Management of HIV in tuberculosis co-infected patients

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Learning objectives

• Identify the optimal timing of antiretroviral therapy in patients with HIV/TB coinfection
• Recognize factors that influence the selection of optimal concurrent HAART regimens in HIV/TB co-infected patients
• Recognize and manage complications associated with concurrent treatment of HIV and TB
Case presentation

- 47-year old female presented to RIH with a 2-month history of abdominal pain, diarrhea, weight loss, fever & night sweats.
- Moved to USA from Zimbabwe 2 years prior to presentation
- T - 102.4°F, HR - 76, RR - 18, BP - 120/80. Wasting, oral thrush. Rest of exam was unremarkable
- CXR- Bilateral multiple tiny nodules. Abdominal CT scan revealed thickening of the colon and terminal ileum wall
Case presentation

• Colonic biopsy revealed focus of histiocytes with necrotic center containing acid fast bacilli
• Sputum collected the day after the biopsy was AFB smear positive, and eventually grew *M. tuberculosis*
• Started on rifampin, isoniazid, pyrazinamide and ethambutol and HIV test sent
• HIV test - positive, CD4 - 63 cells/µL (1.8%) , HIV-1 RNA level – 435,000 copies/mL.
• Bactrim DS one daily and fluconazole 100 mg daily added to therapy
Clinical management issues

• When should HAART be initiated after starting TB treatment?
• What antiretroviral regimens can be used concurrently with TB therapy?
• Toxicities concerns and how should patient be managed?
EPIDEMIOLOGY OF HIV/TB COINFECTION
HIV/TB: Profound Effect on Individuals

The annual risk of TB in HIV infected approximates the lifetime risk of HIV uninfected

TB incidence closely correlated with HIV prevalence in Africa.

Graph: Estimated TB incidence (per 100,000 population) vs. HIV prevalence, adults 15-49y.
Adults and children estimated to be living with HIV, 2008

- **North America**: 1.4 million (1.2 – 1.6 million)
- **Caribbean**: 240 000 (220 000 – 260 000)
- **Latin America**: 2.0 million (1.8 – 2.2 million)
- **Western & Central Europe**: 850 000 (710 000 – 970 000)
- **Eastern Europe & Central Asia**: 1.5 million (1.4 – 1.7 million)
- **Middle East & North Africa**: 310 000 (250 000 – 380 000)
- **Sub-Saharan Africa**: 22.4 million (20.8 – 24.1 million)
- **East Asia**: 850 000 (700 000 – 1.0 million)
- **South & South-East Asia**: 3.8 million (3.4 – 4.3 million)
- **Oceania**: 59 000 (51 000 – 68 000)

**Total**: 33.4 million (31.1 – 35.8 million)
Figure 1.2
Estimated TB incidence rates, by country, 2007

Estimated new TB cases (all forms) per 100,000 population:
- 0-24
- 25-49
- 50-99
- 100-299
- 300-499
- ≥500
- No estimate
FIGURE 1.3
Estimated HIV prevalence in new TB cases, 2007

HIV prevalence in new TB cases, all ages (%)
- 0-4
- 5-19
- 20-49
- ≥50
- No estimate
FIGURE 1.4
Fifteen countries with the highest estimated TB incidence rates per capita (all forms; grey bars) and corresponding incidence rates of HIV-positive TB cases (red bars), 2007
Estimated HIV Coinfection in Persons Reported with TB, United States, 1993–2008*

*Updated as of May 20, 2009.

Note: Minimum estimates based on reported HIV-positive status among all TB cases in the age group.
HIV-associated TB and mortality

• TB is the leading cause of death in HIV-infected patients globally
• Case fatality rate is about 40% or higher
• Estimated 456,000 HIV-TB deaths in 2007. This number represents:
  – 33% of the estimated 1.4 million incident HIV-TB cases
  – 23% of estimated 1.8 million TB deaths

Corbett EL et al. Arch Intern Med 2003;163:1009
Mukadi YD et al. AIDS 2000;15:143-152
WHO TB report 2009
RATIONALE FOR CONCURRENT HIV AND TB THERAPY
Effect of TB treatment on HIV progression

- 111 HIV-infected patients hospitalized with TB (12 died)
- HIV plasma load was high at baseline and remained high despite TB therapy
- TB therapy on significant influence on CD4+ cell count

Outcome of HIV-TB in HAART era

- Outcome of HIV-TB was compared before 1996 (n = 36) and 1996 onwards (n = 60)
- HAART use was associated with marked reduction in event risk – aHR = 0.38 (95%CI, 0.16 – 0.91)

*Dheda K, et al. JID 2004;190:1670-6*
Table 3. Rates of new AIDS-defining illness or death, by follow-up period according to calendar period of starting tuberculosis (TB) treatment and baseline CD4⁺ cell count.

<table>
<thead>
<tr>
<th>Time since starting TB treatment</th>
<th>Group, calendar period of starting TB treatment</th>
<th>CD4⁺ cell count at baseline, cells/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1, before 1996 (n = 36)</td>
<td>≥100 or missing (n = 61)</td>
</tr>
<tr>
<td></td>
<td>2, during or after 1996 (n = 60)</td>
<td>&lt;100 (n = 35)</td>
</tr>
<tr>
<td>0–1.99 months</td>
<td>138.8 (7)</td>
<td>41.3 (4)</td>
</tr>
<tr>
<td></td>
<td>88.3 (8)</td>
<td>248.6 (11)</td>
</tr>
<tr>
<td>2 months–0.99 years</td>
<td>35.6 (7)</td>
<td>26.3 (11)</td>
</tr>
<tr>
<td></td>
<td>32.6 (12)</td>
<td>54.9 (8)</td>
</tr>
<tr>
<td>1–6 years</td>
<td>17.5 (11)</td>
<td>8.3 (12)</td>
</tr>
<tr>
<td></td>
<td>3.6 (4)</td>
<td>10.3 (3)</td>
</tr>
<tr>
<td>Total, 0–6 years</td>
<td>28.5 (25)</td>
<td>13.8 (27)</td>
</tr>
<tr>
<td></td>
<td>15.4 (24)</td>
<td>45.6 (22)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are rate/100 person-years (no. of events). The risk of an AIDS-defining illness was greater in patients with a baseline CD4⁺ cell count <100 cells/mm³ than in those with a baseline CD4⁺ cell count >100 cells/mm³ or with missing data (P = .001) and in group 1 vs. group 2 (P = .027), and the risk decreased over time since the start of TB treatment (P<.001 for trend, Poisson regression). Comparative rates of AIDS-defining illnesses per 100 person-years for all HIV-positive patients at our center were ~35 before 1996 and 5 during or after 1996.

Dheda K, et al. JID 2004;190:1670-6
WHEN TO START ANTIRETROVIRAL THERAPY
## Early versus delayed initiation of antiretroviral therapy during TB treatment

<table>
<thead>
<tr>
<th></th>
<th>Early ART (before 8 wks of TB treatment)</th>
<th>Delayed ART (after 8 wks of TB treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adherence demand</strong></td>
<td>Problematic with use of 4-drug for TB and multidrug therapy for HIV</td>
<td>Less problematic because fewer drugs necessary for TB treatment</td>
</tr>
<tr>
<td><strong>Ability to determine the cause of adverse events</strong></td>
<td>Complex because of the large number of medications started in a short time period and overlapping side effects profiles</td>
<td>Simpler because the number of drugs for TB treatment is less and there has been more time to evaluate response to TB treatment</td>
</tr>
<tr>
<td><strong>Drug-drug interaction</strong></td>
<td>Problematic</td>
<td>Problematic</td>
</tr>
<tr>
<td><strong>Severe immune reconstitution inflammatory events</strong></td>
<td>Risk may be increased</td>
<td>Risk may be decreased</td>
</tr>
<tr>
<td><strong>HIV disease progression (new OI or death)</strong></td>
<td>Risk may be decreased</td>
<td>Risk may be increased</td>
</tr>
</tbody>
</table>

Timing of initiation of antiretroviral drugs during TB therapy

Timing of initiation of antiretroviral drugs during TB therapy

Table 2. Death Rates and Hazard Ratios, Stratified According to CD4+ Cell Count.

<table>
<thead>
<tr>
<th>CD4+ Count</th>
<th>Integrated Therapy</th>
<th>Sequential Therapy</th>
<th>Hazard Ratio (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>No. of Person-Yr</td>
<td>No. of Deaths</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>All patients</td>
<td>429</td>
<td>467</td>
<td>25</td>
<td>5.4 (3.5–7.9)</td>
</tr>
<tr>
<td>≤200 cells/mm³</td>
<td>273</td>
<td>281</td>
<td>23</td>
<td>8.2 (5.2–12.3)</td>
</tr>
<tr>
<td>&gt;200 cells/mm³</td>
<td>156</td>
<td>186</td>
<td>2</td>
<td>1.1 (0.1–3.9)</td>
</tr>
</tbody>
</table>

* Hazard ratios are for the integrated-therapy group, as compared with the sequential-therapy group.

Effect of TB therapy on cART outcome

- Dean et al – significant reduction in ADI and mortality but 99 (54%) 183 patients had toxicities
- Hung et al found no difference in clinical, immunological and virologic outcome at week 48
- Breen et al found no difference in virological and immunological outcome at week 24

Dean et al. AIDS 2002;16:75-83
Hung CC et al. AIDS 2003;17:2615-22
Breen RAM et al. JID 2006;193:1437-40
Effect of TB therapy on viral decay in response to ART

Kwara et al. Unpublished
Effect of TB therapy on long-term virologic outcome

Product-Limit Survival Estimates
With Number of Subjects at Risk

Survival Probability

+ Censored
Logrank p=0.1250

1 2
34 30 27 27 24 24 24 19 19 19 19 19 19 19 19
40 39 34 34 33 33 33 26 28 28 28 28 28 28 28
0 100 200 300
time

TB_Coinfect 1: No active TB 2: With active TB
WHAT CONCURRENT ART REGIMEN TO USE
Challenges to concurrent HIV and TB therapy

- Pill burden
- Overlapping drug toxicities
- Pharmacokinetic drug-drug interactions
- Increased risk of immune restoration inflammatory syndrome

“I’ve thrown in some prescription drugs that don’t interact well.”
INH, rifampin, PZA, and ethambutol
(4 drugs, 10 pills once a day)

Burman WJ. CFAR Symposium 2005, Boston
INH, rifampin, PZA, ethambutol, cotrimoxazole, AZT, 3TC, efavirenz (8 drugs, 14-16 pills, 2-3 doses per day)

“Are you sure that I won’t, like, blow up if I take all of these pills?”

Burman WJ. CFAR Symposium 2005, Boston
Rifamycins and antiretroviral therapy

- Rifampin is a potent inducer of cytochrome P-450 drug metabolizing enzymes
- Rifabutin has less effect on CYP3A4
- Rifampin is the only rifamycin in TB endemic areas

Importance of the rifampin in tuberculosis treatment

• **A.** Mechanism of induction of CYP3A4-mediated metabolism of drug substrate

• **B.** The resulting reduced plasma drug concentration

PXR – Pregnane X receptor; RXR – retinoid X receptor

- a) Duodenal biopsy immunostained for P-gp before administration of rifampin

- b) biopsy after 9 days administration of rifampin 600mg daily
Decrease in serum concentrations (AUC) of HIV-1 protease inhibitors with rifampin or rifabutin

With 100 mg RTV

Clin Infect Dis 1999; 28: 419-30

12th CROI, abstract 657
Decrease in serum concentrations (AUC) of non-nucleoside reverse-transcriptase inhibitors by rifampin or rifabutin

Clin Infect Dis 1999; 28: 419-30
Interactions between efavirenz and rifampin-containing TB treatment

- Rifampin caused a decrease in:
  - mean Cmax by 24%
  - Cmin by 25%
  - AUC by 22%
- “Although minimal effective efavirenz plasma concentration that assures virological success is not currently known, it is advisable to increase dosage of efavirenz to 800 mg/day when co-administered with rifampin”

Distribution of plasma EFV levels between EFV 600 and 800 mg groups (42 patients each)

Figure 1a

Efavirenz (EFV) level in plasma

Figure 1b

Plasma level of efavirenz (EFV)

Time to virologic success

Probability of HIV RNA <50 copies/mL

Weeks

p = 0.848

EFV = 600

EFV = 800
Paradoxical effect of TB therapy on efavirenz concentrations in some patients

- Effect of TB therapy on efavirenz levels is variable
- May be dependent on host genetics
- Thus one dose adjustment will not fit all patients

HAART and *rifampin-based* TB treatment

2 NRTI/NtRTIs plus NNRTI or PI

**Recommended dose of ARVs with rifampin**

- Efavirenz (the preferable) ?600 mg or 800 mg daily
- Nevirapine 200 mg bid (or 300mg bid*)
- Saquinavir/ritonovir 400/400 mg bid or 1000/100 mg bid*
- Lopinavir/ritonovir 400/400 mg bid*
- Maraviroc 600 mg twice-daily (increased dose)  
  *use with caution*
- Raltegravir 400 mg twice daily (no change)

*CDC treatment guidelines for HIV-TB, Dec 2007*
HAART and *rifabutin-based* TB treatment

<table>
<thead>
<tr>
<th>PI</th>
<th>Rifabutin dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPV/r, ATV/r, fAPV/r, SQV/r (standard doses)</td>
<td>150 mg qod or 300 mg 3X/W*</td>
</tr>
<tr>
<td>Atazanavir 400 mg qd</td>
<td>150 mg qd or 300 mg 3XW</td>
</tr>
<tr>
<td>Fosamprenavir 1400 mg bid</td>
<td>150 mg qd or 300 mg 3XW</td>
</tr>
<tr>
<td>Indinavir 1000 mg tid</td>
<td>150 mg qd or 300 mg 3XW</td>
</tr>
<tr>
<td>Nelfinavir 1000 mg tid</td>
<td>150 mg qd or 300 mg 3XW</td>
</tr>
<tr>
<td>Maraviroc or raltegravir (no change)</td>
<td>No change</td>
</tr>
</tbody>
</table>

*associated with TB treatment failure and rifamycin resistance*
HAART and rifabutin-based TB treatment

2 NRTI/NtRTIs plus NNRTI

<table>
<thead>
<tr>
<th>NNRTI</th>
<th>Rifabutin dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine 200 mg bid</td>
<td>300 mg qd or 300 mg 3X/week</td>
</tr>
<tr>
<td>Efavirenz 600 mg qd</td>
<td>600 mg qd or qod</td>
</tr>
</tbody>
</table>
Pregnant women and children

- Efavirenz is contraindicated during at least the first trimester of pregnancy
- Higher risk of hepatotoxicity in women with CD4 >250 cell/µL with nevirapine
- Efavirenz should not be used in children < 3 years old
- No drug-drug interaction studies in pregnant women
- Limited drug-drug interactions studies in children
- Triple nucleoside therapy may be used when options are severely limited
PI-based ART in children aged < 2 years old with and without TB

- 254 HIV-infected children, 99 (39%) co-treated for TB
- Viral suppression rates by week 39 was:
  - 94.8% in absence of TB
  - 74.2% in children who started ART after TB treatment
  - 51.6% in those who started TB treatment while on ART
Immune restoration inflammatory syndrome (IRIS)

- Paradoxical worsening of TB symptoms on TB plus HIV therapy
- Incident TB (unmasked TB) within 4 months of starting ART in HIV-infected patients
- Risk factors include CD4 count < 50, brisk response to HAART and extrapulmonary TB
- Immunopathological response to treatment
- Continue or initiate concurrent therapy
- Symptomatic therapy with NSAIDs or steroids may be necessary
Summary

• The HIV-TB is associated with high mortality
• The timing of concurrent ART should be individualized; in general it should be started as soon as TB therapy is tolerated
• Efavirenz is preferred in setting of rifampin-containing TB therapy
• Both protease inhibitor or non-nucleoside reverse transcriptase inhibitors can be used with rifabutin