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, 2016
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%)<sup>1</sup>
   - HIV+, ART-naïve out-patients in S Africa; 18/274 (8.5%) asymptomatic, but MTB culture<sup>+</sup><sup>2</sup>
   - Symptom screening less sensitive in HIV+ on-ART than off-ART for Cx+ MTB<sup>3</sup>

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

<sup>1</sup>Mtei, CID, 2005;  <sup>2</sup>Oni, Thorax, 2011;  <sup>3</sup>Rangaka, CID, 2012
TB Diagnosis: Microscopy

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

[Graph showing % Negative AFB Smear vs CD4 Cell Count]

TB Diagnosis: Chest x-ray

[Graph showing % with Cavitation vs CD4 Cell Count]

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 Sys Reviews, 2014

• Xpert Ultra:
  – Sensitivity: 5% higher than that of Xpert (95%CI +2.7, +7.8)
    • Sensitivity-increases higher among
      – AFB Smear Negative: (+17%, 95%CI +10, +25)
      – HIV-infected pts: (+12%, 95%CI +4.9, +21)
    – but specificity was 3.2% lower (95%CI -2.1, -4.7).
    • Specificity-decreases higher in patients with a history of TB (-5.4%, 95%CI -9.1, -3.1) than no history of TB (-2.4%, 95%CI -4.0, -1.3)

Schumacher, CROI 2017, Abstract 76LB
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

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
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>64</td>
<td>150 (77-254)</td>
<td>Integrated (6 wks) vs Sequential (39 wks)</td>
<td>↓56%</td>
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<tr>
<td>Karim 2010</td>
<td></td>
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<tr>
<td>SAPIT subgroup</td>
<td>S Africa</td>
<td>42</td>
<td>150 (77-254)</td>
<td>Early (3 wks) vs Late (14 wks)</td>
<td>↓67% in CD4&lt;50 group only</td>
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<tr>
<td>(Karim 2011)</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>CAMELIA</td>
<td>Cambodia</td>
<td>66</td>
<td>25 (10-56)</td>
<td>Immediate (2 wks) vs Early (8 wks)</td>
<td>↓34%</td>
</tr>
<tr>
<td>Blanc 2011</td>
<td></td>
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<tr>
<td>STRIDE</td>
<td>Multiple sites</td>
<td>80</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>
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<tr>
<td>Havlir 2011</td>
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</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).
• 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?

Dx 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

<table>
<thead>
<tr>
<th>TABLE 2. TB IRIS Cases by Treatment Strategy and CD4+ Strata</th>
<th>Earlier ART</th>
<th>Later ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4+ &lt; 50</td>
<td>10.4% (42/405)</td>
<td>4.7% (19/401)</td>
</tr>
<tr>
<td>11.5% (33/285)</td>
<td>18.8% (27/144)</td>
<td>4.3% (6/141)</td>
</tr>
<tr>
<td>CD4+ ≥ 50</td>
<td>5.7% (15/261)</td>
<td>5.0% (13/260)</td>
</tr>
</tbody>
</table>

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

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>
<thead>
<tr>
<th>TABLE 3. Characteristics of TB IRIS</th>
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</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Major TB IRIS criteria (1 or more)</td>
</tr>
<tr>
<td>Lymphadenopathy or other focal tissue involvement</td>
</tr>
<tr>
<td>Radiological features of TB</td>
</tr>
<tr>
<td>Infiltrates</td>
</tr>
<tr>
<td>Adenopathy</td>
</tr>
<tr>
<td>Effusion</td>
</tr>
<tr>
<td>Serositis</td>
</tr>
<tr>
<td>Central nervous system TB</td>
</tr>
<tr>
<td>Minor TB IRIS criteria</td>
</tr>
<tr>
<td>Constitutional symptoms (fever, night sweats, or weight loss)</td>
</tr>
<tr>
<td>Respiratory symptoms (cough, dyspnea, or stridor)</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Management</td>
</tr>
<tr>
<td>Steroids prescribed</td>
</tr>
<tr>
<td>Intravenous procedures</td>
</tr>
<tr>
<td>Hospitalization</td>
</tr>
<tr>
<td>TB treatment interruption</td>
</tr>
<tr>
<td>ART treatment interruption</td>
</tr>
</tbody>
</table>

TB IRIS Management

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

Graeme Meintjes\textsuperscript{a,b,c,}\textsuperscript*, Robert J. Wilkinson\textsuperscript{a,b,c,d,e,}\textsuperscript*, Chelsea Morroni\textsuperscript{a,f,}\textsuperscript*, Dominique J. Pepper\textsuperscript{a,b,c,}\textsuperscript*, Kevin Rebe\textsuperscript{a,c,}\textsuperscript*, Molebogeng X. Rangaka\textsuperscript{a,}\textsuperscript*, Tolu Oni\textsuperscript{a,d,}\textsuperscript* and Gary Maartens\textsuperscript{a,}\textsuperscript*

- 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-

- 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-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
- Rx interruption
- Hospitalization
- Infection/Malignancy

Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo arm (n = 120)</th>
<th>Prednisone arm (n= 120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>36 (29 – 43)</td>
<td>37 (31 – 43)</td>
</tr>
<tr>
<td>Men</td>
<td>73 (61%)</td>
<td>71 (59%)</td>
</tr>
<tr>
<td>CD4 count (cells/µl)</td>
<td>49 (23 – 88)</td>
<td>51 (26 – 84)</td>
</tr>
<tr>
<td>HIV viral load (log10 copies/ml)</td>
<td>5.6 (5.2 – 5.9)</td>
<td>5.5 (5.2 – 5.9)</td>
</tr>
<tr>
<td>TB microbiologically confirmed</td>
<td>89 (74%)</td>
<td>86 (72%)</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>9.8 (8.5 – 10.9)</td>
<td>9.7 (8.8 – 11.1)</td>
</tr>
<tr>
<td>Duration from TB treatment to ART (days)</td>
<td>17 (15 – 21)</td>
<td>16 (15 – 22)</td>
</tr>
<tr>
<td>Karnofsky Performance Score</td>
<td>90 (80 – 90)</td>
<td>80 (80 – 90)</td>
</tr>
</tbody>
</table>

233/240 (97%) initiated on tenofovir + FTC or 3TC + efavirenz as initial ART regimen
RCT of Prednisone for Prevention of Paradoxical TB-IRIS


Primary Endpoint: TB-IRIS

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 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 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 $\geq$ 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, 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.
ART and TB Drug Interactions—General Principles

- 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>✔️ (need to increase RFB)</td>
<td>✔️</td>
</tr>
<tr>
<td>Etravirine</td>
<td>✗ (potentially)</td>
<td>✗</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>
</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.

<table>
<thead>
<tr>
<th>Table 1. Summary of Major AEs in Subjects 1 &amp; 4</th>
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</thead>
<tbody>
<tr>
<td>Adverse Event</td>
</tr>
<tr>
<td>Flu-like syndrome</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Dizziness/ lightheadedness</td>
</tr>
<tr>
<td>Tachycardia</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Chills</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
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<tr>
<td>Rash</td>
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<tr>
<td>Lab abnormalities</td>
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<tr>
<td>Absolute lymphocyte decrease</td>
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<tr>
<td>ALT elevation</td>
</tr>
<tr>
<td>AST elevation</td>
</tr>
<tr>
<td>Direct bilirubin elevation</td>
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</tbody>
</table>

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.

Figure 4. RPT, 25-desacetyl RPT, and INH Plasma Concentration vs. Time Curves by Subject on Day 19
Case 2

• 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
• 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 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!

• **Acknowledgements:**
  – 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!