HIV Pharmacology Update

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Conflict of Interests Statement

• PG has received financial supports for continuous education, consultation services and research activities by:
  – Bristol-Myers Squibb, Gilead Sciences, Abbott Laboratories, ViIV, Merck Frosst, Tibotec
• AT has received financial supports for continuous education and consultation services by:
  – Abbott Laboratories, ViIV, Merck Frosst, Tibotec

2010 HIV PK Workshop

• 155 attendees from over 20 countries
• 2009 workshop:
  – Pharmacogenetics & clinical outcomes, TDM/dose-simplification of PIs in Tx. Exp, some new data on RAL
• 2010 workshop:
  – Focus on PK/PD of newer drugs
  – More class/drug-sparing combinations
  – Special populations (organ dysfunction, gender, age)
  – TB, ADRs

3 Questions

1. Do I have absolutely to take Atazanavir (Reyataz) + Ritonavir (Norvir) with food?
2. I am taking atazanavir with ritonavir and Truvada but I hate ritonavir. Is there a way to discontinue or replace ritonavir?
3. You tell me that jaundice is a potential side effect of Atazanavir. Is this going to last all the time?

Atazanavir/ritonavir and Food

• Monograph
  – Patients must be advised to take REYATAZ with food every day and take other concomitant antiretroviral therapy as prescribed.
  – REYATAZ is taken with food to enhance absorption and reduce the pharmacokinetic variability

• Source
  – With unboosted ATV
  – In healthy volunteers
  – Food
    • ↑ AUC by 15% with high-fat meal and 50% with light meal
    • Food & interpatient variability (CV in AUC 43% with high-fat meal, 37% with light meal, 69% fasting).

What about ATV/RTV in HIV-Infected?

ATV/r + Food

• Characteristics
  N = 12
  All VL<50
  Mean CD4 = 528
  No interacting drugs
**Type of Meals**

<table>
<thead>
<tr>
<th>Meal Type</th>
<th>Calories</th>
<th>Protein</th>
<th>Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer 12 oz</td>
<td>110</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Wine 5 oz</td>
<td>125</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Red wine 5 oz</td>
<td>125</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Red wine 5 oz</td>
<td>125</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Margarine 1 tsp</td>
<td>50</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Peanut butter 1 tbsp</td>
<td>55</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Milk 2% 1 cup</td>
<td>130</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Yogurt &lt;2% M.F. 1 cup</td>
<td>70</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Yogurt &lt;2% M.F. 1 cup</td>
<td>70</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Yogurt &lt;2% M.F. 1 cup</td>
<td>70</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Cream of wheat 3/4 cup</td>
<td>70</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>1 slice bread</td>
<td>70</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>1 slice bread</td>
<td>70</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>1 slice bread</td>
<td>70</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>1 slice bread</td>
<td>70</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>1 medium orange</td>
<td>85</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

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**ATV/r + Food: Results**

All but one had C24 level > 0.15 mg/mL

**ATV/r + Food: Conclusion**

Although in the majority of patients the occasional intake of boosted ATV without food will not lead to subtherapeutic levels, it should be kept in mind that food maximizes the absorption of ATV and therefore we recommend to take ATV with food.

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**ATV/RTV – Alternative to RTV**

**Question #2**

ATV/RTV – Alternative to RTV

**ATV/RTV – Alternative to RTV**

- **Potential Alternative Strategy?**
  - Change ATV dosing (without RTV)
    - 400mg po daily → 200mg po BID
ATV/RTV – Alternative to RTV Results

Atazanavir PK Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (mg/L)</td>
<td>1.44 (0.51-3.5)</td>
</tr>
<tr>
<td>AUC (mg.h/L)</td>
<td>1.9 (0.89-3.9)</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>3.7 (2.4-7.0)</td>
</tr>
<tr>
<td>Cmax (mg/L)</td>
<td>1.44 (0.51-3.5)</td>
</tr>
<tr>
<td>AUC (mg.h/L)</td>
<td>1.9 (0.89-3.9)</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>3.7 (2.4-7.0)</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>0.1 (0.06-0.2)</td>
</tr>
<tr>
<td>Vz (L)</td>
<td>1.4 (1.2-1.5)</td>
</tr>
<tr>
<td>CLr (%)</td>
<td>11.9 (11.9-11.9)</td>
</tr>
</tbody>
</table>


Is Ritonavir Still the Gold Standard for Pharmacokinetic Enhancement?

Roundtable discussion featuring:
- Dr. Rick Bertz (yes)
- Dr. T. Hawkins (no)

Cobicistat (GS-9350)

- Potent, irreversible inhibitor of CYP3A
- No anti-HIV activity
- Non-linear ↑ exposure with dose, primarily circulates as parent drug, <10% Clr
- 150 mg = 100 mg RTV as booster for atazanavir

Mathias et al. 11th IWCPHT 2010, #18; Mathias et al. CROI 2009, #40; Ramanathan et al. ICAAC 2009, #A1-1301.

Phase 2 Studies of Cobicistat in Treatment-Naive Subjects

Cobicistat vs. Ritonavir

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cobicistat</th>
<th>Ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4 inhibition</td>
<td>CYP450</td>
<td>CYP3A4, 2D6, 2C9, 2C19</td>
</tr>
<tr>
<td>Enzyme induction</td>
<td>CYP1A2, UGT, 2C9, 2C19</td>
<td></td>
</tr>
<tr>
<td>Less induction effect</td>
<td>Less toxicity?</td>
<td></td>
</tr>
<tr>
<td>Good aqueous solubility</td>
<td>Insoluble in water</td>
<td></td>
</tr>
<tr>
<td>Novel agent</td>
<td>Possible to co-formulate matrix formulations</td>
<td></td>
</tr>
<tr>
<td>Price</td>
<td>Lower cost</td>
<td></td>
</tr>
</tbody>
</table>

Cohen et al. CROI 2010, #58LB.

Darunavir Boosted with Cobicistat vs. Ritonavir

- Open-label, 2-period, crossover study in healthy volunteers of DRV 800/100 mg ritonavir vs. 800/150 mg cobicistat QD x 10 d
- Darunavir AUC, Cmax equivalent in both arms
  - DRV/cobicistat vs DRV/RTV: GMR AUC 102% (90% CI 97.4-106), Cmax 103% (90% CI 100-106)
  - Darunavir troughs ~30% ↓ with cobicistat vs. RTV (GMR 69.4%, 90% CI 59.0-81.7)
- Darunavir is effectively boosted by cobicistat, which provides bioequivalent exposures (AUC, Cmax) to ritonavir

Mathias et al. 11th IWCPHT 2010, #28.
Cobicistat vs. Ritonavir: Tolerability

<table>
<thead>
<tr>
<th></th>
<th>Cobicistat</th>
<th>Ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=50)</td>
<td>(n=29)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (6%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (10%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Cholesterol, total</td>
<td>3 (6%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>2 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Creatinine (grade 1)</td>
<td>11 (22%)</td>
<td>0</td>
</tr>
<tr>
<td>Mean Scr (mg/dl) wk 0-24</td>
<td>+0.14</td>
<td>+0.18</td>
</tr>
<tr>
<td>Mean eGFR (mL/min) wk 0-24</td>
<td>-14</td>
<td>-15</td>
</tr>
<tr>
<td>Mean eGFR @ wk 24</td>
<td>111</td>
<td>102</td>
</tr>
</tbody>
</table>

- Rate of GI, lipid events not significantly different between cobicistat & ritonavir arms
- Renal signal (?); actual Clcr not affected, but could compromise renal monitoring (NB: TDF)

Cohen et al. CROI 2010, #58LB.

Duration of ATV jaundice / hyperbilirubinemia

- Background
  - ATV is a potent inhibitor of UGT 1A1
  - UGT 1A1 associated with metabolism of bilirubin and other drugs (irinotecan, raltegravir)
  - Incidence of jaundice with ATV 300/100mg daily is 4%
  - Cosmetic issue
  - Correlated with ATV exposure

- Does level of bilirubin changes over time within same day?


Fluctuation of serum Bilirubin

- Does level of bilirubin changes within same day?


Duration of ATV jaundice / hyperbilirubinemia

- Does level of bilirubin changes over time within same day?


- Does level of bilirubin changes within 24-h period?

  - Yes
  - Reversal of hyperbilirubinemia is rapid
  - 4 hrs shift between ATV Tmax and Bilirubin Tmax
  - Is the drop of serum bilirubin associated with clinical jaundice?
  - Can dosing ATV at dinner time decrease ‘daytime’ jaundice?
Theoretically Possible Antiretroviral Drug Combinations

BID on the Pharmacokinetics of Raltegravir in HIV-infected Subjects

- RAL 400 mg BID + ATV 300 mg BID studied in 22 HIV+ subjects
- RAL AUC comparable to historical controls
- Highly significant correlation b/w RAL AUC & ATV AUC (r=0.611, p<0.001)
  - Similar trend with RAL Ctrough
- Wide inter-pt variability observed for both drugs

Pharmacokinetics of QD Maraviroc with Atazanavir/r as an NRTI-Sparing Regimen in Naïve Patients

- PK substudy (n=15) of a phase 2b study randomizing 121 naïve subjects to ATV 300/100 QD plus TDF/FTC vs MVC 150 mg QD x 48 weeks
- All pts exceeded Cavg target of >75 ng/mL at week 2

Pharmacokinetics of Raltegravir, Etravirine and Maraviroc in the Clinical Setting

- 37 treatment-experienced patients on RAL 400 mg BID, ETV 200 mg BID and MVC 600 mg BID
  - C12 at wks 4, 12, 24, 36, 48

- Summary:
  - ETV C12 adequate, RAL C12 higher than previously reported, MVC C12 < 50 ng/mL at least once in 67.5% of subjects*
  - * MVC Cavg may be more robust target

Raltegravir, maraviroc, etravirine: an effective PI- and NRTI-sparing regimen for salvage therapy in HIV-infected patients

- Prospective evaluation in 28 triple-class exp. pts with R5 virus who received RAL, ETV, MVC 600 mg BID
  - 92.8% male, 43.9 yo, 28.6% HCV, CD4 254, RNA 4.16 log, 16.6 yrs since HIV+, 14 yrs previous cART
  - 100% LPVr, 14% TPVr, 36% DRVr, 39% enfuvirtide; GSS 0-2
- Week 48 (OT; no d/c);
  - 100% had VL<400, 92% VL<50, median CD4 267 (136-355) cells
  - BMI, waist circumference, Hgb ↑, Scr ↓, HDL ↑; no change in glucose/insulin
  - 3 serious A/E: anal cancer, Hodgkin lymphoma, mycobacterial spondylodiscitis

Significant Decreases in Antiretroviral Exposures With Rifampin or Rifabutin

- Significant decreases in serum AUC with rifampin or rifabutin

(CDC. MMWR 2009;58:1-206.)
Nevirapine-Rifampin Interaction

- Nevirapine Ctrough ↓ 21-58% with rifampin; potential for poorer virological outcomes

**Modify ARV**
- Replace nevirapine with:
  - efavirenz
  - lopinavir/rtv
  - raltegravir?

**Modify TB agent**
- Rifabutin
- Rifampin

**Nevirapine Ctrough ↓ 21-58% with rifampin; potential for poorer virological outcomes**

- 20 HIV+ pts on stable NVP started RIF-based TB tx
- NVP PK @ days 0 & 14, Ctrough on days 3 & 7
- NVP levels started to decline as early as day 3, Ctrough ↓ 21%
- By day 14, NVP AUC ↓ 22%
  - 6 (30%) had subtherapeutic levels, most by day 7
- Planned study:
  - NVP 200 mg BID vs. 400 mg qpm/200 mg qam with RIF

**Management of Individuals Requiring ART and TB Treatment**

<table>
<thead>
<tr>
<th>Class</th>
<th>Antiretroviral agent</th>
<th>Interaction</th>
<th>ARV with rifampin based TB treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>All class</td>
<td>No clinically significant pharmacokinetic interactions</td>
<td>No dose adjustment required</td>
</tr>
<tr>
<td>NNRTI</td>
<td>Efavirenz</td>
<td>Marked reduction in efavirenz concentrations</td>
<td>No dose adjustment required 600 mg daily</td>
</tr>
<tr>
<td>PI</td>
<td>Ritonavir</td>
<td>Moderate reduction in ritonavir concentrations</td>
<td>No dose adjustment required 300 mg 12-hour, 600 mg 24-hour dose</td>
</tr>
</tbody>
</table>

**Lopinavir/r**

- Lopinavir plasma concentrations are significantly decreased. Exposure from 800/100 mg or 800/200 mg, both dose 12 hourly caused high area of overlap in healthy volunteers already taking rifampin

**Depaxitan/r**

- Depauvican plasma concentrations are significantly decreased. Depauvican 1000mg/1 10-hour Norvir 15 mg 12-hour caused high area of overlap in healthy volunteers already taking rifampin

**ARV Interactions with Rifampin**

- 21 HIV+ pts on stable LPV 400/100 BID started RIF 600 mg/d
- LPV ↑ to 650/150 then 800/200 mg BID at weekly intervals

- Doubling LPV dose overcomes interaction with RIF

**The Effect of Aging on Tenofovir-Induced Decreases in Creatinine Clearance in an HIV Cohort**

  - N = 1031, 17,383 observations, eGFR (MDRD) at every visit
  - 67% male, 32% Caucasian, 68% African-American, median age 43, 25% HCV+, 11% DM
  - Mean 701 days on drug, median 10 visits per patient
  - Average eGFR at start of TDF therapy was 112.7 mL/min

- Multivariate regression analysis to study effect of age, time on drug, comorbidities on renal function

L. Goeddel et al. 11th IWCPHT 2010, #38.