Managing two infections – a review of the treatment of HIV-related tuberculosis

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This presentation is intended for educational use only, and does not in any way constitute medical consultation or advice related to any specific patient.
Objectives

• Gain an understanding of the epidemiology of HIV-associated Tuberculosis (TB) globally

• Become familiar with the spectrum of TB infection/disease among HIV-positive persons

• Be able to discuss specific treatment considerations for TB disease in HIV-positive individuals
1.7 MILLION TB DEATHS INCLUDING 0.4 MILLION TB DEATHS AMONG PEOPLE WITH HIV*

TB is the top infectious killer worldwide
TB is also the leading cause of deaths due to antimicrobial resistance and among people with HIV

MDR-TB crisis with gaps in detection and treatment
Only 1 in 5 needing MDR-TB treatment were enrolled on it

US$ 2.3 BILLION GAP
Funding shortfall for TB implementation

• 10.4 million people with TB in 2016
• 600,000 with DR-TB

www.who.int
Global TB/HIV report

ACHIEVEMENTS IN 2016

- 6.2 million lives saved of people with HIV through scale-up of collaborative TB/HIV activities since 2005
- 82% known HIV status among notified TB cases in Africa, up from 22% in 2006
- 85% ART coverage among notified TB cases living with HIV, up from 46% in 2006
- >1.3 million PLHIV started TB preventive treatment up from 27,000 in 2006

KEY CHALLENGES

- 54% of all people with HIV-associated TB did not reach care according to reported data
- 18/30 countries with high burden of HIV-associated TB did not report IPT for PLHIV newly enrolled in HIV care
The Spectrum of TB Infection in Patients with TB and HIV

Progression accelerated by HIV

- Uninfected
- Quiescent ('latent') infection
- Active 'sub-clinical' infection
- Symptomatic TB disease

Mycobacterial load vs. Time

Infection with *M. tuberculosis*

Symptom onset

Lawn, SD and Wood R, JID 2011
Rates of TB disease depend on incidence in community of origin and underlying immunosuppression.
Diagnostic testing for *M. tuberculosis* Infection

- Tuberculin skin test sensitivity <75%
  - ≥5 mm is considered positive
  - If negative, repeat testing when CD4>200 cells/µL; considered positive if previously ≤4mm and now ≥5mm

- IGRA sensitivity 69-89%
  - greater specificity in BCG-vaccinated individuals
  - If negative repeat testing when CD4>200 cells/µL

Huo Z and Peng L. BMC ID 2016
Cobelens FG et al. CID 2006
EVALUATING FOR TB DISEASE
• CXR—insensitive, may have normal findings in up to 1/3
• (AFB) sputum smear
  • Up to 70% may be AFB smear negative at presentation
• AFB sputum culture—gold standard, limit of detection 10 organisms/mL sputum

Conde MB. Am J Respir Crit Care Med. 2000;162(6):2238
Bakari M, et al., BMC Infect Dis. 2008;8:32
Hassim S, et al., Clin Infect Dis. 2010;50(7):1053
Finding TB earlier to limit transmission, decrease time to effective treatment: Nucleic Acid Amplification Tests

Molecular beacon (Xpert MTB/RIF)
- Identifies *M. tuberculosis* and detects mutations that confer resistance to rifampin
- Up to 67% of AFB smear-negative cases identified
- Newer generation (“Xpert-Ultra”) may approach sensitivity of culture

“Xpert Omni” model is battery powered, wireless, internet connectivity

Alland D et al. CROI 2015, abstract # 9
Finding TB earlier to limit transmission, decrease time to effective treatment: Nucleic Acid Amplification Tests

- **Amplified Mycobacterium Tuberculosis Direct Test**
  - HIV-positive individuals: sensitivity of 87.5% compared to culture, 70% in smear-negative (n=33 positive by solid culture media, 16/33 smear-positive)

- **Line probe assay (Hain)**
  - Tests for resistance to isoniazid and rifampin
  - Not widely available in the US
  - Likely as sensitive as Xpert

Alland D et al. CROI 2015, abstract # 91
Schumacher SG, et al CROI 2017, abstract #76 LB
Barreto et al. J Bras Pneumol 2014
Other Diagnostic tests for M. tuberculosis

- AFB blood cultures
  - Common bloodstream infection in HIV-positive patients living in hyperendemic TB burden settings

- Urine culture for AFB
  - Yield up to 77%

- Urine-Lipoarabinomannan (LAM)
  - Tests for glycolipid in the cell wall of M. tuberculosis
  - Sensitivity higher in individuals with CD4 <50

TB diagnostics for HIV-positive individuals: summary

- The best test is still culture: unacceptable diagnostic delays
- Universal offering of culture not feasible in many countries
- Point of care testing is improving but there are still gaps...
- What to do?
  - Maintain high index of suspicion
  - Empiric treatment followed by assessing clinical response
    - Pending culture results where available
20 y/o woman with newly diagnosed HIV who was admitted with cough, and lymphadenopathy.

Sputum – smear negative X 3
Gene Xpert MTB/RIF negative
IGRA positive
CD4 count 500 cells/µL
Lived in Uganda for most of her life prior to moving to the US
Question #1

What is your next step?

A. Cervical lymph node excisional biopsy
B. Isoniazid/rifampin/pyrazinamide/ethambutol
C. Bronchoscopy
HPI

- Excisional cervical lymph node biopsy performed
  - Caseating granulomas throughout
  - Rare AFB
- Started on isoniazid, rifampin, ethambutol, pyrazinamide two weeks after initial presentation
- Sputum cultures grew *M. tuberculosis* after 13 days
Initial isolate – drug-susceptible *M. tuberculosis*

Patient does well clinically, and her 2-month sputum culture is negative. How long should she be treated for TB?

A. 6 months

B. 9 months

C. 6 months followed by 6 additional months of INH
TB recurrences most likely due to reinfection in higher burden settings in patients not on ART,

(TB-HAART): prospective, international, randomized, placebo-controlled trial: 6 months of treatment associated with low relapse rates

- N=1675 patients, analyzed 1538; followed for 12 months, early vs. delayed ART, CD4 >350
- Primary endpoint: composite of death, failure of TB treatment, and recurrence at 12 months
- Proportion of recurrences did not differ significantly by group:
  - 19 (2.6%) in early ART compared to 11 (1.5%) in delayed ART (RR 1.7, 95% CI 0.8–3.6; p=0.15).
- When stratified by CD4 cells count, treatment failure and recurrence did not differ significantly between groups
  - 28 (4.3%) of 647 in the early ART group compared with 39 (5.8%) of 675 in the delayed ART group (RR 0.74, 95% CI 0.47–1.20; p=0.23).

Summary of the Evidence: IDSA/ATS TB treatment Guidelines

• Standard 6-month regimens for most patients with drug-susceptible pulmonary TB

• Extend therapy to 9 months:
  – positive cultures at 2 months and cavitary disease
  – ART is not administered or CD4 <100
  – Other considerations for extending therapy: cavitary disease, diabetes, other immunocompromised state
  – WHO guidelines: no recommendations to extend treatment for drug-susceptible pulmonary TB

Daily directly observed therapy may be inconvenient for the patient and expensive for the TB Program. Is it safe and effective to use intermittent TB therapy?

A. No – daily therapy should be used for the entire TB treatment course

B. Yes, thrice-weekly is fine after the first 2 months

C. Yes, thrice-weekly therapy is fine after 2 weeks
RCT, N=331 patients
Primary outcome: proportion with a favorable response, defined as treatment completion with negative sputum cultures in the last 2 months of treatment

Outcome:
Daily: 91%
Fully Intermittent 77%
P=0.006

Acquired rifamycin resistance only in intermittent therapy arms
• Twice weekly therapy with rifabutin (RBT) and PI-based ART:
  • Associated with higher rates of relapse and the emergence of rifamycin resistance
  • Resistance more common in those with baseline CD4 counts <100 cells/µL
– Thrice-weekly RIF-based regimens during the intensive and continuation phase:
  • Higher rates of relapse and emergence of rifamycin resistance in HIV-positive individuals
  • Higher risk of death

Gopalan JAMA Int Med., 3/5/2018
HPI continued

- She returns to clinic in 2 weeks feeling well.
  - When should we offer antiretroviral therapy?
  - What options are available for antiretroviral therapy?
  - What is the role for trimethoprim-sulfamethoxaxole (TMP-SMX or co-trimoxazole) and when should this be offered?
Trimethoprim-sulfamethoxazole/co-trimoxazole therapy for HIV-TB co-infected individuals

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study Design</th>
<th>Country</th>
<th>number</th>
<th>Mortality reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wiktor et al.</td>
<td>1999</td>
<td>randomized controlled trial</td>
<td>Cote D'Ivoire</td>
<td>771</td>
<td>46%</td>
</tr>
<tr>
<td>Zachariah et al</td>
<td>2003</td>
<td>cohort study</td>
<td>Malawi</td>
<td>1,986</td>
<td>19%</td>
</tr>
<tr>
<td>Mwaungulu et al</td>
<td>2004</td>
<td>cohort study</td>
<td>Malawi</td>
<td>717</td>
<td>22%</td>
</tr>
<tr>
<td>Grimwalde</td>
<td>2005</td>
<td>cohort study</td>
<td>South Africa</td>
<td>3,325</td>
<td>29%</td>
</tr>
<tr>
<td>Nunn</td>
<td>2008</td>
<td>randomized controlled trial</td>
<td>Zambia</td>
<td>1,003</td>
<td>21%</td>
</tr>
</tbody>
</table>
Trimethoprim-sulfamethoxazole (co-trimoxazole) therapy for patients with TB and HIV

- US guidelines: initiate when CD4 count is less than 200 cells/µL, stop when the CD4 count >200 for 3 months
- WHO guidelines: initiate irrespective of CD4 count, continue while on TB treatment
  - Discontinue after TB treatment if:
    - clinically stable on ART, with evidence of immune recovery and viral suppression
  - However, continue if malaria and severe bacterial infections are highly prevalent, irrespective of CD4 count
Question #4

Should this patient be started on antiretroviral therapy (ART) during TB treatment, and if so, when?

A. No – wait until TB treatment has been completed
B. Yes, start ART after 2 months of TB treatment
C. Yes, start ART after 2 weeks of TB treatment
# 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>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAMELIA NEJM 2011</strong></td>
<td>Cambodia, n=661</td>
<td>Smear +, CD4 &lt; 200</td>
<td>25 (10 - 56)</td>
<td>Death</td>
<td>Decreased mortality (34%, p=0.004)</td>
</tr>
<tr>
<td><strong>STRIDE NEJM 2011</strong></td>
<td>Multi-national, n=809</td>
<td>Clinical TB, CD4 &lt; 250</td>
<td>77 (36 – 145)</td>
<td>AIDS or death</td>
<td>Decreased mortality if CD4&lt;50-42% ↓ p=0.02) (overall relative decrease: 19%, p=0.45)</td>
</tr>
<tr>
<td><strong>SAPiT NEJM 2010, 2011</strong></td>
<td>South Africa, n=642</td>
<td>Smear +, CD4 &lt; 500</td>
<td>150 (77 – 254)</td>
<td>AIDS or death</td>
<td>Mortality if CD4&lt;50 68% ↓ p=0.06 (overall relative decrease 11% in early group, p=0.73)</td>
</tr>
<tr>
<td><strong>TB-HAART Lancet ID, 2014</strong></td>
<td>Multi-national, operational conditions, n=1675</td>
<td>Smear +, CD4 &gt;220</td>
<td>367 (289-456)</td>
<td>composite endpoint: relapse, treatment failure or death</td>
<td>No difference: early ART 3.0% mortality, late ART 2.0% mortality</td>
</tr>
</tbody>
</table>

Timing of ART in patients with TB

- **Advanced AIDS (CD4 < 50):** *Immediate ART* (within 2 weeks) improves survival
  - Markedly increased risk of IRIS, including fatal IRIS events
  - Overall survival benefit despite IRIS
- **CD4 > 50:** *Early ART* (~ 2 months) provides good balance of competing risks of death/AIDS vs. IRIS
- **Caveats**
  - CNS involvement – no benefit to immediate therapy, and there may be increased risk
Adverse events during treatment of HIV-TB

- 54% (99/167) had adverse events
- 34% interrupted TB or HIV therapy
- Common adverse events
  - GI intolerance
  - Skin rash (17%) - TB drugs (16), co-trimoxazole (7), nevirapine (2), other drugs (4)
  - hepatitis (6%) - TB drugs (6), unknown (5)
Our patient is doing well on standard 4-drug therapy. What antiretroviral therapy regimen would you recommend starting?

A. **Dolutegravir**, tenofovir/emtricitabine (Truvada)
B. **Dolutegravir**, tenofovir alafenamide/emtricitabine (Descovy)
C. **Efavirenz**, tenofovir/emtricitabine (Atripla)
D. Switch rifampin to **rifabutin**, and then start darunavir/ritonavir, tenofovir/emtricitabine (Truvada)
Virological failure of efavirenz-based ART, among patients with and without TB

Modest reductions in EFV levels does not appear to reduce EFV activity
Use of 800 mg dose of EFV – increased risk of neurological side effects

Comparison of the effects of Rifampin vs. Rifabutin on trough concentrations of boosted protease inhibitors

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Rifampin</th>
<th>Rifabutin</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPV/r</td>
<td>1</td>
<td>120</td>
</tr>
<tr>
<td>ATZ/r</td>
<td>2.5</td>
<td>113</td>
</tr>
<tr>
<td>DRV/r</td>
<td>ND</td>
<td>0</td>
</tr>
<tr>
<td>FPV/r</td>
<td>ND</td>
<td>0</td>
</tr>
</tbody>
</table>

AAC 2204;48:1553-60, AAC 2006; 50:3336-42, AAC 2010;54:4440-5, AAC 2008;52:534-8,
Rifabutin (RBT) and TB therapy

- Rifabutin is likely as active as rifampin
- No dose adjustments of commonly-used protease inhibitors
- Decrease RBT from 300 mg daily to 150 mg daily when given with boosted PIs
- Caution – RBT dose would be inadequate if patient stopped PI
- No dose adjustment needed for dolutegravir and raltegravir
Effect of rifampin on serum concentrations of dolutegravir (DTG) 50mg BID

- INSPIRING Phase 3b non-comparative open label RCT HIV-TB:
  - DTG 50mg BID + 2NRTIs during TB tx and 2 weeks post therapy vs. Efavirenz (EFV) + 2NRTIs
  - Week 24 of 52:
    - 69 received DTG, 44 EFV
    - Proportions with VL <50 c/mL:
      - DTG 56/69 (81%)
        » 5 discontinued due to protocol deviations/LTFU
      - EVF 39/44 (89%)
        » 2 discontinued due to adverse events

Dooley K et al. CROI #33,2018
Rifampin Effect on Tenofovir Alafenamide (TAF) Plasma/Intracellular Pharmacokinetics

- Healthy volunteers between the ages of 18-65, n=17
- TAF/FTC once daily x 28 days with food, followed by TAF/FTC once daily with rifampin 600mg daily for 28 days followed by TDF 300mg daily x 38 days
- Intensive PK sampling on day 28, day 56 (TAF/FTC+ rifampin) and 84.
  - Measured TAF, TFV, FTC and (intracellular) IC TFV diphosphate
- Plasma TAF Cmax and AUC decreased by 45% and 47% respectively
- IC TFV-DP decreased by 40% but still 82% higher than those achieved by standard dose of TDF

Cerrone, M et al. CROI, Boston, 2018
Rifampin and Raltegravir

- Raltegravir concentrations are decreased when co-administered with rifampin
  - Increasing the dose to 800mg BID mitigates this interaction
  - Unclear if this is necessary to achieve virological suppression: REFLATE TB, Lancet 2014:

N=155
51 in each arm

virological suppression at 24 weeks:
Raltegravir
400mg:
39 patients
(76%, 95% CI 65–88)

Efavirenz:
32 patients
(63%, 49–76)

87% completed follow-up at 48 weeks

Recommended regimens for co-treatment of HIV-TB

- Efavirenz + 2 nucleosides (preferred)
  - Extensive experience among patients with HIV-TB
- Raltegravir (RAL) or dolutegravir (DTG) + 2 nucleosides
  - Recommendation is still to increase doses of Raltegravir to 800mg BID; likely 400mg BID is safe
  - Use increased doses of dolutegravir of 50mg BID
  - Do not use elvitegravir-containing regimens
- Rifabutin-based TB treatment
  - Alternative when PI class needed or would prefer not to double the dose of dolutegravir
Types of immune reconstitution inflammatory syndrome (IRIS) events in HIV-TB

Fevers
New or worsening adenitis
New or worsening pulmonary infiltrates, including respiratory failure
New or worsening pleuritis, pericarditis, or ascites
Intracranial tuberculomas, worsening meningitis
Disseminated skin lesions
Epididymitis, hepatosplenomegaly, soft tissue abscesses
Management of IRIS

- Anticipate IRIS events – discuss beforehand with patient and other care providers
- Rule out other possible causes – bacterial infections, a 2nd OI, inadequate Rx for OI, drug-resistant pathogen
- For relatively severe manifestations, prednisone is reasonable
  - 1 mg/kg (1.5 mg/kg with rifampin), tapering over 4-6 weeks
Starting ART during TB treatment – summary of the steps required

- Start TB therapy, manage side effects
  - Start TMP-SMX if indicated
  - Discuss initiating ART
  - Coordinate start of ART: (~2 weeks for CD4 < 50, ~2 months for CD4 > 50)
  - Use DOT visits to increase adherence to ART
  - Anticipate and manage IRIS

- Provide psychosocial support and coaching
Latent tuberculosis infection

Updated and consolidated guidelines for programmatic management

WE WILL END TB

END TB

END HIV

AETC AIDS Education & Training Center Program

World Health Organization
LTBI regimens

• INH daily for 9 months + B6 25mg daily

• Rifampin (RIF) given daily for 4 months
  – Substantial drug interactions, all medications should be reviewed

• INH-rifapentine once weekly for 12 doses
  – 2.6% HIV-infected—unclear if on ART in initial studies
  – Can now be given self-administered or as directly observed therapy
  – Likely safe if patients are on efavirenz or raltegravir based regimens

Podany, CROI abstract # 455, 2018
Weiner M, J antimicrob Chemother 2014
ONE MONTH OF RIFAPENTINE/ISONIAZID TO PREVENT TB IN PEOPLE WITH HIV: BRIEF-TB/A5279

- Phase 3 RCT, open-label, 10 countries participating, n=3,000
  - >13 years, living in high TB-burden areas OR who were TST/IGRA positive
  - ART with efavirenz or nevirapine; followed for 3 years
  - Randomized to 1HP* or 9H*
  - Primary endpoint: incidence rates of active TB, TB death or death from an unknown cause

- Results:
  - 634 (21%) had positive TST or IGRA
  - Primary endpoint:
    - N=34 1HP arm; 35 9H arm, for incidence rates of 0.69/100 PY for 1HP and 0.72/100 PY for 9H (IR difference = -0.025, upper 95% CI: 0.31, Table).
    - TB incidence rates were higher among those with +TST/IGRA but not different between the two arms
    - Treatment completion was 97% with 1 HP vs. 90% in the 9H arm, p<0.01

Swindells, S. et al. CROI 2018

*1HP=isoniazid/rifapentine daily x 4 weeks; 9H=isoniazid daily x 9 months
Summary – treatment of HIV-related TB:
active TB treatment issues

• How long should active TB treatment be given?
  – 6 months for pulmonary disease (selected individuals may be offered 9 months)

• Daily DOT is a hassle – can intermittent therapy be used?
  – Intermittent therapy is no longer recommended, even three times per week
Summary – treatment of HIV-related TB: issues with antiretroviral therapy

• Should antiretroviral therapy be used during active TB treatment?
  – Yes, for all patients

• What regimens can be used for co-treatment of HIV and TB?
  – Preferred: efavirenz-based ART + rifampin-based TB treatment
  – Integrase-inhibitor based ART (rifampin or rifabutin)
  – PI-based ART + rifabutin-based TB treatment

• When should ART be started?
  – 2 weeks to 2 months after starting active TB treatment
Patient follow-up

- In addition to being newly diagnosed with TB and HIV, she was also 15 weeks pregnant
  - emtricitabine/tenofovir/efavirenz initiated after 2 weeks of tolerating TB treatment
  - TB treatment completed at 6 months
Thank You!