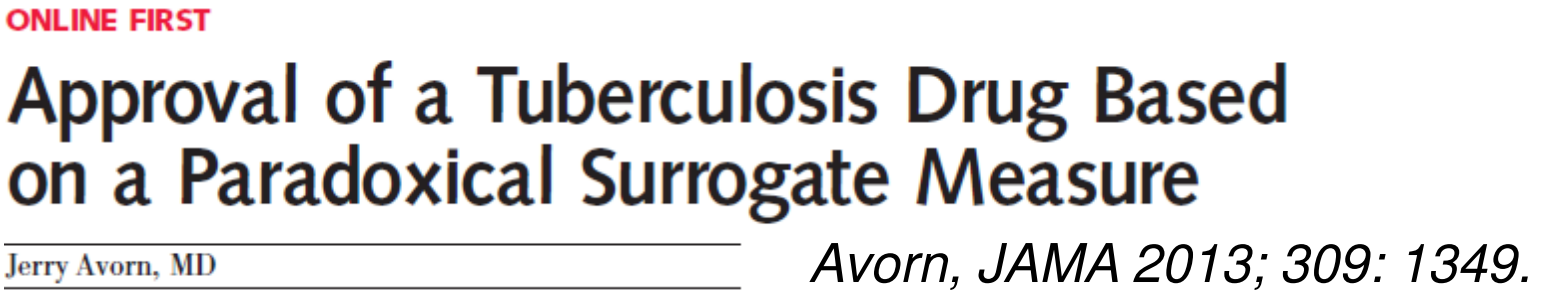
Which of the following drugs is not indicated:

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

Correct answer: G

Bedaquiline (BDQ, Sirturo™)

- Approved in US for MDR-TB on Dec. 31, 2012
- 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:

Summary Recommendations		
	Pre-ART(CD4>350)	**On ART**
TST not done*	IPT for 6 months	IPT for 6 months
TST negative	IPT for 6 months	IPT for 12 months
TST positive	IPT for at least 36 months	IPT for at least 36 months

- 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

Regimen	Duration	Freq	Comment
INH	6-9 mo	daily	well-studied; 30-60% completion
RIF daily	4 mo	daily	Never studied. **When possible INH-R** or intolerance Not for HIV+
INH + RIF	3 mo	daily	Not ATS endorsed An alternative
INH + Rifapentine	12 weeks	weekly	New, only 12 doses
RIF/PZA	2 mo	daily	**No longer recommended**

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 *Case 1*
- IRIS with TB-HIV coinfection *Case 2*
- Latent TB and Prevention of TB *Case 3*

Thank you