FIRST LINE TB DRUGS AND 2nd LINE ART INTERACTIONS

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Access to ARVs have dramatically improved

TB still continues to be our most common OI

Therefore co-administration is very common

3 major complications exist as a result
1. Immune reconstitution inflammatory syndrome

2. Toxicities of both anti-TB and ARV drugs can overlap, and lead to poor adherence, failure and premature termination of treatment.

3. And finally induction of cytochrome P-450 enzymes and p-glycoprotein by rifampicin results in reduced levels of and Protease Inhibitors
   - This potentially results in loss of antiviral efficacy and the development of viral resistance
The WHO estimates that, in low and middle-income countries, more than 100,000 persons currently receive 2\textsuperscript{nd}-line ART.

The global need for 2\textsuperscript{nd}-line ART is predicted to reach beyond 500,000 by the end of 2012.

Importantly, the number receiving 2\textsuperscript{nd}-line ART is far smaller than the global need:
- Poor sensitivity of immunological monitoring
- Cost of 2\textsuperscript{nd}-line ART remains relatively high
Key causes of 2nd-line ART failure

- Suboptimal adherence
  - Side effects
  - Unable to correct poor adherence during 1st-line ART
  - Local factors: user fees, stock-outs, distance, alternative med

- Antiretroviral drug resistance
  - PI mutations may be important

- Drug-drug interactions
  - Example: Concomitant rifampicin-containing TB therapy
    - Rifampicin lowers lopinavir drug concentrations
Six months after initiation of 2\textsuperscript{nd}-line ART with AZT + 3TC + LPV/r, a patient notes cough and night sweats. Physical exam reveals a temperature of 38.5.

- A chest radiograph reveals a right mid-lung infiltrate and a sputum sample reveals acid-fast bacilli.
- Xpert testing reveals no rifampicin-resistance.
- The viral load is \(<400\text{ c/ml}\)

How should this patient be managed?

WHAT'S THE EVIDENCE?
The management of TB coinfection in patients receiving a PI is a challenge because rifampicin reduces the trough concentration of most PIs.

Rifampicin induces cytochrome p450 isoenzyme 3A4 and p-glycoprotein resulting in a 90% reduction in lopinavir trough concentrations.

- For example, when administered with LPV/r (Aluvia), rifampicin markedly reduces lopinavir concentrations.

This reduction can be attenuated by using higher doses of ritonavir or higher doses of lopinavir.

PI-containing ART in TB
What should we do?
A previous recommendation in South Africa was to super-boost LPV/r (Aluvia) in this setting:

- For adults, this involved increasing the ritonavir dose resulting in a total dose of during TB treatment of lopinavir/ritonavir 400 /400 mg twice daily.
  - Involved providing supplemental dose of RTV 300 mg twice daily

- Although reasonably well tolerated in HIV-infected children, this strategy has been poorly well tolerated in adult patients.
McCord Hospital: Toxicity associated with coadministered super-boosted LPV/r and rifampicin

Figure 1. Adverse events during coadministration of LPV/r-based ART and rifampicin-containing TB therapy

Proportion with event (%) vs. Treatment Modification

- Symptomatic transaminitis
- Gastrointestinal toxicity

- LPV/r (400 mg/100mg) twice daily
- LPV/r (400 mg/400mg) twice daily
## McCord Hospital: Outcomes associated with coadministered super-boosted LPV/r and rifampicin

<table>
<thead>
<tr>
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<th>LPV/r (400/400mg) twice daily</th>
<th>LPV/r (400/100mg) twice daily</th>
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<tbody>
<tr>
<td></td>
<td>N=15</td>
<td>N=14</td>
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<tr>
<td>HIV outcomes</td>
<td></td>
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<tr>
<td>Virologic failure (&gt;200 c/mL), number (%)</td>
<td>3 (20)</td>
<td>4 (29)</td>
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<tr>
<td>Tuberculosis treatment outcomes</td>
<td></td>
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<tr>
<td>Months of overlapping therapy completed (mean)</td>
<td>5.4</td>
<td>8.1 *</td>
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<tr>
<td>Completed</td>
<td>12 (80)</td>
<td>13 (93)</td>
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<tr>
<td>Died or lost to follow-up</td>
<td>3 (20)</td>
<td>1 (7)</td>
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T-test, Chi-square, and Fisher’s tests used for comparisons, * p<0.05
Patients (n=32, median CD4 count 44 cells/ul)) receiving LPV/r-containing 2\textsuperscript{nd}-line ART were given LPV/r 400/400 mg twice daily during TB therapy.

**Results**

- 25% had ALT elevations
  - Grade 3, 2 patients
  - Grade 4, 0 patients
- Only 66% completed the course of treatment
  - 2 deaths, 3 LTFU

CROI, 2012
Can rifabutin solve the problem?

Unlike rifampicin, rifabutin (RFB) has minor effects on 
\textit{Can it be used to fill this gap?}

Cost issues may not be prohibitive
- 6 months of LPV/r + rifabutin containing TB therapy = $410
- 6 months of super boosted LPV/r + std TB therapy = $455

Compatibility is superior
RFB has only minor effects on PI levels in serum

But….
Rifabutin is not currently produced in FDCs and TB control programs in resource limited countries depend on FDCs rather than individual agents.

\textit{Int J Tuberc Lung Dis 2011}
Decloedt *et al* (South Africa) conducted a small study consisting of 20 patients, 11 of whom received double dose LPV/r during TB treatment.

Lopinavir concentrations remain above 1mg/L in most patients:
- 10/11 (91%) patients maintained an undetectable viral load.

No grade III or IV toxicities, but 5/11 (45%) developed at least one AE:
- Grade 1 and 2 transaminitis common but no severe hepatotoxicity.
- 1 patient receiving double-dose LPV/r had “intolerable diarrhea”.

*Authors recommend monitoring adverse effects and transaminases closely if double dose LPV/r administered.*
We conducted a retrospective study of HIV-infected patients who received double-dose LPV/r-based ART during concomitant rifampicin-containing TB treatment.

Overall, during co-administration:
- 9 (36%) had gastrointestinal toxicity
- 3 (12%) had a symptomatic rise in AST or ALT with 2 grade III events
- Neither grade III events were fatal
- 3 (12%) patients required treatment discontinuation.
McCord Hospital (II): Using historical data, we compared adverse events and treatment discontinuation with two LPV/r (Aluvia) strategies used at McCord during TB therapy:

- Hepatotoxicity (Any grade)
- Need for treatment discontinuation

Double-dose LPV/r
Super-boosted LPV/r

\[ P = 0.17 \]
\[ *P = 0.024 \]

% experiencing

Unpublished, in peer review
Furthermore, the double-dose LPV/r strategy presents an additional advantage on a practical level:

- It does not require the use of ritonavir 100 mg soft-gel, a formulation which requires refrigeration and is difficult to store in the developing world where most tuberculosis coinfections occur.
- The double-dose LPV/r strategy only requires escalating the dose of heat-stable LPV/r tablets (Aluvia) which are widely available.

The use of double-dose lopinavir/ritonavir during rifampicin-based treatment appears to be a pragmatic interim strategy until more appropriate agents become available for HIV/TB coinfected patients.

Since this is a new strategy, reporting of serious toxicities associated with this treatment strategy is critical.
Patients receiving lopinavir/ritonavir (Aluvia) should have their dose doubled slowly over 2 weeks to 800/200 mg twice a day (4 tabs bd). The total ritonavir dose with the new recommendation is 400 mg/day (LPV/r 4 tabs bd contains 400 mg RTV) versus 800 mg/day with prior strategy.
Six months after initiation of 2\textsuperscript{nd}-line ART with AZT + 3TC + LPV/r, a patient notes cough and night sweats. Physical exam reveals a temperature of 38.5.
- A chest radiograph reveals a right mid-lung infiltrate and a sputum sample reveals acid-fast bacilli.
- Xpert testing reveals no rifampicin-resistance.
- The viral load is $<400$ c/ml

How should this patient be managed?
a) Stop ARVs and finish TB treatment. Then restart ARVs
b) Call Drs Sunpath, Moosa, Gandhi
c) Super-boost LVP/r and continue standard TB treatment
d) Switch rifampicin to rifabutin and continue standard LPV/r
e) Use Double dose LPV/r with standard TB treatment with close monitoring
Future options? Use of raltegravir in HIV/TB coinfection

**Raltegravir 400 mg bid acceptable, maybe preferable**

Prior data showed that when raltegravir is combined with rifampicin, trough RAL concentrations are reduced 61% and AUC drops 40%.

This effect partially compensated if RAL is increased to 800 mg bid.

But a randomized clinical trial showed that among patients who received rifampicin-based TB therapy followed after a median of 8 wks by TDF + 3TC + RAL 400 mg OR 800 mg BID the following 24 week outcomes were observed (n=~50 per group):

- RAL 400 mg bid: 24 wk suppression rate 76%, 0 AE with discontinuation
- RAL 800 mg bid: 24 wk suppression rate 78%, 3 AE with discontinuation (2 with severe hepatotoxicity including 1 fulminant failure → liver tranpt.)
  - Trend to ↑ integrase resistance in RAL 400 bid arm (4 pts.) vs 800 bid (1 pt.)
  - Suggestion of ↑ toxicity in the RAL 800 mg bid arm

Grinsztejn B et al IAC 2012
Take Home

- 2nd line ARVs becoming more widely used and available
- In the presence of TB, double dose LPV/r recommended
- Gradual increase to double dose over a 2 week period recommended
- Monitor close for AE
- Rifabutin a possible alternative
- Watch as new ARVs become more easily available
Research work at McCord hospital

- Murphy R, Ebrahim S, Sunpath H I. "Coadministration of lopinavir/ritonavir and rifampicin in HIV and tuberculosis co-infected adults in" PLos, August 2012. PONE-D-12-09610


- Sunpath H; Gandhi R; Winternheimer P; Shawn C; Chelin N; Tennant I; Murphy R. "Double-dose lopinavir/ritonavir in combination with rifampicin-based tuberculosis treatment in South Africa" PLos One Sept 2013.