HIV/TB Co-infection

*TB Clinical Intensive*

*September 6, 2019*

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- TB is the leading cause of death among HIV-infected persons worldwide
- HIV infection leads to increased TB incidence in multiple settings
  - Antiretroviral therapy (ART) reversing this trend
HIV/TB: Negative interactions

- HIV infection increases risk of both accelerated progression to active TB following infection and reactivation disease
  - Depletion of TB specific T-cells
    - In lungs at air-tissue interface & in lymph nodes
    - Leads to defective granuloma formation & dissemination
  - This risk is reduced, but not eliminated, with ART
- Active TB accelerates HIV disease progression

Who is at greatest risk of TB disease?

<table>
<thead>
<tr>
<th>High-Risk Group</th>
<th>Incidence of Active Tuberculosis</th>
<th>Prevalence of Latent Tuberculosis Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>median rate per 1000 population (range)</td>
<td>median percentage (range)</td>
</tr>
<tr>
<td>Persons with HIV infection</td>
<td>16.2 (12.4–28.0)</td>
<td>14.5 (7.7–21.3)</td>
</tr>
<tr>
<td>Adult contacts of persons with tuberculosis</td>
<td>0.6%</td>
<td>21.1 (6.6–55.1)</td>
</tr>
<tr>
<td>Patients receiving human necrosis factor</td>
<td>1.4%</td>
<td>11.8 (4.0–22.3)</td>
</tr>
<tr>
<td>Migrants</td>
<td>26.6 (1.3–22.0)</td>
<td>33.4 (17.4–44.2)</td>
</tr>
<tr>
<td>Patients undergoing hemodialysis</td>
<td>21.9 (16.4–23.5)</td>
<td>29.5 (20.5–38.5)</td>
</tr>
<tr>
<td>Patients with silicosis</td>
<td>32.1%</td>
<td>46.6%</td>
</tr>
<tr>
<td>Prisoners</td>
<td>2.6 (0.3–9.8)</td>
<td>—</td>
</tr>
<tr>
<td>Health care workers</td>
<td>1.3 (0.4–4.1)</td>
<td>14.1 (0.9–76.7)</td>
</tr>
<tr>
<td>Immigrants from countries with a high tuberculosis burden</td>
<td>3.6 (1.3–41.2)</td>
<td>30.2 (8.6–53.3)</td>
</tr>
<tr>
<td>Homeless persons</td>
<td>2.2 (0.1–4.3)</td>
<td>53.8 (18.4–79.9)</td>
</tr>
<tr>
<td>HIV-drug users</td>
<td>6.0%</td>
<td>63.0 (14.4–64.4)</td>
</tr>
<tr>
<td>Elderly persons</td>
<td>—</td>
<td>16.3%</td>
</tr>
</tbody>
</table>

Getahun, NEJM, 2015
Overview

Considerations in persons living with HIV
- Clinical presentation of active TB
- HIV/TB Treatment
  - Timing of ART in TB disease
  - Immune reconstitution inflammatory syndrome (IRIS)
  - Drug-drug interactions in HIV/TB
- LTBI treatment

Other forms of immunosuppression
- Transplant
- Biologics

TB Diagnosis

- Symptoms
  - Prolonged cough, hemoptysis, fevers, weight-loss, night sweats
- Sputum microscopy (AFB smear)
- Chest X-ray
- Xpert MTB/RIF Assay
- MTB Culture

*Sensitivity of typical methods for TB disease diagnosis are reduced in advanced HIV infection (CD4<200)*
HIV & Subclinical TB

Challenges with TB dx in advanced HIV (CD4<200)

1. Increased risk of sub-clinical TB disease
   - Ambulatory HIV+ adults w/ CD4>200 enrolled in TB vaccine trial; 10/500 w/ subclinical TB (2%)\(^1\)
   - HIV+, ART-naïve out-patients in S Africa; 18/274 (8.5%) asymptomatic, but MTB culture+\(^2\)

2. Other opportunistic infections (OIs), and HIV/AIDS infection alone, commonly cause symptoms often associated with TB
   - Wasting, lymphadenopathy, night sweats, fevers

\(^1\)Mtei, CID, 2005; \(^2\)Oni, Thorax, 2011

TB Diagnosis: Microscopy

- Overall sensitivity of sputum microscopy ~50%
- Lower in HIV+, especially at lower CD4 counts

Chamie, IJTLD 2010
TB Diagnosis: Chest x-ray

Early reports of possible lower sensitivity in HIV+ persons likely due to greater smear-neg disease

- “Xpert MTB/RIF detected 79% of pulmonary TB cases in people infected with HIV and 86% of pulmonary TB cases in people without HIV. However, after adjustment for smear status, there was no evidence of a difference between the HIV-positive and HIV-negative subgroups.”
  - Steingart, Cochrane Database of Systematic Reviews, 2014

TB Diagnosis: Xpert Assay

Chamie, IJTLID 2010

Boehme, NEJM, 2010
TB Diagnosis: Xpert Ultra

Xpert Ultra (next generation assay)
• Two different amplification targets/new design
• Designed to overcome lower sensitivity in smear-negative pulmonary TB (PTB)¹
• PTB diagnostic accuracy study: 8 countries
  – Increased sensitivity (17%) in smear-negative PTB
  – Decreased specificity (98% to 96%)
    • Greater loss in specificity if history of prior TB
  – No difference in detection of Rif-resistance
  – No decrease in sensitivity if HIV+

¹Dorman, Lancet ID, 2018

Clinical Presentation of TB

• Most HIV/TB still presents as Pulmonary TB
  – ↓ sputum bacillary burden with advanced HIV
  – ↑ EPTB with advanced immune suppression
    • Patients with EPTB should undergo sputum eval
    • NB: >1 opportunistic infection in advanced HIV not uncommon: do not assume that all extrapulmonary sites of disease are certain to be TB
TB Treatment in HIV+

- For drug-sensitive PTB/EPTB*
  - 6-months (2HRZE/4HR) recommended, if taking ART with suppressed HIV viral load
  - Daily (5-7 days/week) as DOT recommended
    - Twice or thrice weekly dosing not recommended in either intensive or continuation phase
      - Associated with increased failure and relapse with rifampin-resistance in HIV+ adults
  - 9 months in rare instances where HIV+ patient not on ART, or if cavity or culture+ at 2 months into TB Rx
- Culture Neg TB
  - 6 months total (vs. 4 months if HIV-)

* Longer duration (12 months) in TB meningitis and TB osteomyelitis

CDC, 2019
DHHS, 2019

Treatment of the HIV/TB Co-infected Patient

Case 1

- 23 Brazilian man, recently moved to US
- Presents with fever, night sweats, severely debilitated
- Wasted, diffuse lymphadenopathy
- AFB smear positive
- Newly diagnosed HIV+
- CD4 count is 2 cells/μL
- He is started on HRZE/B6
**Case 1**

**Competing Risks in the timing of ART during TB treatment**

**“Immediate” ART (<2 weeks)**

**Benefits**
- ↓ Risk of OIs/death

**Risks**
- ↑ Drug-drug Interactions
- ↑ IRIS risk
- ↑ pill burden, and possible ↓ adherence
- Decrease ART efficacy?

**“Early” ART (<2 months)**

**Benefits**
- ↓ Risk of IRIS

**Risks**
- ↑ OIs/death

Adapted from: W. Burman, CROI - Boston, 2011

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**Timing of ART Start in TB**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Location</th>
<th>N</th>
<th>Median CD4 (IQR)</th>
<th>Arms</th>
<th>Effect of Earlier Rx on Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPIT (Karim 2010)</td>
<td>S Africa</td>
<td>642</td>
<td>150 (77-254)</td>
<td>Integrated (6 wks) vs Sequential (39 wks)</td>
<td>↓56%</td>
</tr>
<tr>
<td>SAPIT subgroup (Karim 2011)</td>
<td>S Africa</td>
<td>429</td>
<td>150 (77-254)</td>
<td>Early (3 wks) vs Late (14 wks)</td>
<td>↓67% in CD4&lt;50 group only</td>
</tr>
<tr>
<td>CAMELIA (Blanc 2011)</td>
<td>Cambodia</td>
<td>661</td>
<td>25 (10-56)</td>
<td>Immediate (2 wks) vs Early (8 wks)</td>
<td>↓34%</td>
</tr>
<tr>
<td>STRIDE (Havlir 2011)</td>
<td>Multiple sites</td>
<td>806</td>
<td>77 (36-145)</td>
<td>Immediate (2 wks) vs Early (8-12 wks)</td>
<td>↓40% in CD4&lt;50 group only</td>
</tr>
</tbody>
</table>

*All studies excluded CNS TB*
Timing of ART Start in TB

DHHS Guidelines
• ART is recommended in all HIV-infected persons with TB (AI).
• For ART-naive patients, ART should be started within 2 weeks when the CD4 count is <50 cells/mm³ and by 8 to 12 weeks for all others (AI).

Back to Case 1
• Your patient starts ART within 14 days of TB treatment, and he reports he is feeling better
• 2 weeks later in clinic, he reports increasing size of tender “bumps” on his neck
• FNA reveals: AFB smear + necrotizing, granulomatous inflammation
• What’s going on?
Ddx of worsening OI after starting ARVs

- Immune Reconstitution Inflammatory Syndrome (IRIS)
- Adverse effect to medication
- Treatment failure
  - Non-adherence
  - Drug resistance
  - Poor/non-absorption of medication
- Undiagnosed process (e.g. another OI, malignancy, etc.)

What is IRIS?

- Immune Reconstitution Inflammatory Syndrome

- Broadly defined as a syndrome of an exaggerated immune response to antigens after starting ARVs
  - To persistent antigens of an OI that is being treated (paradoxical IRIS)
  - To viable pathogens that were subclinical and not being treated (unmasking IRIS)

- Usually occurs in response to infections but can also occur with malignancy, autoimmune disorders

Paradoxical IRIS

- **Diagnosis**
  - Improvement of OI symptoms on OI treatment prior to ART
  - Deterioration with features of the OI soon after starting ART; and
  - Demonstration of a CD4 and/or HIV viral load response to ART
  AND
  - Exclusion of alternative causes for deterioration (such as a bacterial infection or an additional OI, a drug reaction, poor adherence, or resistance to OI treatment).

Paradoxical TB IRIS

- Incidence estimated at 15.7% (case fatality of ~3%)^2
- Typically 1-4 weeks after ART
- Symptoms last 2-3 months on average
- Risk factors: low CD4 at ART start; EPTB; early ART start^3


IRIS & Early ART

Sub-analyses from STRIDE

**TABLE 2. TB IRIS Cases by Treatment Strategy and CD4**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 61)</th>
<th>Earlier ART (n = 46)</th>
<th>Later ART (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major TB IRIS criteria</td>
<td>57 (93.4%)</td>
<td>38 (90.5%)</td>
<td>19 (100.0%)</td>
</tr>
<tr>
<td>Only minor criteria (1 or more)</td>
<td>4 (6.6%)</td>
<td>4 (9.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Major TB IRIS criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphadenopathy or effort</td>
<td>35 (57.5%)</td>
<td>24 (52.2%)</td>
<td>11 (73.3%)</td>
</tr>
<tr>
<td>Radiologic features of TB</td>
<td>29 (47.5%)</td>
<td>16 (34.8%)</td>
<td>13 (86.7%)</td>
</tr>
<tr>
<td>Infiltrates</td>
<td>20</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Adenopathy</td>
<td>13</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Effusion</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Serositis</td>
<td>5</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Central nervous system TB</td>
<td>4 (6.5%)</td>
<td>3 (1.7%)</td>
<td>1 (5.3%)</td>
</tr>
<tr>
<td>Major TB IRIS criteria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constitutional symptoms (fever, night sweats, or weight loss)</td>
<td>33 (54.1%)</td>
<td>20 (43.5%)</td>
<td>13 (86.7%)</td>
</tr>
<tr>
<td>Respiratory symptoms (cough, dyspnea, or sputum)</td>
<td>21 (34.4%)</td>
<td>17 (37.2%)</td>
<td>4 (26.7%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (4.9%)</td>
<td>8 (17.4%)</td>
<td>3 (15.8%)</td>
</tr>
</tbody>
</table>

**TABLE 3. Characteristics of TB IRIS**

**Key points**
- Increased IRIS w/ earlier ART driven by CD4 <50
- LAN, new/worsening infiltrates on cxr, constitutional sx, abdominal pain common
- No TB IRIS deaths occurred

TB IRIS Management

110 HIV+, non-life-threatening TB-IRIS cases in a South African Hospital:
- 55 randomized to prednisone,
- 55 to placebo
- Prednisone dosing: 1.5 mg/kg/day x 2 weeks, then 0.75 mg/kg/day x 2 weeks
- Primary Endpoint: Days of hospitalization and outpatient therapeutic procedures (the latter counted as one hospital day)

Results
- 1° endpoint: Placebo: 3 days (IQR: 0-9) vs. Pred: 0 days (IQR: 0-3); p=0.04
- 2° endpoints: Prednisone = greater improvements in symptoms, Karnofsky score, quality of life, and chest x-ray abnormalities
- No increase in severe infections in prednisone arm
RCT of Prednisone for Prevention of Paradoxical TB-IRIS
Meintjes, et al, NEJM. 2018

- 1:1 randomized, double-blind, placebo-controlled trial in Cape Town
- Intervention: Prednisone 40mg/day x 2 weeks, then 20mg/day x 2 weeks – started at same time as ARVs - to prevent TB IRIS in HIV/TB pts
- Inclusion: ≥18, ARV-naïve, CD4 ≤100, within 30 days of TB Rx start
- Exclusion: KS, CNS TB, RIF resistance, HBsAg+

1° Outcome: Paradoxical TB-IRIS

2° Endpoints:
- Time to TB-IRIS
- Mortality
- Treatment interruption
- Hospitalization
- Infection/Malignancy

Prednisone prophylaxis vs. placebo:
- Decreased use of high-dose prednisone for IRIS Rx (13% vs. 28%, p=0.007)
- No significant difference in mortality (3% vs. 4%), or hospitalization (14% vs. 23%, p=0.1)
- Trend toward decreased ART or TB drug change or interruption (16% vs. 8%, p=0.07)
- Fewer clinical Grade 3 AEs (29 vs. 45%, p=0.01)
- No significant increase in new AIDS-defining illnesses or invasive BIs (Pred: 9%, placebo: 15%)

"Suggests prednisone is working to alter the immunologic trigger of TB-IRIS, rather than merely suppressing IRIS." – G Meintjes
Are there any trade-offs or other benefits for starting ART early?

– No impact on ART efficacy or toxicity

HIV RNA suppression 74% at 48 weeks
No difference between arms

CD4 change from entry 156 cells/mm³
No difference between arms

Toxicity similar between Arms

Havlir D, ACTG 5221 (Stride), CROI 2011

Does immediate ART enhance clearance of TB?

No difference in time to TB culture negative

No difference to AFB smear negativity

Chamie, CID, 2010
HIV Treatment = TB Prevention

- CIPRA HT001: Starting ART between 200-350 vs. < 200 reduced TB by 50%
- HPTN 052: Early ART in HIV+ patient with CD4 > 350 led to a 47% reduction in risk of TB
- Impact on a population level: East Africa


ART & TB Drug-Drug Interactions
Case 2

• 45 yo man, US-born, marginally-housed, newly-diagnosed with HIV, CD4=100, and started on TAF/FTC & DTG daily 6 months ago
  – TST at the time of HIV diagnosis was 0mm
• Back in clinic now, and CD4=400, HIV viral load is undetectable. Taking ART daily and feeling well.

• Should this patient have repeat testing for LTBI?

Indications for LTBI screening & treatment in HIV+ adults in the US

• Indications for LTBI screening in HIV+ adults
  – At HIV diagnosis or entry to care
  – Annually, if at ongoing risk for TB exposure
  – Repeat testing in those with CD4<200 and a negative TST or QFT performed prior to ART start and immune recovery
• Indications for LTBI treatment in HIV+ adults (without clinical/radiographic evidence of active TB):
  – TST ≥5mm induration
  – Positive IGRA
  – HIV+ close contact of an infectious case of TB

DHHS, 2019
## Case 2

- Patient is QFT+ on repeat screening
- What is the preferred first-line therapy for latent TB infection in HIV+ persons?

## LTBI Treatment in HIV+ Patients

**LTBI Treatment in HIV-Infected Patients**
- INH/B6 daily or twice weekly x 9 months (*preferred 1st line*)
- INH/Rifapentine weekly x 12 weeks
- Rifampin (or rifabutin) daily x 4 months
- RZ x 4 months (high risk of hepatotoxicity)

**Recent trial**
- *Swindles et al, Brief-TB, NEJM 2019*: INH/Rifapentine daily x 1 month non-inferior to 9H in HIV+ adults
- Not yet reflected in CDC/DHHS guidelines

DHHS, 2019
Case 2

• Your patient is initially treated with INH/B6 for a planned 9 month course, but quickly developed hepatotoxicity and failed INH re-challenge
• You are considering 2nd line LTBI preventive treatment options.

Case 2

How would you treat his LTBI? Recall that he is taking: TAF/FTC & DTG daily
1. Rifampin daily x 4 months: switch from TAF/FTC to TDF/FTC and dose DTG bid
2. Rifabutin daily x 4 months: no ARV changes
3. Weekly INH/Rifapentine x 12 weeks
4. Moxifloxacin x 6 months
• Rifampin potent inducer of CYP3A and interacts with a number of ART drugs
• Rifabutin is a less potent inducer of CYP3A than rifampin and preferred TB rifamycin agent when rifampin cannot be used
• ART+ TB treatment regimens may call for adjustment of ART dose, rifabutin dose or both
• Data covering all possible drug interactions are incomplete

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<table>
<thead>
<tr>
<th>Case 2 – Rifamycins &amp; ARVs</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Rifampin</th>
<th>Rifabutin</th>
<th>Rifapentine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF/FTC &amp; ABC/3TC</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>TAF¹</td>
<td>✗️</td>
<td></td>
<td>✗️</td>
</tr>
<tr>
<td><strong>NNRTIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>✔️</td>
<td>✔️ (need to increase RFB)</td>
<td>✔️</td>
</tr>
<tr>
<td>Etravirine</td>
<td>✗️</td>
<td>(potentially) ✗️</td>
<td>✗️</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>✗️</td>
<td>✗️</td>
<td>✗️</td>
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<tr>
<td><strong>PI/r</strong></td>
<td>✗️</td>
<td>Dose 150mg QD</td>
<td>✗️</td>
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<tr>
<td><strong>INSTI</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Raltegravir</td>
<td>✔️ (800mg BID)</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Elvitegravir/Cobi</td>
<td>✗️</td>
<td>✗️</td>
<td>✗️</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>✔️ (50mg BID)</td>
<td>✔️</td>
<td>?</td>
</tr>
<tr>
<td>Bicaptegravir</td>
<td>✗️</td>
<td>✗️</td>
<td>✗️</td>
</tr>
</tbody>
</table>

¹Descovy [prescribing information]. Gilead Sciences Inc; April 2016. TAF levels lowered by Rifamycins
Case 2 – Rifamycins & DTG

Dooley, et al. **DTG + Rifampin**. (“INSPIRING”) CID, 2019
HIV+ adults with active TB randomized to:
- DTG 50mg BID vs. EFV + 2NRTIs during TB Rx
- Primary endpoint: HIV RNA <50 copies/ml at 52 wks
- Study not powered to compare arms
- VL <50: DTG: 75%  EFV: 82%
- DTG non-response driven by lost-to-follow-up
- 2 DTG virologic failures: no acquired resistance
- No HP-related >3 AEs
- HP decreased DTG bioavailability by 29%,
- 59/60 with trough levels >DTG IC90
- Concluded that DTG may be given with RIF

* Not yet reflected in guidelines!

Case 2 – Rifamycins & Bictegravir

Custodio et al, **BIC/FTC/TAF + Rifampin**, CROI 2018, Abstract 34
- Biktarvy qD vs. Biktarvy BID + Rif (n=52)
- AUC BIC reduced 61% and trough reduced 80% even with BID
- Co-administration not recommended
Case 2: Summary

- LTBI Treatment in HIV+ persons
  - INH/B6 x 9 months = first line
- 2nd Line options:
  - RIF or RFB x 4 months
    - NB: drug-drug interactions
  - 3HP: with EFV- or RAL-based regimens, with either ABC/3TC or TDF/FTC
    - Avoid Rifapentine + other ARVs, including TAF or DTG
    - No data yet on daily Rifapentine with INSTIs
- MDR or XDR-exposure
  - Very limited data.
  - FQ often used x 6-12 months following MDR-exposure
  - Trials are underway
    - 2 trials: Levofloxacin vs. placebo x 6 months
    - 1 trial: Delaminid vs. INH x 26 wks

HIV/TB: Conclusions

1. HIV greatly increases risk of TB disease and impacts the clinical presentation/diagnosis of TB, especially if CD4<200
2. CO-TREATMENT OF HIV AND TB SAVES LIVES
3. ART should be started immediately (within 2 weeks of TB therapy) in TB/HIV patients with <50 CD4 cells
   - ART should be started between 2 weeks and 2 months (though why wait?) in all other patients with HIV and TB, even those with high CD4
4. TB IRIS has broad differential and remains a challenging management problem
5. Rifamycins have multiple interactions with ART, and special modifications of dosing of ART and/or TB regimen may be required
   - Frequent introduction of newer agents requires keeping up to date on drug-drug interactions
### TB & Transplant

**Concerns**
- Reactivation TB with transplant immune suppression
- Donor-derived infections (active TB/LTBI) in Solid Organ Transplant
- Drug-drug interactions

**Recipient (prior to transplant):**
- TST and/or IGRA
- Chest imaging
- Epi risk assessment

**Donors (solid organ):**
- Living: LTBI screening
- Deceased: mod-high risk -> imaging and culture
- Donor with LTBI, recent exposure or radiographic evidence of untreated TB -> LTBI treatment for recipient

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**Drug-drug Interactions**
- Rifampin lowers levels of corticosteroids, calcineurin inhibitors (tacrolimus, cyclosporine), and mTORS (mammalian target of rapamycins): sirolimus, everolimus
  - ↑ Risk of graft rejection
- Increase dose of calcineurin inhibitors 3-5x and monitor levels

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*Horne, CID, 2013*
TB & Biologics

• Increased risk of TB with TNFα inhibitors >> non-TNFα inhibitors (e.g. Rituximab)
• Screen for and treat LTBI prior to TNFα inhibitor administration

![Diagram of TNFα and LTBI]

Goletti, Expert Rev Anti Infect Ther, 2018

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• Thank you for your time and attention!