HIV/TB Co-infection

TB Clinical Intensive
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HIV and TB

• TB is the leading cause of death among HIV-infected persons worldwide
• HIV infection lead to increased TB incidence in multiple settings
  – Antiretroviral therapy scale-up reversing this trend

WHO Global TB Report, 2017
HIV/TB: Negative interactions

- HIV infection increases risk of both reactivation disease and accelerated progression to active TB
  - Depletion of TB specific T-cells
  - This risk is reduced, but not eliminated, with HIV Rx
- Active TB accelerates HIV disease progression

Overview

- What’s the latest in:
  - Impact of HIV on TB diagnosis
  - HIV/TB Treatment
    - Timing of ART in TB disease
    - TB IRIS in HIV-infected persons
    - Drug-drug interactions in HIV/TB co-infected persons
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) and persons not on ART*

HIV & Subclinical TB

Challenges with TB dx in advanced HIV
1. Increased risk of asymptomatic (sub-clinical) TB disease
   - Ambulatory HIV+ adults w/ CD4>200 enrolled in TB vaccine trial; 10/500 w/ subclinical TB (2%)\(^1\)
   - HIV+, ART-naive out-patients in S Africa; 18/274 (8.5%) asymptomatic, but MTB culture+\(^2\)
   - Symptom screening less sensitive in HIV+ on-ART than off-ART for Cx+ MTB\(^3\)
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; \(^3\)Rangaka, CID, 2012
TB Diagnosis: Microscopy

- Overall sensitivity of sputum microscopy ~50%
- Lower in HIV+

![Graph showing % Negative AFB Smear vs CD4 Cell Count (cells/μL)]

Chamie, IJTLD 2010

TB Diagnosis: Chest x-ray

- % with Cavitation
- % Normal Chest X-ray

![Graph showing % with Cavitation and % Normal Chest X-ray vs CD4 Cell Count (cells/μL)]

Chamie, IJTLD 2010
• 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 Syt Reviews, 2014

2. 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
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 RIPE

When should you start ART in this patient?
- 1) The same day you start TB treatment
- 2) Within 2 weeks of starting TB treatment
- 3) Within 8 weeks of starting TB treatment
- 4) Wait until after completing TB treatment, then start ART
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</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>sub group</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</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</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>

*Studies excluded CNS 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.)

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 start³

IRIS & Early ART
Sub-analyses from STRIDE

**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


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

<table>
<thead>
<tr>
<th>CD4+</th>
<th>Earlier ART</th>
<th>Later ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>18.8% (27/144)</td>
<td>4.3% (6/141)</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>5.7% (15/263)</td>
<td>5.0% (13/260)</td>
</tr>
</tbody>
</table>

Significant interaction between CD4+ strata and treatment strategy, logistic regression, P < 0.014.

**TABLE 3. Characteristics of TB IRIS**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 61)</th>
<th>Earlier ART (n = 42)</th>
<th>Later ART (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major TB IRIS criteria (1 or more)</td>
<td>57 (93.4%)</td>
<td>38 (90.5%)</td>
<td>19 (100.0%)</td>
</tr>
<tr>
<td>Only minor criteria met (2 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 other focal tissue involvement</td>
<td>38 (62.3%)</td>
<td>24 (57.1%)</td>
<td>12 (63.2%)</td>
</tr>
<tr>
<td>Radiologic features of TB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infiltrates</td>
<td>25 (41.0%)</td>
<td>17 (40.5%)</td>
<td>8 (42.1%)</td>
</tr>
<tr>
<td>Adenopathy</td>
<td>20</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>Erosion</td>
<td>19</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>6</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Central nervous system TB</td>
<td>4 (6.6%)</td>
<td>3 (7.1%)</td>
<td>1 (5.3%)</td>
</tr>
<tr>
<td>Constitutional symptoms (fever, night sweats, or weight loss)</td>
<td>33 (54.1%)</td>
<td>20 (47.6%)</td>
<td>13 (68.4%)</td>
</tr>
<tr>
<td>Respiratory symptoms (cough, dyspnea, or sputum)</td>
<td>21 (34.4%)</td>
<td>17 (40.5%)</td>
<td>4 (21.1%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>21 (34.4%)</td>
<td>12 (28.6%)</td>
<td>9 (47.4%)</td>
</tr>
</tbody>
</table>

TB IRIS Management
Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome

Graeme Meintjes¹h, Robert J. Wilkinson¹h, Chelsea Morton¹i, Dominique J. Pepper¹h, Kevin Rebe¹h, Molebogeng X. Rangaka*, Tolu Oni³h and Gary Maartens*²

- 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


- 1:1 randomized, double-blind, placebo-controlled trial in Cape Town
- Intervention:
  - Prednisone 40mg/day x 2 weeks, then 20mg/day x 2 weeks (4 weeks total)
  - Started at same time as ARVs to prevent TB IRIS in HIV/TB pts
- Inclusion: ≥18, ARV-naive, 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
- Rx interruption
- Hospitalization
- Infxn/Malignancy
RCT of Prednisone for Prevention of Paradoxical TB-IRIS


**Primary Endpoint: TB-IRIS**

![Graph showing TB-IRIS incidence over 12 weeks]

- Placebo: 56/120 (46.7%)
- Prednisone: 39/120 (32.5%)
- Relative risk = 0.70 (95%CI = 0.51 - 0.96)
- p = 0.02 (Chi square)

**Secondary Endpoints**

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 (median, IQR)
  - No difference between arms

**Toxicity similar between Arms**

Havlir D, ACTG 5221 (Stride), CROI 2011
Does immediate ART enhance clearance of TB?

- No differences in TB Rx response by ART use
- No TB therapy failures occurred in either study arm
- TB recurrences:
  - ART = 3
  - No ART = 4 (p = 0.5)

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 TB¹
- Impact on a population level: East Africa²

¹Grinsztejn, Lancet ID, 2014; ²Saito, JAIDS, 2016
Case 2

- 45 yo man, marginally housed, well-controlled HIV on TAF/FTC & DTG.
- Patient is newly QFT+ on annual screening
- Initially treated with INH/B6 for planned 9 month course, but quickly developed hepatotoxicity and failed INH re-challenge
- You are considering 2nd line LTBI preventive treatment options.
How would you treat his LTBI?

1. Rifampin daily x 4 months, and dose DTG bid
2. Rifabutin daily x 4 months and switch from TAF/FTC to TDF/FTC
3. Weekly INH/Rifapentine x 12 weeks
4. Moxifloxacin x 6 months

Case 2

• 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
Case 2 – Rifamycins & ARVs

<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>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>(need to increase RFB)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etravirine</td>
<td>✗</td>
<td>✗</td>
<td>✔️</td>
</tr>
<tr>
<td>(potentially)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>✗</td>
<td>✗</td>
<td>✗</td>
</tr>
<tr>
<td><strong>PI/r</strong></td>
<td>✗</td>
<td>✔️</td>
<td>✗</td>
</tr>
<tr>
<td>Dose 150mg QD</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>INSTI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
</tbody>
</table>

1Descovy [prescribing information]. Gilead Sciences Inc; April 2016. TAF levels lowered by Rifamycins.

Case 2

- Open-label, intra-subject drug interaction study in HIV-negative healthy volunteers comprised of 2 phases:
  1. DTG once daily alone
  2. DTG once daily with INH/Rifapentine.
- Of 4 enrolled subjects (3 males, 1 female, age 22-46 years), 3 completed the study and 1 withdrew prior to the 3rd dose of HP.
- 2 of 3 developed flu-like illness with transaminase elevations (Table 1) with symptom onset ~8-10 hours after the last doses of DTG, RPT, and INH.
Case 2

  - In prior trials of 3HP:
    - flu-like sx occurred in <4%;
    - hepatotoxicity 0.4-1%
  - Exposure to RPT and its metabolite were similar to reference PK data for all subjects.
  - INH exposure was higher than expected in the 2 subjects that developed flu-like syndrome.

![Graphs showing plasma concentration vs. time for RPT, 25-desacetyl RPT, and INH](image)

Case 2

- LTBI Treatment in HIV+ persons
  - INH/B6 x 9 months = first line
- 2\textsuperscript{nd} 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
- MDR or XDR-exposure
  - Very limited data. FQ often used x 6-12 months.
Conclusions

1. HIV greatly increases risk of TB disease and impacts the clinical presentation/diagnosis of TB
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

Thank you!

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  – Dr. Annie Leutkemeyer, Division of HIV, Infectious Diseases & Global Medicine, UCSF
  – Thank you to Lisa Chen and Jeannie Fong

• **Disclosures:** None

• Thank you for your time and attention!