Some Key Clinical Pharmacology Issues in 2010

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BHIVA/BASHH – April 2010

New Drugs
New Regimens
New Tests
### Some Antiretrovirals in Development

- **NRTIs**
  - Apricitabine
  - Elvucitabine

- **NNRTIs**
  - Rilpivirine
  - Lersivirine
  - IDX899
  - RDEA427/640
  - NVP XR

- **PIs**
  - Combination of ATV and DRV with PK enhancers.

- **Integrase Inhibitors**
  - Elvitegravir
  - Soltegravir (S/GSK1349572)

- **CCR5 Antagonists**
  - Vicriviroc
  - TBR652
  - PF232798

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### Antiretrovirals in Development

- **FDCs**
  - QUAD – *ELV/GS9350/TDF/FTC*
    - Truvada/Rilpivirine

- **Other Boosters**
  - PF3716539 (PK enhancer)
  - SPI-452 (PK enhancer)
NRTIs

Apricitabine
*(Formerly BCH10618, SPD754 and AVX754)*

- Plasma half life ~ 3h
- Intracellular TP half life ~ 7h
- Interacts with 3TC
- Renally eliminated
- Low potential for cross resistance with current NRTIs
- Currently in Phase III at a dose of 800 mg BID.
May provide some benefit to patients with limited options, but....

NNRTIs
Rilpivirine (TMC278)

Key PK Characteristics

- Half-life of ≈ 45 hours - supports once-daily dosing (25 mg)
- Absorption pH dependent; increased AUC with food (≈ 60%);
- Metabolism: mainly CYP3A4; Renal elimination is minor.
- Expect Rilpivirine to be affected by drugs that:
  i) alter gastric pH
  ii) induce or inhibit CYP3A4
- Only induces at high doses.

Effect of co-medication on Rilpivirine AUC$_{24h}$

- Atorvastatin
- Chloroxazone
- Tamoxifen
- Famotidine 2h before
- Famotidine 4h after
- Famotidine 12h before
- Ketoconazole
- Lopinavir/ritrav
- Omeprazole
- Paracetamol
- Rifabutin
- Rifampin
- TDF
- Sildenafil

Legend:
- pH increase
- CYP3A induction
- CYP3A inhibition
- pH decrease
- no effect boundaries 0.8 to 1.25

LSMean ratio (AUC$_{24h}$)
Lersivirine PK Characteristics

- Phase II; dose 750 or 1000 mg QD
- Well absorbed; negligible food effect.
- $T_{1/2} \sim 6–7$ hours
- Highly metabolized
  - UGT2B7
  - CYP3A4
- Modest CYP3A4 induction.
- P-gp inhibition (in vitro)

Effect of Co-Medication on Lersivirine AUC

<table>
<thead>
<tr>
<th>Co-Medication</th>
<th>Geometric Mean Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>0.5</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>0.8</td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>1.0</td>
</tr>
<tr>
<td>Atazanavir/r</td>
<td>1.25</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>1.5</td>
</tr>
<tr>
<td>TDF/FTC</td>
<td>2.0</td>
</tr>
<tr>
<td>Antacid (Maalox)</td>
<td>2.5</td>
</tr>
</tbody>
</table>

CYP3A Inhibition

Lersivirine

No effect boundaries 0.8 – 1.25
PK of NVP Extended Release (XR) vs. Immediate Release (IR)

- 48 stable patients on NVP IR 200mg BID
- HIV-RNA < 50 copies/mL
- Switched to NVP XR

*Overall, XR showed slower absorption with comparable $C_{min}$ but modestly lower $C_{max}$ and bioavailability*


Protease Inhibitors with novel PK enhancers
GS-9350 (Cobicistat)

- Potent inhibitor of CYP3A4
- No antiviral activity
- Less induction potential than RTV
- Physicochemical properties make it amenable to co-formulation.
- QUAD pill.

Introduction: Atazanavir Pharmacokinetics

<table>
<thead>
<tr>
<th>Mean (CV%)</th>
<th>ATV PK (n = 34 - 36)</th>
<th>+ GS-9350 100 mg</th>
<th>+ GS-9350 150 mg</th>
<th>+ RTV 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0→¥} (ng·hr/mL)</td>
<td>45100 (31)</td>
<td>55900 (28)</td>
<td>55200 (28)</td>
<td></td>
</tr>
<tr>
<td>C_{max} (ng/mL)</td>
<td>4420 (21)</td>
<td>4880 (25)</td>
<td>5270 (24)</td>
<td></td>
</tr>
<tr>
<td>C_{min} (ng/mL)</td>
<td>837 (59)</td>
<td>1330 (43)</td>
<td>1340 (41)</td>
<td></td>
</tr>
</tbody>
</table>

Bioequivalent ATV PK achieved GS-9350 150 mg vs. RTV 100 mg
**Virologic Efficacy of ATV boosted with GS-9350 and RTV in Naive Pts**

- Phase II study comparing cobicistat (GS-9350) vs ritonavir as boosting agent for atazanavir

![Graph showing virologic efficacy](image)

**GS-9350 Appears to Alter Estimated GFR, Not Actual GFR**

- Most creatinine excretion occurs by filtration, but 10-15% by active tubular secretion.
- 7-day GS-9350 v placebo in healthy subjects – no effect on actual GFR (iohexol CL) – but lower estimated GFR.
- Mechanism: inhibition of tubular secretion?

![Graph showing GFR](image)
### Results: DRV Pharmacokinetics

<table>
<thead>
<tr>
<th>Mean (CV%)</th>
<th>+ 150 mg GS-9350</th>
<th>+ 100 mg RTV</th>
<th>GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRV PK (n = 31)</td>
<td>AUC&lt;sub&gt;τ&lt;/sub&gt; (ng·hr/mL)</td>
<td>81100 (31.0)</td>
<td>80060 (34.0)</td>
</tr>
<tr>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>7740 (21.8)</td>
<td>7460 (29.3)</td>
</tr>
<tr>
<td></td>
<td>C&lt;sub&gt;τ&lt;/sub&gt; (ng/mL)</td>
<td>1330 (66.8)</td>
<td>1870 (83.3)</td>
</tr>
<tr>
<td></td>
<td>C&lt;sub&gt;0&lt;/sub&gt; (ng/mL)</td>
<td>2400 (50.7)</td>
<td>2480 (34.3)</td>
</tr>
</tbody>
</table>

Presented at the 11th International Workshop on Clinical Pharmacology of HIV Therapy, 2010

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**Integrase Inhibitors**
S/GSK1349572 PK and Exposure-Response Relationship (Phase IIa)\(^1\)

**S/GSK1349572 (unboosted; QD dosing) Plasma Concentrations on Day 10**

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>S/GSK1349572 Concentration (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.01</td>
</tr>
<tr>
<td>10</td>
<td>0.10</td>
</tr>
<tr>
<td>20</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**Emax model of S/GSK1349572 Exposure vs. Response**

<table>
<thead>
<tr>
<th>Ctau (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.036 µg/mL</td>
</tr>
</tbody>
</table>

1. Song I, et al. IAS 2009, Cape Town, Wednesday poster #WEPEB250

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**S/GSK1349572 Drug Interaction Profile**

- Metabolised by UGT1A1; CYP3A4 minor
- Drug interaction profile:
  - **As Perpetrator** – limited (ie no effect on Midazolam, a CYP3A4 drug or Tenofovir);
  - **As Victim** – care.

  *Simultaneously with antacid, AUC ↓ 70% With ATV AUC ↑ 90%*

Song, I et al. 49th ICAAC, 2009, abstracts 1303
S/GSK1349572 Interaction with Etravirine

PK of Raltegravir + Etravirine

- Healthy subjects (n=19)
- ETR decreased RAL C₁₂ by 34% and AUC by 10%
- Conclusions: ETR combined with RAL - no dose adjustment necessary for either drug.

Etravirine – Raltegravir: A marked interaction in HIV-1 infected patients

Menard A et al. AIDS 2009; 23:869-871

Raltegravir (RAL) in combination with etravirine (ETV) – is there a case for TDM in clinical practice.

Leake Date H et al BHIVA?BASHH 2010 Ps
Limitation in experienced cf Placebo
Ongoing considerations - Naive

Box 1. Drug summary.

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Victrexil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>Phase III</td>
</tr>
<tr>
<td>Indication</td>
<td>Infection, HIV/AIDS</td>
</tr>
<tr>
<td>Pharmacology description</td>
<td>CC chemokine receptor 5 antagonist</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Alimentary, p.o.</td>
</tr>
</tbody>
</table>

Provental trial(s)

Two identical, designed randomized, double-blind, placebo-controlled, parallel-group Phase II trials (VICTOE3 and -4) in 372 treatment-experienced patients each with CCR5-tropic HIV in Canada, Europe, N America, S Africa and S America, to evaluate safety and efficacy of sodium malate 30 mg once-daily + optimized background therapy vs new optimized background therapy alone.


Boosted PI increases exposure by 5-fold

t1/2 = ~24h
2. New regimens

NEAT 001:
RAL (400 mg bid) + DRV/r (800 mg QD)

EARNEST:
RAL (400 mg bid) + LPV/r (400/100 bid)
Atazanavir + Raltegravir

- Numerous PK studies
  - Atazanavir 300 mg BID + Raltegravir 400 mg BID (Zhu et al CROI 2009)
  - Atazanavir 200 mg BID + Raltegravir 400 mg BID (Ripamonti et al. Pharm Workshop 2009)
  - Atazanavir 400 mg QD + Raltegravir 800 mg QD (Molto et al IAS 2009)
  - Atazanavir 400 mg QD + Raltegravir 400 mg QD (Neely et al IAS 2009)

Metabolized by CYP3A4

Metabolized by UGT1A1

\( \text{ATV} \rightarrow \text{RAL} \)

\( \text{ATV} \rightarrow \text{Metabolized by CYP3A4} \)

\( \text{RAL} \rightarrow \text{Metabolized by UGT1A1} \)
Phase IIIB. Atazanavir + Raltegravir (SPARTAN)
(HIV+ Naïve; >5000 VL)
ATV (300 mg BID) + RAL (400 mg BID) vs
ATV/r (300/100 mg QD) + TDF/FTC (300/200 mg QD)
Primary Outcome: < 50 at week 24.

Phase III. Atazanavir + Raltegravir (SPARTA)
(HIV+; suppressed)
ATV (300 mg BID) + RAL (400 mg BID) for 4 weeks then
ATV/r (300/100 mg QD) + RAL (800 mg QD) for 4 weeks.
ARMS A & B.

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Atazanavir + Maraviroc

Study A4001078
Open-label, randomized, international phase 2b study
Primary endpoint: Proportions < 50 copies/mL at week 48*

Randomization
1:1
N = 121

Screening
(6 weeks)
0 16 wk 24 wk 48 wk
Interim analyses
Primary analysis

ATV/r (300/100 mg QD) + Truvada (TDF/FTC)
ATV/r (300/100 mg QD) + MVC (150 mg QD)

Week 2
First 15 US Patients
Serial PK of MVC

Interim analysis
(Viral decay)

Patient eligibility criteria:
- ≥ 16 years of age
- Treatment naive
- R5 HIV-1 infection (enhanced Trofile™)
- HIV-1 RNA ≥ 1000 copies/mL
- CD4 ≥ 100 cells/mm³
- No evidence of resistance to ATV/r, TDF, or FTC

* Study is not powered to show a treatment difference and no comparative statistics will be performed.
Sparse PK sampling on all patients at Weeks 2 (non-PK substudy), 12 and 24.

Presented at the 11th International Workshop on Clinical Pharmacology of HIV Therapy - 2010
3. New Tests (PGx)
Implementation of pharmacogenetic testing

**Clinical validation**
- Exploratory clinical studies: Candidate gene association studies to define whether an association exists.
- Mechanistic studies: Define mechanisms and identify biologically plausible candidate genes.

**Clinical confirmation**
- Confirmatory clinical studies: Genotype-directed clinical management to define the clinical benefit.
- Cost effectiveness studies: Risk–benefit analyses to assess whether the association is affordable.

**Mechanistic studies**
- Define mechanisms and identify biologically plausible candidate genes.

**Exploratory clinical studies**
- Candidate gene association study (GWAS) to discover novel associations.

**Cost effectiveness studies**
- Risk–benefit analyses to assess whether the association is affordable.

**Confirmatory clinical studies**
- Genotype-directed clinical management to define the clinical benefit.

### Interindividual variability in Efavirenz plasma concentrations.

\((n = 300\text{ patients})\)

![Graph showing plasma efavirenz concentrations](image)

- Plasma efavirenz concentration (ng/mL)
- Time post dose

**Legend**
- \(< 1000\text{ ng/mL}\): Higher chance of resistance
- \(> 4,5000\text{ ng/mL}\): Higher chance of CNS toxicity
- \(530\text{ ng/mL}\)

**References**
Implementation of pharmacogenetic testing

Clinical validation

Mechanistic studies
Define mechanisms and identify biologically plausible candidate genes.

Exploratory clinical studies
Candidate gene association studies to define whether an association exists.

Confirmatory clinical studies
Genotypes - directed clinical management to define the clinical benefit.

Cost effectiveness studies
Risk - benefit analyses to assess whether the association is affordable.

Clinical confirmation

Confirmatory clinical studies
Genotype - directed clinical management to define the clinical benefit.

Cost effectiveness studies
Risk - benefit analyses to assess whether the association is affordable.

Exploratory clinical studies
Genome Wide association study (GWAS) to discover novel associations.

Mechanistic studies
Explore the mechanism for the association to ensure biological plausibility.
Pharmacogenetics Pyramid: Efavirenz

Genetic Determinants of Antiretroviral PK and Toxicity

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Gene, Allele, Polymorphism</th>
<th>Reported Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABACAVIR</td>
<td>HLA-B*5701</td>
<td>Risk of HSR</td>
</tr>
<tr>
<td>TENOFVIR</td>
<td>ABCC2 (MRP2)</td>
<td>Risk of renal proximal tubulopathy</td>
</tr>
<tr>
<td>NEVIRAPINE</td>
<td>HLA-DRB1*0101, HLA-cw8</td>
<td>Risk of HSR and hepatotoxicity</td>
</tr>
<tr>
<td>EFAVIRENZ</td>
<td>CYP2B6 516G&gt;T, 983T&gt;C; CYP2A6, UGT2B7; CAR</td>
<td>Increased plasma exposure</td>
</tr>
<tr>
<td>ATAZANAVIR</td>
<td>UGT1A1*28</td>
<td>Unconjugated hyperbilirubinaemia</td>
</tr>
<tr>
<td>PIs</td>
<td>APOA5, APOC3, APOE, ABCA1</td>
<td>Increased risk of hyperlipidemia</td>
</tr>
<tr>
<td>LOPINAVIR</td>
<td>SLC01B1 521T&gt;C</td>
<td>Increased plasma concentrations</td>
</tr>
<tr>
<td>RALTEGRAVIR</td>
<td>UGT1A1*28</td>
<td>Modest increase in plasma levels</td>
</tr>
</tbody>
</table>
Thanks

For Slides
Colleagues at Merck, GSK, Pfizer, Viiv, Tibotec, Gi lead.