LTBI: Diagnosis and Treatment

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TB Clinical Intensive
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Disclosures

• None Relevant
Objectives

By the end of this session, participants should be able to:

• Define what LTBI is
• Identify those who should be tested for TB infection
• Describe current testing for LTBI
• Interpret results of LTBI testing
• Prescribe treatment for LTBI
• Monitor patients on treatment for LTBI
What is TB Infection (LTBI)
Mycobacterium tuberculosis
What it does

• TB is spread person to person through the air via droplet nuclei

• Exposure to M. tuberculosis occurs when an infectious person:
  • Coughs
  • Sneezes
  • Speaks
  • Sings

• Transmission occurs when another person inhales droplet nuclei
TB Pathogenesis
What it does
TB Pathogenesis
What it does

Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to the small alveoli.
TB Pathogenesis
What it does

Tubercle bacilli multiply in alveoli, where infection begins
TB Pathogenesis
What it does

A small number of tubercle bacilli enter bloodstream and spread throughout body.
Immune Response to TB

• Within 2 to 10 weeks, the body's immune system intervenes, halting multiplication and further spread.

• Macrophages directly phagocytize TB, processing and presenting antigens to lymphocyte

• T lymphocytes (CD4+): induce protection through the production of lymphokines

• Immune cells form a barrier
Persons with LTBI

- Do not have TB symptoms
- Are not infectious
- Radiograph is typically normal
TB Pathogenesis
What it does

• If the immune system CANNOT keep tubercle bacilli under control, bacilli begin to multiply rapidly and cause TB disease

• This process can occur in different places in the body
Natural History of TB Infection in Patients Without HIV

Exposure to TB

No infection (70-90%)

Infection (10-30%)

Latent TB (90%)
Never develop Active disease

Active TB (5-10%)

Treated

Die/Relapse/Recurr
Cured
Risk of Developing TB disease

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Risk of Developing TB</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB infection and no risk factors</td>
<td></td>
<td>For people with TB infection, no risk factors, and no treatment, the risk is about 5% in the first 2 years after infection and about 10% over a lifetime.</td>
</tr>
<tr>
<td></td>
<td>About 10% over a lifetime</td>
<td></td>
</tr>
<tr>
<td>TB infection and diabetes</td>
<td></td>
<td>For people with TB infection and diabetes, and with no treatment, the risk is three times as high, or about 30% over a lifetime.</td>
</tr>
<tr>
<td></td>
<td>About 30% over a lifetime</td>
<td></td>
</tr>
<tr>
<td>TB infection and HIV infection</td>
<td></td>
<td>For people with TB infection and untreated HIV infection and with no LTBI treatment, the risk is about 7% to 10% PER YEAR, a very high risk over a lifetime.</td>
</tr>
<tr>
<td></td>
<td>About 7% to 10% PER YEAR</td>
<td></td>
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</tbody>
</table>
In 2014, a total of 9,412 new tuberculosis (TB) cases were reported in the US.

- Incidence: 3.0/100,000 persons
- Identifying and treatment of LTBI can prevent
  - Infected persons from developing TB disease
  - From infecting others
Who Should be Tested for LTBI?
Targeted Testing for LTBI: Why?

11 million LTBI cases—roughly 1 in 24 people—in the U.S.
- 550,000 - 1.1 million future TB cases

Unfocused population-based testing is not cost-effective or useful and leads to unnecessary treatment.

Targeted testing is used to focus program activities, provider practices, and financial resources on groups at the highest risk for LTBI.

CDC Morbidity and Mortality Weekly Report (MMWR), March 20, 2015 / 64(10);265-269.
# Targets for LTBI Testing

| High Likelihood of TB Exposure and Acquiring TB Infection | High Likelihood of Progression to Active TB |
Patients at Increased Risk for Acquiring TB Infection

- Close contacts of persons known or suspected to have active tuberculosis
- Foreign-born persons from areas that have a high incidence of active tuberculosis
- Visitors of TB endemic countries, especially if visits are frequent or prolonged
- Residents and employees of congregate settings whose clients are at increased risk for active tuberculosis (e.g., correctional facilities, long-term care facilities, and homeless shelters)
- Health-care workers who serve patients who are at increased risk for active tuberculosis
- Populations defined locally as having an increased incidence of latent *M. tuberculosis* infection or active tuberculosis, possibly including medically underserved, low-income populations, or persons who abuse drugs or alcohol
- Infants, children, and adolescents exposed to adults who are at increased risk for latent *M. tuberculosis* infection or active tuberculosis

MMWR 2000;49(No. RR-6)
**Patients at Increased Risk of Progression from LTBI to Active TB Disease**

<table>
<thead>
<tr>
<th>Persons at Increased Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Persons infected with HIV;</td>
</tr>
<tr>
<td>- Children younger than 5 years of age;</td>
</tr>
<tr>
<td>- Persons who were recently infected with <em>M. tuberculosis</em> (within the past 2 years);</td>
</tr>
<tr>
<td>- Persons with a history of untreated or inadequately treated TB disease, including persons with fibrotic changes on chest radiograph consistent with prior TB disease;</td>
</tr>
<tr>
<td>- Persons who are receiving immunosuppressive therapy such as tumor necrosis factor-alpha (TNF) antagonists, systemic corticosteroids equivalent to/greater than 15 mg of prednisone per day, or immunosuppressive drug therapy following organ transplantation;</td>
</tr>
<tr>
<td>- Persons with silicosis, diabetes mellitus, chronic renal failure, leukemia, or cancer of the head, neck, or lung;</td>
</tr>
<tr>
<td>- Persons who have had a gastrectomy or jejunoileal bypass;</td>
</tr>
<tr>
<td>- Persons who weigh less than 90% of their ideal body weight;</td>
</tr>
<tr>
<td>- Cigarette smokers and persons who abuse drugs and/or alcohol; and</td>
</tr>
<tr>
<td>- Populations defined locally as having an increased incidence of disease due to <em>M. tuberculosis</em>, including medically underserved, low-income populations.</td>
</tr>
</tbody>
</table>
How Do We Test for LTBI?
Principle of Testing for LTBI

Presentation of mycobacterial antigens

Antigen presenting cell

Memory T-cell

IFN-γ

IL-8, etc.

TNF-α
Tuberculin Skin Test (TST)

Inject 0.1 ml of PPD (5 tuberculin units) into forearm between skin layers
Produce wheal (raised area) 6–10 mm in diameter

- Assesses 48–72 hours after injection
- Palpate injection site
- Measure diameter of induration across forearm; only measure induration, not redness
- Record size of induration in millimeters; record “0” if no induration
TST interpretation (Review)

> 5 mm induration = “Positive” result

*Highest risk patients for progression to active TB*

- Human immunodeficiency virus (HIV)-positive persons
- Recent contacts of TB case patients
- Persons with fibrotic changes on chest radiograph consistent with prior TB
- Patients with organ transplants and other immunosuppressive conditions
  - e.g. Patients receiving > 15 mg/d of prednisone for > 1 month)
  - Risk of TB in patients with corticosteroids increases with higher dose and longer duration.)
TST interpretation (Review)

> 10 mm induration = “Positive” result

- Recent immigrants (i.e., within past 5 years) from TB endemic countries
- Injection drug users
- Residents and employees of select congregate settings – Examples:
  - Prisons and jails, nursing homes and other long-term care facilities
  - Health care employees - hospitals and other health care facilities
  - Homeless shelters
- Mycobacteriology laboratory personnel
- Persons with immunomodulatory medical conditions – Examples:
  - Silicosis, diabetes mellitus, chronic renal failure, hematologic malignancies (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinoma of the head, neck, or lung), weight loss >10% of ideal body weight, gastrectomy, and jejunoileal bypass
- Children < 4 years of age, or infants, children and adolescents exposed to adults at high-risk
TST interpretation (Review)

> 15 mm induration = “Positive” result

- Persons with no known risk factors for TB
  - Raises question ‘why was a TST performed?’
  - Further exploration of patient’s risk factors and exposure history warranted
  - Ensure results of TST are indeed accurate
Currently Available IGRAs

- **QuantiFERON®** (Cellestis)
  - 2\(^{nd}\) generation QFT\(^{®}\)-Gold (QFT-G) FDA approved May 2005
  - 3\(^{rd}\) generation QFT\(^{®}\)-Gold In-Tube (QFT-IT) FDA approved October 2007

- **T-SPOT.® \textit{TB}** (Oxford Immunotec)
  - Evolved from Elispot
  - FDA approved July 2008
Basic Principle Behind IGRAs

- T-cell lymphocytes release IFN-γ in response to specific antigens
- 3 synthetic TB-specific antigens identified:
  - RD1: ESAT-6, CFP-10
  - RD11: TB7.7
- IFN-γ is stable and measurable in the plasma
QuantiFERON-TB IT methodology

1. Collect 1mL of blood into Nil, Antigen and Mitogen tubes. Shake well. Incubate tubes at 37°C for 16-24 hrs.

2. Centrifuge tubes for 15 minutes. Harvested plasma is stable refrigerated for at least 4 weeks.

3. Add conjugate, plasma samples and standards to ELISA. Incubate for 120 minutes at room temperature.

4. Wash and add substrate. Read absorbance after 30 minutes.

5. Software calculates results and prints reports.

http://www.cellestis.com
### QuantiFERON-TB tubes & roles

#### TB Antigen tube
Assesses IFN-γ response to highly-specific TB antigens.

#### Mitogen tube (Positive control)
Can be useful to indicate
- Patient’s immune status
- Correct blood handling and incubation

Note: a low-mitogen result, in conjunction with a negative TB result, is classified as an “indeterminate”.

#### Nil tube (Negative control)
Adjusts for background noise.
IFN-γ measurement by QuantiFERON-TB GIT

IFN-γ released in response to ESAT-6, CFP-10 or TB7.7 stimulation

• Calculated as the difference in antigen-stimulated IFN-γ production in blood minus the IFN-γ concentration in blood incubated with saline (e.g. Nil; negative control)

TB Ag – Nil = measured result
QuantiFERON-TB Gold In-Tube (QFN-GIT) Interpretation Criteria

<table>
<thead>
<tr>
<th>Interpretation</th>
<th>TB specific antigen response (IU/mL)*</th>
<th>Nil control (IU/mL)</th>
<th>Mitogen control (IU/mL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>≥ 0.35 (and ≥ 25% of Nil)</td>
<td>≤ 8.0</td>
<td>any</td>
</tr>
<tr>
<td>Negative</td>
<td>&lt; 0.35 OR ≥ 0.35 and &lt; 25% of Nil</td>
<td>≤ 8.0</td>
<td>≥ 0.5</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>&lt; 0.35 OR ≥ 0.35 and &lt; 25% of Nil</td>
<td>≤ 8.0</td>
<td>&lt; 0.5</td>
</tr>
<tr>
<td></td>
<td>any</td>
<td>&gt; 8.0</td>
<td>any</td>
</tr>
</tbody>
</table>

*Corrected for Nil response.

http://www.cellestis.com
T.Spot TB procedural steps

Methodology rationale:

- Removes background interferon gamma to maximize sensitivity
- Utilizes a standard number of PBMCs to correct for a patient’s immune status

1. Collect the blood sample. At the lab, PBMCs are separated from whole blood, washed, counted and inoculated into 4 separate microtiter wells.

2. PBMCs and specific TB antigens are added to wells pre-coated with antibodies to IFN-γ and incubated 16 to 20 hours (37°C, CO2).

3. IFN-γ is released from activated T cells and captured. Wash wells, add secondary conjugated antibody. Incubate for one hour.

4. Wells are washed. A substrate is added which produces spots where interferon gamma was secreted by T cells. Spots are counted.

http://www.oxfordimmunotec.com
Comparing TST and IGRA platforms

<table>
<thead>
<tr>
<th>TST</th>
<th>IGRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculin is injected under the skin and produces a delayed-type</td>
<td>Blood is drawn for testing; test measures the immune response to the</td>
</tr>
<tr>
<td>hypersensitivity reaction if the person has been infected with M.</td>
<td>TB bacteria in whole blood</td>
</tr>
<tr>
<td>tuberculosis</td>
<td></td>
</tr>
<tr>
<td>Requires two or more patient visits to conduct the test</td>
<td>Requires one patient visit to conduct the test</td>
</tr>
<tr>
<td>Results are available 48 to 72 hours later</td>
<td>Results can be available in 24 hours (depending on the batching of</td>
</tr>
<tr>
<td></td>
<td>specimens by the laboratory and transport)</td>
</tr>
<tr>
<td>Can cause booster phenomenon</td>
<td>Does not cause booster phenomenon</td>
</tr>
<tr>
<td>Reading by HCW may be subjective</td>
<td>Laboratory test not affected by HCW perception or bias</td>
</tr>
<tr>
<td>BCG vaccination can cause false-positive result</td>
<td>BCG vaccination does not cause false-positive result and infection</td>
</tr>
<tr>
<td></td>
<td>with most nontuberculous mycobacteria does not cause false-positive</td>
</tr>
<tr>
<td></td>
<td>result</td>
</tr>
<tr>
<td>A negative reaction to the test does not exclude the diagnosis of</td>
<td>A negative reaction to the test does not exclude the diagnosis of</td>
</tr>
<tr>
<td>LTBI or TB disease</td>
<td>LTBI or TB disease</td>
</tr>
</tbody>
</table>

CDC 2013: Core Curriculum on Tuberculosis
Limitations of IGRAs

- Blood samples must be processed within 8-30 hours after collection while white blood cells are still viable.
- Errors in collecting or transporting blood specimens or in running and interpreting the assay can decrease the accuracy of IGRAs.
- Limited data on the use of IGRAs to predict who will progress to TB disease in the future.
- Limited data on the use of IGRAs for:
  - Children younger than 5 years of age;
  - Persons recently exposed to *M. tuberculosis*;
  - Immunocompromised persons; and
  - Serial testing.
- Tests may be expensive.
## TST vs. IGRAs: Sensitivity

<table>
<thead>
<tr>
<th></th>
<th># Studies</th>
<th>Sensitivity (95% CI)</th>
<th>Chi-Square for heterogeneity (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TST</strong></td>
<td>14</td>
<td>0.71 (0.65-0.74)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Size of reaction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 mm</td>
<td>9</td>
<td>0.74 (0.66-0.82)</td>
<td>0.001</td>
</tr>
<tr>
<td>10 mm</td>
<td>4</td>
<td>0.72 (0.50-0.95)</td>
<td>0.01</td>
</tr>
<tr>
<td>15 mm</td>
<td>1</td>
<td>0.40 (0.25-0.56)</td>
<td>-</td>
</tr>
<tr>
<td><strong>QuantiFERON-TB Gold™</strong></td>
<td>13</td>
<td>0.76 (0.70-0.83)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Elispot™ or T-SPOT.TB™</strong></td>
<td>12</td>
<td>0.88 (0.81-0.95)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th># Studies</th>
<th>Specificity (95% CI)</th>
<th>Chi-Square for heterogeneity (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TST</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not BCG vaccinated</td>
<td>3</td>
<td>0.98 (0.96-1.00)</td>
<td>NS</td>
</tr>
<tr>
<td>BCG Vaccinated</td>
<td>5</td>
<td>0.56 (0.34-0.78)</td>
<td>0.001</td>
</tr>
<tr>
<td>≥ 10 mm</td>
<td>6</td>
<td>0.58 (0.37-0.79)</td>
<td>0.001</td>
</tr>
<tr>
<td>≥ 15 mm</td>
<td>3</td>
<td>0.87 (0.70-1.00)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>QuantiFERON-TB Gold™</strong></td>
<td>9</td>
<td>0.97 (0.95-0.99)</td>
<td>0.01</td>
</tr>
<tr>
<td>Not BCG vaccinated</td>
<td>2</td>
<td>1.0 (0.94-1.0)</td>
<td>NS</td>
</tr>
<tr>
<td>BCG Vaccinated</td>
<td>7</td>
<td>0.96 (0.94-0.99)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Elispot™ or T-SPOT.TB™</strong></td>
<td>4</td>
<td>0.92 (0.88-0.95)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

CDC Guidelines

- TST or IGRA can be used for surveillance or for treatment decisions in pts at risk of TB infection or progression to active TB
- Test selection should be made based on clinical reason and context and availability, cost and effectiveness of testing
- An IGRA can be used in place (but typically not in addition to) a TST in all situations that a TST is recommended to diagnose TB infection, with select considerations

Mazurek G et al. MMWR June 25, 2010/Vol 59/No. RR-5
IGRA preferred, but TST is acceptable:
- Low likelihood to return for TST reading (e.g., homeless, drug abusers)
- Prior BCG vaccination (improve acceptance of LTBI Tx)

TST preferred, but IGRA is acceptable:
- Children < 5 yo

Either TST or IGRA may be used without preference:
- Recent TB contacts with active case (Repeat testing 8-10 wks after end of exposure if negative test)
- Periodic screening of HCW

Both TST and IGRA can be considered:
- High risk of TB infection and progression, and risk of poor outcome
  - HIV
  - Children < 5 yo
- Investigation of active TB (?)
- To enhance compliance to LTBI Tx (?)

Mazurek G et al. MMWR June 25, 2010/Vol 59/No. RR-5
Special Considerations: Boosting

- Some may have negative (waned) TST reaction when tested years after infection (e.g., older adults)
- Initial skin test may stimulate (boost) ability to react to PPD
- Subsequent positive boosted reaction may be misinterpreted as a new infection
- May still be considered for treatment if currently at high risk for TB disease
Special Considerations: Two-Step Testing

- Used for initial skin testing of adults to be retested periodically, to reduce likelihood that boosted reaction will be misinterpreted as recent infection
- If 1st test positive, consider infected; if negative, give 2nd test 1–3 weeks later
- If 2nd test positive, consider infected; if negative, consider uninfected
Treatment of LTBI
Latent TB Infection (LTBI) Treatment

• Rationale
  • To prevent the development of active disease
  • Component of TB control

• A decision to test for LTBI is a decision to treat
**Identify TB DILI risks:**
- Chronic ethanol consumption?
- Viral hepatitis?
- Pre-existing liver disease?
- Within 3 months post-partum?
- Concomitant hepatotoxic medication?
- Previous ALT or bilirubin abnormal?

**Hepatology evaluation**

**Check ALT, bilirubin (INR,PTT)**

**ALT ≥ 3 x ULN, Bili >2, or liver-related coagulopathy**

**Defer treatment & re-evaluate.**

**Regimen selection according to indication and TB DILI risks:**
- Isoniazid x 9 months, 6 months acceptable
- Rifampin x 4 months
  - e.g. if ALT 2-3 x ULN, isoniazid-resistance or -hepatotoxicity)
- Isoniazid with rifampin x 4 months

**Monitoring plan in medical record**

**Patient education:**
- Use patient’s preferred language
- Hepatitis symptoms and signs
- Discontinue treatment at symptom onset & contact clinic
Prior to Treatment

- Rule out active disease
  - Symptom screen
  - Chest X-ray

- Assess for medical conditions and medications that may affect treatment choices

- Determine whether patient has ever been treated for LTBI or TB disease

- Establish rapport with patient; explain therapy and adverse effects
## LTBI Treatment Regimens

<table>
<thead>
<tr>
<th>Medication(s)</th>
<th>Recommended Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td><strong>Preferred:</strong> Isoniazid 300 mg daily x 9 months</td>
</tr>
<tr>
<td></td>
<td><strong>Alternative:</strong> 300 mg daily x 6 months, 900 mg twice weekly x 9 months (DOT), 900 mg twice weekly x 6 months (DOT)</td>
</tr>
<tr>
<td>Isoniazid + Rifapentine</td>
<td>Isoniazid 900 mg weekly x 12 weeks (DOT) + Rifapentine once weekly x 12 weeks (DOT)</td>
</tr>
<tr>
<td></td>
<td>10-14 kg 300 mg, 14.1-25 kg 450 mg, 25.1-32 kg 600 mg, 32.1-49.9 kg 750 mg, &gt;50 kg 900 mg (maximum dose)</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Rifampin 600 mg daily x 4 months</td>
</tr>
</tbody>
</table>
Pyridoxine and Isoniazid – Who Needs It?

• Those at increased risk for peripheral neuropathy
  • Diabetes mellitus
  • Alcohol dependence
  • HIV
  • Chronic kidney disease
  • Malnutrition
  • Pregnant/breastfeeding women
Monitoring of LTBI Therapy

• Everyone should have initial clinical evaluation prior to starting therapy with monthly clinical monitoring for signs/symptoms of hepatitis and adherence to medication while on therapy

• For weekly INH/RPT, ask about signs/symptoms with each dose

• Baseline liver enzyme testing in those with:
  • Underlying liver disease
  • HIV infection
  • Pregnant /postpartum (≤ 3 mo after delivery)
  • Regular alcohol consumption
  • Medication(s) with potential hepatotoxicity

• Routine lab monitoring during treatment for those whose baseline liver function tests are abnormal or those at risk for hepatic disease

Pregnant Women

- For most LTBI treatment can be delayed until after delivery, unless they have significant immunocompromising conditions, HIV, or recent TB contact

- INH is safe during pregnancy

- Preferred LTBI treatment regimen is 9 months of INH with pyridoxine

- INH is safe for breastfeeding, give with pyridoxine
Biologics

Used for RA, Crohn’s disease, Psoriasis and a variety of other immune mediated diseases

- Remicade (inflixamab)
- Embril (entanercept)
- Humira (adalimumab)

- Block TNFα activity required for containment of MTB

- Patients should be evaluated for LTBI
- Treatment of LTBI should be initiated prior to Rx
LTBI Treatment Key Points

• Test and treat those at high risk for TB exposure and/or progression to active disease

• LTBI treatment regimens that include weekly or bi-weekly dosing require DOT

• Prior to treatment for LTBI, patients need clinical evaluation + CXR to rule out active TB disease

• While on therapy patients need monthly clinical monitoring

• Baseline liver enzymes for those at risk
Review Cases
Case #1

- 36-year-old Native American female
- History of diabetes
- 35 weeks pregnant
- TST = 18 mm of induration
- No symptoms of TB disease
- CXR, CBC, LFTs normal
- No HIV
- No known contact with TB patient
Which of the following statements regarding this case is correct?

A. She has no known contact with TB. Therefore, this is likely a false-positive result due to pregnancy, therefore retest for LTBI after pregnancy

B. She has LTBI; as pregnancy is a risk factor for progression of TB, she should be treated immediately

C. She has LTBI but treatment can be deferred until post partum

D. Check IGRA as TST tends to be falsely positive in pregnancy

E. T-SPOT TB is the best test for LTBI in pregnancy
Case #2

- 41-year-old Hispanic male
- Moved to U.S. from Mexico 4 years ago
- No known TB contact
- TST = 5 mm of induration (for employment)
- No symptoms of TB disease
- Normal CXR, CBC, AST, and bilirubin
- No HIV or other comorbidity
Which of the following statements regarding this case is correct?

A. He is a recent immigrant and therefore this indicates LTBI requiring treatment
B. He is a foreign national with possible BCG in the past, therefore check IGRA
C. He is a foreign national from a TB endemic country, therefore recheck TST in 8 weeks
D. He is a foreign national from a TB endemic country, therefore check TST and IGRA to be absolutely sure that he has no LTBI
E. No evidence for LTBI, no treatment