TB and HIV

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TB is a leading cause of death in HIV

<table>
<thead>
<tr>
<th>Estimated number of cases</th>
<th>Estimated number of deaths</th>
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<tbody>
<tr>
<td>All forms of TB</td>
<td>9.6 million</td>
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<tr>
<td>HIV-associated TB</td>
<td>1.2 million</td>
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<td>(peaked at 570,000 in 2004)</td>
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<tr>
<td>HIV positive people</td>
<td>392,000</td>
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<tr>
<td>with TB who are on ART</td>
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</tbody>
</table>

Global TB Report 2015, WHO/STOP TB

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Outline

- Effect of HIV on clinical presentation of TB
- TB diagnostics in HIV patients
- Timing of ART start in TB patients
- TB IRIS
- Use of ART drugs in TB patients
What changes with HIV?

- Multiple effects of HIV infection on the course of TB infection and disease

PLWHIV 24-28 times more likely to develop TB

Source: Murray & Nadell’s Text of Respiratory Medicine

Case 1: HIV patient with cough

- 46 yo HIV positive patient (last CD4 190, VL undetectable), bipolar, who presents to urgent care with cough x 3 weeks.
- Out of care for 3 months, last visit had a positive QFT. Currently off of antiretroviral therapy (ART)
TB Diagnosis

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

TB Diagnosis in HIV: Microscopy

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

TB Diagnosis in HIV: Chest x-ray

Chamie, IJTLD 2010
## Xpert MTB/RIF Assay

- Automated, PCR-based sputum assay: amplification of MTB-specific sequence of *rpoB* gene
- TB identification & probes for mutations in *rpoB* associated with rifampin-resistance
- Trend towards decreased sensitivity in HIV+

### Table 1: Overall Sensitivity and Specificity of the MTB/RIF Test, According to the Number of Tests per Patient, as Compared with Three Smears and Four Cultures

<table>
<thead>
<tr>
<th>Site and No. of Tests</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td></td>
<td>All Cultures Positive and Cultures Negative</td>
<td>All Cultures Positive and Cultures Negative</td>
</tr>
<tr>
<td>Correct-tos/total-no.</td>
<td>65/77 (83.7)</td>
<td>104/151 (68.8)</td>
</tr>
<tr>
<td>5% CI</td>
<td>58.2-73.2</td>
<td>60.5-76.2</td>
</tr>
</tbody>
</table>

Boehme, NEJM, 2010; Theron AJRCCM 2011

## Case 1: HIV patient with cough

- Admitted to the hospital to rule out TB.
- AFB smear negative
- Rapid improvement on antibiotics, so he was discharged with diagnosis of bacterial pneumonia.
- Other imaging? Discharge with LTBI treatment?
- Labs from initial visit reveal VL of 900 and CD4 of 190. AFB sputum negative, AFB cultures ultimately negative.
- He is loss to follow up, but returns to the emergency room 10 months later with disseminated zoster and syncope. Continues to have cough
HIV and TB
- High risk of primary progression or reactivation
- Often paucibacillary, smear negative disease
- Significant variations in CXR, especially across CD4 strata

Case 1: TB and low CD4
- 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 do you start ART?

Updates on ART Start
- 57% Reduced risk of Serious events or deaths within the immediate ART group
- 44% lower risk of HIV related illness and 35% lower risk of death in patients randomized to immediate ART + IPT vs. deferred ART and no IPT
Data Overwhelmingly Support Universal ART

- Reduces risk of AIDS-event and/or death in ART-naïve
  - NSIGHT START Study Group. NEJM 2015 Aug 27;373(9)
  - TEMPRANO ANRS 12136 Study Group. NEJM 2015 Aug 27;373(9)
- Improves survival and AIDS-progression in those presenting with OIs
- Improves survival in patients with active TB (esp CD4 <50)
  - Blanc et al. NEJM 2011 Oct 20;365(16):1471-81
  - Odame et al. PLOS One. 2014 Nov 12;9(11)
- Reduces HIV transmission
  - Cohen MS, et al. NEJM. 2011 Aug 11;365(6)
- Reduces patient’s long term viral reservoir
  - Ganne et al. Antiviral Ther. 2011;16(4)
- Associated with fewer long-term metabolic abnormalities
- ART start, regardless of CD4, is now recommended by both DHHS (2013) and WHO (2016)

Few exceptions to immediate ART start in setting of OI and in general

- Generally speaking, immediate ART start beneficial except with space-occupying and/or inflammatory lesions of CNS

When to start ART during TB treatment?

Competing Risks in the timing of ART during TB treatment

<table>
<thead>
<tr>
<th>Immediate ART (&lt;2 weeks)</th>
<th>Early” ART (&lt;2 months)</th>
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</thead>
<tbody>
<tr>
<td>Benefits</td>
<td>Benefits</td>
</tr>
<tr>
<td>Risk of OIs</td>
<td>Risk of IRIS</td>
</tr>
<tr>
<td>Risks</td>
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</tr>
<tr>
<td>Drug-drug Interactions</td>
<td>OIs</td>
</tr>
<tr>
<td>IRIS risk</td>
<td></td>
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<td>pil burden, and possible adherence</td>
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<td>Could decrease ART efficacy</td>
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Adapted from: W. Burman, CROI - Boston, 2011
### Key characteristics of trials of timing of ART during TB treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Key enrollment criteria</th>
<th>Median CD4 (IQR)</th>
<th>Primary endpoint</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAMELIA</td>
<td>Cambodia</td>
<td>Smear +, CD4 &lt; 200</td>
<td>25 (10 - 56)</td>
<td>Death</td>
<td>Early within 2 weeks, late within 2 months</td>
</tr>
<tr>
<td>STRIDE</td>
<td>Multi-national</td>
<td>Clinical TB, CD4 &lt; 250</td>
<td>77 (36 - 145)</td>
<td>AIDS or death</td>
<td>Early within 2 weeks, late within 2 months</td>
</tr>
<tr>
<td>SAPIT</td>
<td>South Africa</td>
<td>Smear +, CD4 &lt; 500</td>
<td>150 (77 - 254)</td>
<td>AIDS or death</td>
<td>Within 4 weeks of TB treatment initiation (early), completion (sequential)</td>
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### Effect of ART timing on death (CAMELIA) or death/AIDS (STRIDE, SAPIT)

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<th>SAPIT</th>
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<td>Death</td>
<td>34% ↓</td>
<td>19% ↓</td>
<td>11% ↓</td>
</tr>
<tr>
<td>p</td>
<td>0.004</td>
<td>0.45</td>
<td>0.73</td>
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### All studies showed significant reduction in death/AIDS among those with CD4 < 50

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<td>68% ↓</td>
</tr>
<tr>
<td>p</td>
<td>0.004</td>
<td>0.02</td>
<td>0.06</td>
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Timing is everything – why does a 6 weeks delay in ART matter so much?

When to start ART?

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
  - Could decrease ART efficacy

Early ART (<2 months)
- Benefits
  - ↓ Risk of IRIS
- Risks
  - ↑ OIs

TB IRIS Greater in Immediate vs. Early Arms

- STRIDE
  - Immediate: 18
  - Early: 8
  - p=0.009

- SAPIT
  - Immediate: 14
  - Early: 6
  - p=0.02
TB IRIS Predictors

- Low CD4
- High Viral Load
- Hispanic Ethnicity
- South African
- Early ART
- Culture confirmed

TB-IRIS common, but does not increase mortality
- Occurred in 7.8% of patients, 10.4% in earlier vs. 4.7% in later ART arm
- TB-IRIS Highest in CD4<50 (11.5%)
- 28% cases mild (no hospitalization, steroids, procedure), 40% (corticosteroid use/invasive procedure), 31% severe (hospitalization)
- Majority of cases were mild (no hospitalization/procedures/steroids)
- No deaths due to IRIS in STRIDE
- TB IRIS increased in early ART, but does not increase mortality

HIV RNA and CD4 Responses Similar at 48 weeks

- 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

Case 1: TB and low CD4

- 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
- He is started on RIPE

Key Points

- Start within 2 weeks of TB therapy
- Anticipate TB IRIS as a complication
Case 2: TB and high CD4

- 47 yo latino male in ER with cough and weight loss
- Chest radiograph consistent with TB, AFB+
- Initially refuses HIV test
- Seen in TB clinic, starts on 4 drug therapy, with rifampin
- On the day he starts TB Rx, agrees to HIV test
- HIV + and CD4 680
- Is ART necessary? If so, when?

SAPIT Study

- 642 HIV+ adults in Durban, South Africa
- AFB smear + pulmonary TB
- CD4 count <500
- Randomized to
  - ART during TB therapy at 2 weeks
  - ART during TB therapy after induction
  - ART after TB therapy completion ("sequential therapy")


Mortality reduced when ART started during vs. after TB treatment: SAPIT

When to start ART?

**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
    - Could decrease ART efficacy

- **Early** ART (<2 months)
  - **Benefits**
    - ↓ Risk of IRIS
  - **Risks**
    - ↑ OIs

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

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**Case 2: TB and high CD4**

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- Chest radiograph consistent with TB, AFB+
- Initially refuses HIV test
- Seen in TB clinic, starts on 4 drug therapy, with rifampin
- On the day he starts TB Rx, agrees to HIV test
- HIV + and CD4 680

**Key Points**

- Get HIV genotype
- Start ART – favor early start, ideally within 2 weeks
- ART regimen may require replacing rifampin with rifabutin

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**TB meningitis: No benefit to immediate ART**

- RCT in Vietnam in 253 with HIV related TBM
- ART within 2 weeks vs. 2 months
- No survival benefit
- More Grade 4 adverse events
- High mortality: 58% mortality at 9 months
- Generalizability?

Torok, CID, 2011

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TB/HIV Coinfection
**Case 3: Clinical worsening after ART**

- 29 yo man w/ HIV p/w fevers, diarrhea, abd pain
- Dx’d with TB ileitis (cx+)
- CD4 310, VL=385,000
- Started on TB therapy, then ART (EFV, tenofovir/emtricitabine: "Atripla") within 2 weeks
- Comes to clinic 4 weeks after ART start: diarrhea, abd pain have resolved; complains of neck swelling & pain
- CD4 is now 615, VL=83

**Differential Diagnosis**

- Drug resistant TB
- Other opportunistic infection
- Non adherence
- Malabsorption
- Drug reactions
- TB Immune Reconstitution Inflammatory Syndrome (IRIS)

**Case 3**

FNA: AFB smear + necrotizing, granulomatous inflammation
TB IRIS – A constant challenge to the clinician

- **TB IRIS**: New or worsening or recurrent symptoms/signs and/or radiographic manifestations of TB
  - Fever, lymphadenopathy, enlarging CNS lesion, respiratory decompensation
  - Can be seen in HIV negative patients, but usually associated with immune reconstitution associated with ART
- **ART induced viral suppression → immune recovery → restoration of TB-specific immune response**

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2 Types of TB Immune Reconstitution Inflammatory Syndrome (IRIS)

- **Patients NOT on TB treatment**
  - Start ART → Unmasking TB IRIS
- **Patients ON TB treatment**
  - Start ART → Paradoxical TB IRIS

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Paradoxical TB-IRIS

- Patient diagnosed with TB and started on TB treatment
- Improving on TB treatment then start ART
- Resurgence of TB symptoms and new or recurrent clinical manifestations of TB (Usually 1-4 weeks after starting ART)

Slide from Meintjes stoptb.org
Paradoxical TB IRIS

- **Diagnosis:**
  - Improvement of TB symptoms on TB treatment prior to ART
  - Deterioration with features of worsening TB 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 TB treatment


Case 4: Clinical worsening after ART

- 25 female pulmonary TB, fevers, wasting, diffuse lymphadenopathy
- CD4 29
- Started on TB therapy, then Atripla within 2 weeks
- Initial improvement
- Comes to clinic 3 weeks after ART start with headache, fever, meningismus and stridor

Patient has TB IRIS with compression of trachea

- Steroids recommended for life threatening situations such as airway compromise, respiratory failure and enlarging mass lesions
- For not life threatening TB IRIS, a 4 week course reduced hospitalization and procedures
- More extended duration of prednisone may be required
- ART should be continued

There is no diagnostic test for TB IRIS, although there are biomarkers associated with higher risk

Meintjes, AIDS, 2010
Cases 3 & 4: Clinical worsening after ART

Key Points

• Continue ART and TB treatment
• Start steroids
• Look for and treat OIs
• Monitor closely

www.niaid.nih.gov

ART & TB Drug Interactions

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
Updates on First Line ART Regimens in the Treatment Naïve Patient

- ART regimen consists of two nucleoside reverse transcriptase inhibitors (NRTI) in combination with a 3rd agent (Integrase inhibitor or protease inhibitor- Darunavir)
- Non nucleoside inhibitors (NNRTIs) like efavirenz are no longer first line.
- Common Integrase Inhibitor Based Regimens:
  - Triumeq (Dolutegravir, Abacavir, Lamivudine)
  - Genvoya (Elvitegravir, Cobicistat, Emtricitabine, Tenofovir Alafenamide-TAF)
  - Stribild (Elvitegravir, Cobicistat, Emtricitabine, Tenofovir disoproxil fumarate-TDF)

Dose Adjustments with ART and TB Medications

<table>
<thead>
<tr>
<th>ART Regimen</th>
<th>Rifampin</th>
<th>Rifabutin</th>
<th>Efavirenz</th>
<th>No NVP lead in</th>
<th>Etravirine</th>
<th>Limited clinical data</th>
<th>DRV/r or ATZ/r</th>
<th>Decrease rifabutin</th>
<th>Lopinavir/r</th>
<th>Decrease rifabutin</th>
<th>Raltegravir</th>
<th>Increase RAL</th>
<th>EVG trough decr. 67%</th>
<th>Maraviroc</th>
<th>Increase MVC</th>
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<tbody>
<tr>
<td>Integrase Inhibitors</td>
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</table>

HIV+ pts with RIF-sensitive TB should only be treated with a regimen not containing a rifamycin if they have had a serious event that is highly likely to be due to the drug.
**Dolutegravir**

- If using rifampin then increase dolutegravir dose to 50mg BID
  - Rifampin decreases dolutegravir AUC and Cmin by 54% and 72%
- Ok to continue dolutegravir 50mg daily dosing if using rifabutin 300mg daily.
  - Rifabutin lowers dolutegravir Cmin by 30%, but does no significantly change the AUC or Cmax.
- Caution in treatment experienced patients
- Side Effects: Headache, Bloating, Insomnia

**Raltegravir (RAL) + Rifampin**

- Current recommendations to increase RAL to 800 mg BID
  - Compensates for AUC decrease but trough remains low
- No dose adjustment of RAL needed if co-administered with Rifabutin

- Braininard, J Clin Pharm, 2011

**Protease Inhibitors**
**Rifabutin and Protease inhibitors**

- All PIs increase Rifabutin concentrations
- Current recommendation: Decrease Rifabutin from 300 mg daily to 150 mg daily for boosted PIs
- CAUTION: Rifabutin dose would then be inadequate if patient stopped Protease inhibitor!

**Another Caution: Rifampin resistance with PI/rifabutin**

- 3 cases of relapse with acquired rifampin resistant TB, while on boosted PI + rifabutin 150 mg QOD TB regimen
- 7 of 10 patients on Kaletra/ Rifabutin 150 QOD subtherapeutic rifabutin AUC
  - One acquired Rifamycin resistance

Higher dose of rifabutin now recommended with protease inhibitors - 150 mg QD (vs. QOD)

Prescobix

- Prescobix = Darunavir + cobicistat
  - TAF+FTC+DRV+c- single tablet combination pending

- Cobicistat ≠ Ritonavir

- Package Insert Rifabutin Dosing recommendations: 150mg every other day. Limited PK and clinical data and would avoid during TB treatment for now.

NNRTIs

For the patient still on efavarinz/Atripla....

- Previously recommended increasing EFV to 800 mg when coadministered with RIF if weight >50 kg
  (http://packageinserts.bms.com/pi/pi_sustiva.pdf)

- Very limited evidence to support this

- One study of HIV/TB coinfected Spanish patients
  - EFV troughs and AUC on average decreased 22-25% if EFV 600
  - Highly variable and EFV levels went UP with RIF in some patients
  - EFV 800 mg+RIF associated with same levels as EFV 600 without RIF


  NIH/CDC OI Guidelines 2013

Current Recommendation: Dose EFV at 600 mg daily (standard dosing)
### Dose Adjustments with ART and TB Medications

<table>
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<tr>
<th>NNRTI</th>
<th>Rifampin</th>
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HIV+ pts with Rif-sensitive TB should only be treated with a regimen not containing rifamycin if they have had a serious event that is highly likely to be due to the drug.

### Conclusions

- **CO-TREATMENT OF HIV AND TB SAVES LIVES**
- **ART should be started immediately (within 2 weeks of TB therapy) in TB/HIV patients with <50 CD4 cells**
- **ART should be started early in all other patients with HIV and TB, even those with high CD4**
- **TB IRIS has broad differential and remains a challenging management problem**
- **Rifamycins have multiple interactions with ART, and special modifications of dosing of ART and/or TB regimen may be required**

### Thank you!

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  - Annie Leutkemeyer and Gabriel Chamie, Division of HIV, ID, and Global Medicine, UCSF, SFGH
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