Pharmacokinetics (PK) and HIV

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Meena Gorowora, Pharmacologist
Pharmacokinetics and short-term efficacy of a double-boosted protease inhibitor regimen in treatment-naive HIV-1-infected adults

Jasper van der Lugt, Reshma Saskia Autar, Sasiwimol Ubolyam, Evian Fernandez Garcia, Jongkol Sankote, Anchalee Avihingsan, Theshinee Chuenyam, David A. Cooper, Joep Lange, Praphan Phanuphak, Ferdinand Wit, Kiat Ruxrungtham and David Burger on behalf of the HIV-NAT 019 Study Team

A Low Dose of Ritonavir-Boosted Atazanavir Provides Adequate Pharmacokinetic Parameter in HIV-1-Infected Thai Adults

A Avihingsan, J van der Lugt, SF Kerr, M Gorowara, S Chanmano, P Ohata, J Lange, DA Cooper, P Phanuphak, DM Burger and K Ruxrungtham

Nevirapine plasma concentrations and concomitant use of rifampin in patients coinfected with HIV-1 and tuberculosis

Reshma S Autar, Ferdinand WNM Wit, Jongkol Sankote, Apicha Mahanontharit, Thanomsak Anekthananon, Piros Mootsikapun, Kanjitta Sujsaikaew, David A Cooper, Joep MA Lange, Praphan Phanuphak, Kiat Ruxrungtham and David M Burger

Safety and efficacy of a double-boosted protease inhibitor combination, saquinavir and lopinavir/ritonavir, in pretreated children at 96 weeks

Torsak Bunupuradil, Jasper van der Lugt, Pong Kosakulakso, Chulaporn Engcharit, Pitch Boonrod, Thanyawee Puthanakit, Tawan Mengchosong, Apicha Mahanontharit, Pongpimon Lumbigano, Emily Tompkins, David Burger, Kiat Ruxrungtham and Jintanat Ananwaranich on behalf of the HIV-NAT 017 Study Team

Saquinavir trough concentration before and after switching NRTI to tenofovir in patients treated with once-daily saquinavir hard gel capsule/ritonavir 1600 mg/100 mg

Jintanat Ananwaranich, Umaporn Siangphoe, Apicha Mahanontharit, Andrew Hill, Bernard Hirschel and Kiat Ruxrungtham

Pharmacokinetics of lower doses of saquinavir soft-gel caps (800 and 1200 mg twice daily) boosted with itraconazole in HIV-1-positive patients

Peter G Cardillo, Tarika Samor, David Burger, Richard Hoetelmans, Apicha Mahanontharit, Kiat Ruxrungtham, Joep M Lange, David A Cooper and Praphan Phanuphak
Contents

- Introduction general principles PK
- Remarks about ARV and PK
- Interactions
- TDM as a clinical tool
What is PK

- Pharmaco = medications
- Kinetics = movement

“Definition”:
P(K) is the process what the body does with the drugs.

or

What the body does to eliminate the drugs
Which processes happen to eliminate the drugs?

- Absorption
- Distribution
- Metabolism
- Excretion

We call this the ADME
PK Processes
Absorption

- Get the product from extra-vascular to intra-vascular
- Strongly influenced by:
  - Food
  - Formulation
The influence of food on SQV PK

SQV with food

SQV with food

MEC

without food

SQV plasma level (mg/L)

0 4 8 12 16 20 24

time after intake of 1000mg SQV/r (hr)
PK Processes
Distribution

Equilibria

- From the blood to the tissues
- Very quick and dynamic process
- Body constitution influence this process
PK processes
Metabolism

- Enzymes in liver metabolize medication
- Same enzyme used by most of ARV
- Genetics may effect metabolism process
- Part of the ARVs are excreted by the kidney
Which drugs is metabolized and which drugs excreted by the kidney?

<table>
<thead>
<tr>
<th>NRTIs</th>
<th>NNRTIs</th>
<th>PIs</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zidovudine (AZT)</td>
<td>Nevirapine (NVP)</td>
<td>Saquinavir</td>
<td>Enfuvirtide (FI)</td>
</tr>
<tr>
<td>Didanosine (ddI)</td>
<td>Efavirenz (EFV)</td>
<td>Ritonavir</td>
<td>Raltegravir (Intg.I)</td>
</tr>
<tr>
<td>Zalcitabine (ddC)</td>
<td>Etravirine (ETV)</td>
<td>Indinavir</td>
<td>Maraviroc (CCR5-antgonist)</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir (TDF)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emtricitabine (FTC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
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</tbody>
</table>

Blue = metabolized by the liver  
Red = excreted by the Kidney
Table 3. Relationship between genetic polymorphisms and efavirenz AUC_{0-24 h}

<table>
<thead>
<tr>
<th>Genetic polymorphism</th>
<th>CYP2B6 (G516T)</th>
<th>CYP2B6 (C1459T)</th>
<th></th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>All subjects (n = 152)</td>
<td>European-Americans (n = 86)</td>
<td>African-Americans (n = 48)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>n</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>78</td>
<td>44.0 (38.0 to 52.4)</td>
<td>50</td>
<td>42.9 (35.9 to 48.1)</td>
<td>20</td>
</tr>
<tr>
<td>GT</td>
<td>60</td>
<td>60.3 (46.0 to 70.9)</td>
<td>33</td>
<td>57.8 (39.7 to 65.0)</td>
<td>18</td>
</tr>
<tr>
<td>TT</td>
<td>14</td>
<td>130 (30.3 to 158)</td>
<td>3</td>
<td>176.2 (80.2 to 183)</td>
<td>10</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.0001</td>
<td></td>
<td>0.001</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td>131</td>
<td>52.1 (39.0 to 71.2)</td>
<td>67</td>
<td>47.5 (37.6 to 60.0)</td>
<td>47</td>
</tr>
<tr>
<td>CT</td>
<td>20</td>
<td>46.2 (40.3 to 56.2)</td>
<td>18</td>
<td>44.5 (40.1 to 53.7)</td>
<td>1</td>
</tr>
<tr>
<td>TT</td>
<td>1</td>
<td>46.0 (46.0 to 46.0)</td>
<td>1</td>
<td>46.0 (46.0 to 46.0)</td>
<td>0</td>
</tr>
<tr>
<td>P value</td>
<td>0.19</td>
<td></td>
<td>0.87</td>
<td>0.30</td>
<td></td>
</tr>
</tbody>
</table>
Q: Which of the drugs below should be taken with food

1. Lopinavir/ritonavir (tablet formulation)
2. Saquinavir/r
3. Lamivudine
4. All of the above

90% 10% 0% 0% 0%

Lopinavir/ritonavir (tablet formulation) Saquinavir/r Lamivudine All of the above
Q: PK consists of different processes, what are these, and in what order do they occur?

1. 1) Absorption 2) Distribution 3) Metabolism 4) Excretion
2. 1) Aspiration 2) Development 3) Metabolism 4) Extension
3. 1) Absorption 2) Metabolism 3) Distribution 4) Excretion
4. None of the above answers are correct
Q: What process is likely the most affected by genetics?

1. Absorption
2. Distribution
3. Metabolism (★)
4. Excretion
PK Language

Concentration mg/L

AUC = Area under the curve

Cmax

Cmin

Tmax

time (hr)
PK language

- **Cmax** = maximum concentration reached after intake of a drugs

- **Cmin** (Clast/Cthough) = lowest concentration after intake of a drugs.

- **AUC** = area under the curve = total exposure of the drugs of an individual patient

- **Tmax** = time of highest concentration reached
PK language

- **PD** = pharmacodynamics = what the drugs does to the body

- **Half life** = is the time the body needs to clear half of the drugs

- **Inter-variability**: Different drug levels between different patients

- **Intra-variability**: Different drug levels within the same patients
How can we use PK in clinical practice

- Studying PK is only useful if there is a correlation with the drugs concentration and its effect (toxicity or efficacy)
ARV and PK

- PI good correlation
- NNRTI good correlation
- NRTI not good correlation, at least with plasma concentrations
- We call this PK/PD relation
Above this level toxic

Below this level suppression HIV
Q: What is the most favorable time to do blood draw if we want to know something about the adequacy of the blood concentration?

1. Just after the intake of the ARV
2. Just before intake of the next dose
3. Exactly between 2 doses
4. Any time is fine
Q: Which statement is true

1. Not all ARV are suitable to study with (plasma) PK
2. High intra-variability makes PK in clinical practice less useful
3. Tmax, is the time at which the drugs concentration is the highest
4. All the above are correct

According to the bar chart, 70% of the respondents chose the fourth option. 
PK, how to use it?
How to use it

- In clinical practice PK can be used by means of therapeutic drug monitoring (TDM). This is usually, 1 timepoint.

- In a study setting a 12 or 24hr PK generates more information, and can be used to interpret TDM.
Indications to use TDM?

- Virological failure
- Toxicity
- Drug-Drug interaction
- GI disease and hepatic insufficiency
- Pregnancy
- Children
- Adherence
- Ethnicity ???
Drug-Drug interaction

- 2 kinds of interaction
  - Inhibition
  - Induction
Drug-Drug interaction

- Inhibition
  - 2 medication using the same enzyme
  - One stronger inhibition than the other (competition)
  - Result: Level of other drugs getting high!
  - Most famous, (inhibition) interaction: RTV with other PIs
Induction

- Induce the enzyme system
- Makes is work harder
- No time for the other drugs to be effective
- Most famous induction interaction: Rifampin with almost all ARV. More with PI than NNRTI.
## Enzyme Inhibition and Induction

<table>
<thead>
<tr>
<th>Drug</th>
<th>Enzyme Inhibition</th>
<th>Enzyme Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>++</td>
<td>—</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Indinavir</td>
<td>++</td>
<td>—</td>
</tr>
<tr>
<td>Lopinavir/ritonavir*</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>Tipranavir/ritonavir*</td>
<td>++++</td>
<td>+++</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>—</td>
<td>++</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>Saquinavir†</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Assessment includes the effects of ritonavir.
†Saquinavir can inhibit P450 3A4 in vitro, but this is not generally manifested clinically.
Adapted from Fletcher CW. http://clinicaloptions.com/2004PK.
Examples of HIV drug interactions

- Anti HIV drugs itself
- Ritonavir
- **Tuberculosis drugs**
- Anti-acid
- Oral anticonceptives
- Benzodiazepines
- Herbal drugs
TB and HIV

- Most common opportunistic infection
- Associated with substantial morbidity and mortality
- Rifamycin antibiotics using CYP450 metabolism pathway like most ARV
- How to treat, when to treat
When to start both treatments

- It’s recommended to start ARV as soon as possible after TB drugs has been initiated in most cases.

- Challenges:
  - Adherence multidrugs regimen
  - Overlapping site effects profile
  - Interaction
Interaction

- All besides NRTI and enfurvitide have no interaction with rifamycin antibiotics
EFV + Rifampin

- Moderate decrease in EFV levels (up to 25%)
- Although increase to 800 mg compensate for this decrease not been said that it’s necessary.
- NO DOSE ADJUSTMENT needed, especially not in Asian setting
- Some recommend to do so above 60 kg, we think, no need
When EFV is not available

- EFV is the first choice when HAART need to be combined with Rifampin
- BUT not always possible:
  - NNRTI resistance
  - Pregnancy
  - Intolerant to EFV
NVP and Rifampin

- More decrease in drugs exposure (up to 55%)
- Skin rash and hepatitis, overlapping toxicity
- NVP cannot be started when CD4 cells high
- Data available are not powered nor conclusive
- Based on the data available, no dose adjustment needed, and toxicity acceptable
- If dose was increased, more hypersensitivity reported (Asian population)
PIs + Rifampin

- PI have up to 90% reduction of serum concentrations (LPV, ATV, IDV all boosted)
- Standard dose PI cannot be given
- LPV 800/100 or 400/400 mg obtained good levels, but high rate of toxicity (healthy volunteers)
- Only be used when no other options and close monitoring of liver functions
NRTI and Rifampin

- Overall NRTI based regimen, less potent than HAART
- But triple and quadruple NRTI regimen have been reported and showed acceptable results (both with TDF in it)
- Can be considered as an option
DRUG-DRUG interaction

• For all the other drug-drug interaction or when in doubt use:
  • www.HIV-druginteractions.org
  • www.HIVpharmacology.com
  • www.AIDSinfo.nih.gov

• All very useful and free
Q: When is it useful to use TDM

1. With all NRTIs
2. When non-adherence is suspected
3. As routine in all patients
4. All the above
Q: What can you do if you suspect a drugs-drugs interaction, but not sure

1. Consult the websites
2. Consult a colleague how does know (= Dr Anchalee)
3. Do TDM
4. All the above are correct

![Survey Results]

- Consult the website: 0%
- Consult a colleague: 30%
- Do TDM: 17%
- All the above: 52%
Are all people the same?
Question to start with?

- What influence the PK parameters?

- Is this different in Asian population?
Results from PK studies done in this region

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Registered Dose</th>
<th>Clinical practice Thailand</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZT</td>
<td>300 mg BID</td>
<td>200 mg BID</td>
</tr>
<tr>
<td>IDV/r</td>
<td>800/100mg BID</td>
<td>400/100 mg BID</td>
</tr>
<tr>
<td>SQV/r</td>
<td>1000/100 mg BID</td>
<td>1500/100 mg OD</td>
</tr>
</tbody>
</table>
Q: Two patients, one Thai and 1 American. Both take Kaletra 400 mg bid. Which curve is most likely the from the Thai?

1. A

2. B
Q-Two patients, one takes saquinavir without RTV and the other one with. Which curve is most likely the taken with RTV?

1. A

2. B
Q- 1 patient 2 curves, one in the 3\textsuperscript{rd} trimester of pregnancy and one postpartum
Which curve is most likely the from the 3\textsuperscript{rd} trimester?

1. A

2. B

Figure A

Figure B
Q: Please point on the curve, what is the best time to take blood for the Minimum concentration, if the patient was on Kaletra BID regimen?

If the patient was on SQV OD, would you choose the same time point?

1. T=2
2. T=3
3. ✷ T=12
4. T=6
Conclusions

- PK: What the body does with the drugs
- TDM can be used to optimize treatment
- Very important to counsel patient in terms of food, possible interaction, time of intake
- For $C_{min}$ should draw blood as close to next dose as possible
Optimal Timing for Blood Collection

TDM

- **Cmin**
  - Prior to the next ARV dosing
    - BID dose: between 11 to 13 hours after the intake of last dose.
    - OD dose: between 23 to 24 hours after the intake of last dose.

- **Cmax**
  - 4 hours after the intake of last dose
    - exception: IDV – 2 hours
Optimal Timing for Blood Collection

Full PK

- BID dose: pre-dose down to 12 hours
- OD dose: pre-dose till 24 hours

Note: Collect blood in Lithium Heparin tube
TDM Requisition Form

- Demographic data
- Indications
  - Sub-optimal level, toxicity, drug-drug interactions, non-compliance, routine monitoring
- Date and time of sample collection
- ARV
  - Which ARV, dose (mg), frequency (bid, od), date and time of last intake
  - Concomitant medications
- Transport the blood to the lab within 6 hours after collection
Interpret Results

- Indication requested

<table>
<thead>
<tr>
<th>ARV</th>
<th>Effective C-Min (mg/L)</th>
<th>Estimated C-Max (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir</td>
<td>0.15 - 0.85</td>
<td>5.2</td>
</tr>
<tr>
<td>Indinavir</td>
<td>0.1</td>
<td>10.0</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>1.0 - 4.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>0.1</td>
<td>ND</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>3.1</td>
<td>5.7</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>1.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>0.8 - 2.2</td>
<td>4.0</td>
</tr>
</tbody>
</table>

References:
1. Pharmacokinetics of the NNRTIs and PIs (standard dosing) (European Medicines Agency) (EMEA) 2004
2. U.S. Food and Drug administration (FDA) - Center for drug evaluation and research (CDER) 2004.
3. www.hivpharmacology.com
Thankyou for your attention!
Predictive Value of Known and Novel Alleles of CYP2B6 for Efavirenz Plasma Concentrations in HIV-infected Individuals

M Rotger, H Tegude, S Colombo, M Cavassini, H Furrer, L Décoyter, J Blievernicht, T Saussele, HF Günthard, M Schwab, M Eichelbaum, A Telenti, and UM Zanger, and the Swiss HIV Cohort Study