What can HIV pharmacology offer to the clinician?

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Clinical Investigation Unit
Assistant Professor of Medicine
Ottawa, Canada
What can HIV pharmacology offer to the clinician?

- Understanding of:
  - Lack of viral efficacy
  - Emergence of toxicity
- What is pharmacology
- What factors influence pharmacology
- Real life situations in HIV
- A tool to control; TDM
- Take home messages
Pharmacokinetics
What the body does to the drug

Drug in tissues

Drug in systemic circulation

Drug metabolized & excreted

absorption
distribution

Drug administration

Pharmacodynamics
What the drug does to the body

Drug at site of action

Drug at site of action

Metabolism/excretion

effect
Pharmacokinetics refresher

- ADME
- Cmax
- Tmax
- AUC
- Cmin or Ctrough
- Half life
- Steady state
Steady state

- Repeated dosing will result in drug accumulation until “steady state” is reached.
- Steady state is reached after 4-5 times half life.
Absorption

DRUG

Oral, rectal → Intestines

Topical → Skin

Intravascular (IV, IA) → BLOOD

I.M., S.C. → Membranes

Inhalation → Lungs
# Factors influencing absorption

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Particle size</td>
<td>pH in GI tract</td>
</tr>
<tr>
<td>Solubility</td>
<td>Gastric emptying rate</td>
</tr>
<tr>
<td>pKa</td>
<td>Intestinal motility</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>Perfusion of GI tract</td>
</tr>
<tr>
<td>Formulation</td>
<td>Presystemic metabolism</td>
</tr>
<tr>
<td></td>
<td>Age, sex, weight</td>
</tr>
<tr>
<td></td>
<td>Disease states</td>
</tr>
<tr>
<td></td>
<td>Food</td>
</tr>
<tr>
<td></td>
<td>Other drugs</td>
</tr>
</tbody>
</table>
Distribution

Central compartment (blood)

Peripheral compartment (fluid/tissues)

Administration

Excretion

Protein Bound \rightleftharpoons \text{Unbound}; \text{ Unbound Drug has a clinical activity}
Distribution

- Reversible transfer of drug
- Between general circulation and compartments/tissues
  - e.g. brain, liver, kidney, fat, genital tract

- Distribution is dependent on:
  - **Drug:**
    - affinity to protein binding
    - amount of proteins (albumin, alpha-glycoprotein)
    - lipid solubility
    - molecular weight
  - **Patient:**
    - tissue perfusion
    - body composition/size
    - disease
Metabolism

- Metabolism mainly occurs in the liver
- Other sites include:
  - GI tract, kidneys and lungs

- Metabolites can be inactive or active
- Metabolism converts drugs to a water-soluble form
  - Elimination via the kidneys
Phase I and Phase II Metabolism

- Phase I metabolism: biotransformation
  - e.g. oxidation, reduction, hydroxylation, dealkylation
- Phase II metabolism: conjugation
  - e.g. glucuronidation, sulfation, acetylation

Not all drugs undergo phase I and II metabolism
Cytochrome P450 isoenzymes (Phase I)

Key P450’s: 1A2, 2C9, 2C19, 2D6, and 3A4
First pass metabolism

Oral dose

Metabolism in gut wall

CYPs

Hepatic metabolism

General circulation
Excretion

• Excretion into urine is the main route for elimination of drugs
• Other routes include:
  – feces, bile, lungs, breastmilk, sweat
• Nearly all drugs cross the glomerular filter freely
  – except those bound to plasma protein
• Only unbound drug can be filtered since protein molecules are too large
Between patient variability in ADME

Fig. 1. Lopinavir and saquinavir individual plasma concentration-time profiles. Presented are the data of seven patients: — — — patient 1; — — — patient 2; — — patient 3; — — patient 4; — — — patient 5; — — — patient 6; — — — patient 7.

C. la Porte et al. AIDS 2003 17(11), 1700-2
Factors influencing ADME

- gender
- bodyweight
- age
- food
- alcohol
- smoking
- ethnicity
- non-adherence
- drug interactions
- genomics
- organ dysfunction
- disease
- herbs
Factors influencing ADME

- gender
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- smoking
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- drug interactions
- ethnicity
- non-adherence
Adherence
Factors influencing ADME

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- disease
- genomics
- alcohol
Drug-food interactions

Saquinavir 1,200 mg tid
- With food: Higher concentration
- Without food: Lower concentration

Indinavir 800 mg tid
- With food: Lower concentration
- Without food: Higher concentration
Case report: darunavir, etravirine and raltegravir in HD

- 49 year old HIV-infected man
- Nephrectomy for renal cell carcinoma, after remote acute renal failure due to remote electrocution and rhabdomyolysis
- HD thrice weekly pending renal transplantation
- Previously multiple PI intolerance
- Failure of NNRTI-based therapy associated with the initiation of HD
- Current regimen DRV/r 600/100mg BID, ETV 200mg BID and RTG 400mg BID
- Virological suppressed

<table>
<thead>
<tr>
<th></th>
<th>darunavir</th>
<th>etravirine</th>
<th>raltegravir</th>
<th>ritonavir</th>
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</thead>
<tbody>
<tr>
<td><strong>Before dosing adjustment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-HD</td>
<td>2.6</td>
<td>0.38</td>
<td>0.17</td>
<td>0.05</td>
</tr>
<tr>
<td>Post-HD</td>
<td>1.1 (-57%)</td>
<td>0.27 (-29%)</td>
<td>0.03 (-82%)</td>
<td>0.02 (-60%)</td>
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<tr>
<td><strong>After single supplemental dose of raltegravir and darunavir</strong></td>
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<tr>
<td>Pre-HD</td>
<td>1.6</td>
<td>0.32</td>
<td>0.19</td>
<td>0.05</td>
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<tr>
<td>Post-HD</td>
<td>3.3</td>
<td>0.29</td>
<td>0.04</td>
<td>0.05</td>
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<tr>
<td><strong>After continuous supplemental dose of raltegravir and darunavir</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-HD</td>
<td>1.3</td>
<td>0.38</td>
<td>0.08</td>
<td>0.03</td>
</tr>
<tr>
<td>Post-HD</td>
<td>2.9</td>
<td>0.29</td>
<td>0.06</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Hist. mean trough</strong></td>
<td>3.0¹</td>
<td>0.24¹</td>
<td>0.06²</td>
<td>0.21¹</td>
</tr>
</tbody>
</table>

Pre HD sampling occurred 13 hrs after last dose.
Post HD sampling occurred at the end of a 4-hour dialysis session
Case report: Conclusion

- Plasma levels for all 4 drugs decreased during HD
- DRV corrected by a supplemental 600 mg pre HD dose
- RTG variability not instructive for supplemental dosing
- TDM helpful to manage case
Factors influencing ADME

- gender
- bodyweight
- age
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- smoking
- ethnicity
- non-adherence
- genomics
- drug interactions
- herbs
- organ dysfunction
- disease
- non-adherence
Kalori study

Day 1 – 10; LPV/r 400/100 mg BID; Day 11 – 15; LPV/r 400/100 mg BID + RIF; Day 16 – 17; LPV/r dose escalation + RIF; Day 18 – 24; Arm 1: LPV/r 800/200 mg BID + RIF, Arm 2: LPV/r 400/400 mg BID + RIF; Data are presented as mean values with standard deviation

C. la Porte AAC 2004
Factors influencing ADME

- gender
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Pharmacogenomics

study of genetically controlled variation in drug response

Pharmacokinetic
- Metabolism
- Transporters
- Protein binding

Pharmacodynamic
- Receptors
- Enzymes
- Ion Channels
- Immune system
Genetic polymorphism

• Multiple forms of genes (Polymorphisms)
• Encoding for metabolic enzymes and drug transporters

• Polymorphism can cause
  – Increased activity/expression of enzymes/transporters
  – Decreased activity/expression of enzymes/transporters
  – CYP2C9, 2C19, 2D6 resulting in
  – Ultra-rapid, extensive and poor metabolizers
  – Drug transporters (e.g. P-glycoprotein)
Abacavir hypersensitivity

Number of hypersensitivity cases

Median time to onset is 11 days

94% of reported cases occurred within the first 6 weeks of starting abacavir

n=1,514
HLA-B*5701 Screening for Hypersensitivity to Abacavir

Simon Mallal, M.B., B.S., Elizabeth Phillips, M.D., Giampiero Carosi, M.D., Jean-Michel Molina, M.D., Cassy Workman, M.B., B.S., Janez Tomažič, M.D., Eva Jägel-Guedes, M.D., Sorin Rugina, M.D., Oleg Kozyrev, M.D., Juan Flores Cid, M.D., Phillip Hay, M.B., B.S., David Nolan, M.B., B.S., Sara Hughes, M.Sc., Arlene Hughes, Ph.D., Susanna Ryan, Ph.D., Nicholas Fitch, Ph.D., Daren Thorborn, Ph.D., and Alastair Benbow, M.B., B.S., for the PREDICT-1 Study Team*
PREDICT-1 Study Results

- Control arm
  - Clinically Diagnosed HSR: 7.8% (66/847)
  - Immunologically Confirmed HSR: 2.7% (23/842)

- Prospective HLA-B*5701 screening arm
  - Clinically Diagnosed HSR: 3.4% (27/803)
  - Immunologically Confirmed HSR: 0.0% (0/802)

P < 0.0001
CYP2B6 genotypes and efavirenz pharmacokinetics

- 219 patients were enrolled during the months of September through December of 2008 at Fundación Arriarán
- 215 patients (13 females) had measurable EFV levels
- CYP2B6 G516T polymorphism is known to be associated with EFV
- CAR is known to regulate CYP2B6 expression
- CYP2B6 and CAR genotype were analyzed
- Clinical parameters were also taken into account
EFV plasma concentrations by CYP2B6 polymorphism

C. Cortes et al. 10th International Workshop on Clinical Pharmacology of HIV Therapy, Amsterdam 2009 abstract P_04
EFV plasma concentrations by CAR polymorphism

C. Cortes et al. 10th International Workshop on Clinical Pharmacology of HIV Therapy, Amsterdam 2009 abstract P_04
Factors influencing ADME

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- smoking
- organ dysfunction
- disease
- herbs
EFV plasma concentrations grouped by smoking status

P = 0.02

C. Cortes et al. 10th International Workshop on Clinical Pharmacology of HIV Therapy, Amsterdam 2009 abstract P_04
Factors influencing ADME

- Gender
- Bodyweight
- Age
- Alcohol
- Smoking
- Ethnicity
- Food
- Non-adherence
- Drug interactions
- Genomics
- Organ dysfunction
- Herbs
- Disease
Ethnicity

- EFV levels higher in non-caucasians / women
Factors influencing ADME

- gender
- bodyweight
- age
- food
- alcohol
- smoking
- ethnicity
- non-adherence
- drug interactions
- genomics
- herbs
- organ dysfunction
- disease
What is Therapeutic Drug Monitoring

Individualizing drug therapy, guided by drug concentrations
Goal: maximize efficacy and minimize toxicity
## TDM Studies (RCTs)

<table>
<thead>
<tr>
<th>Study</th>
<th>TDM beneficial</th>
<th>patients</th>
<th>drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDV CBV</td>
<td>yes</td>
<td>naive</td>
<td>IDV</td>
</tr>
<tr>
<td>Fletcher et al. AIDS 2002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PharmAdapt</td>
<td>no</td>
<td>experienced</td>
<td>PIs + NNRTIs</td>
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<tr>
<td>Clevenbergh et al. AIDS 2002</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Athena</td>
<td>yes</td>
<td>naive</td>
<td>NFV and IDV</td>
</tr>
<tr>
<td>Burger et al. AIDS 2003</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Genophar</td>
<td>no</td>
<td>experienced</td>
<td>PIs + NNRTIs</td>
</tr>
<tr>
<td>Bossi et al. HIV Med 2004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radar</td>
<td>no</td>
<td>experienced</td>
<td>PIs + NNRTIs</td>
</tr>
<tr>
<td>Torti et al. CID 2005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POPIN</td>
<td>no</td>
<td>mixed</td>
<td>PIs + NNRTIs</td>
</tr>
<tr>
<td>Khoo et al. J Acquir Immune Defic Syndr 2006</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demeter et al. AIDS 2009</td>
<td>no</td>
<td>experienced</td>
<td>PIs</td>
</tr>
</tbody>
</table>
Guidelines

• DHHS and BHIVA
• TDM has value in specific cases
• But also challenges
  – Availability of labs
  – Cutoff values
  – Prospective studies
• Cutoff values are subject to change
## TDM target concentrations (DHHS 2008)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fosamprenavir</td>
<td>400</td>
</tr>
<tr>
<td></td>
<td>(measured as amprenavir concentration)</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>150</td>
</tr>
<tr>
<td>Indinavir</td>
<td>100</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>1,000</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>800</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>100–250</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>1,000</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>3,000</td>
</tr>
</tbody>
</table>

**Recommendations applicable only to treatment-experienced persons who have resistant HIV-1 strains**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maraviroc</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>20,500</td>
</tr>
</tbody>
</table>

*a. Measurable active (M8) metabolite.*
Consider TDM for specific indications

- Adherence
- Adverse events
- Virologic failure
- Pregnancy
- Pediatrics
- Co-infections
- Use of unlicensed dose
- Hepatic or renal change
- Interactions

Indications
TDM in special populations

• Supported by HIV treatment guidelines including DHHS and BHIVA
• To define those populations that could benefit most from TDM
• To utilize TDM as effective as possible
• How well are populations defined?
• Use of TDM in special populations is same as in general population
What are special populations?

- Ethnicity
- Gender
- Pregnant women
- Pediatric patients
- Organ transplant recipients
- Hepatic impairment
- Kidney failure
- And more?
PK Laboratory

- Bioanalysis of drugs
- Difficult matrixes
- Complex molecules
- Sample pretreatment
- Separation techniques
- Selective detector

- HPLC/MS/MS with SPE
PK parameter used in TDM

- Plasma versus intracellular
- AUC, Cmax, Ctrough or random sample
- Plasma Ctrough most commonly used
- Random sample, extrapolation to Ctrough
  - Pharmacokinetic model needed
- Random sample, Concentration Ratio (CR)
  - Compare individual concentration to population average
  - Works throughout dosing interval
TDM and resistance data: The Inhibitory Quotient

- Concentration based cutoffs for naïve patient
- What if pretreated patient?

- Resistance data in equation: The Inhibitory Quotient

- GIQ = Ctrough / PAM
- PIQ = Ctrough / IC50 or IC90
Steps in TDM (how to do TDM)

- Quantification of drug concentrations
- Determination of patients PK characteristics
- Interpretation of the concentrations
- Adjustment of the drug dose to achieve desired concentrations
Take home messages

• The process of ADME is influenced by many factors
• A number of these factors have been identified
• TDM can be a tool to control for influence on ADME
• Knowledge of Clinical Pharmacology in HIV will help the clinician to:
  – Identify possible problems in drug treatment of HIV
  – Understand failure of treatment
  – Understand emergence of toxicity
• A clinical pharmacist can assist in these tasks
The clinical pharmacist

- Dispense medications
- Answer patient questions regarding medications
  - Adverse events
  - Food requirements
  - Other medications
  - Adherence
- Monitoring of pharmacotherapy
  - Laboratory monitoring (request and follow up)
  - Therapeutic drug monitoring
  - Lab parameters toxicity (liver, renal, HLA B*5701)
  - Lab parameters efficacy (ex: adjusting statins for dyslipidemia)
  - Discussion AEs and their treatment (switch or medical treatment)
The clinical pharmacist

• Advice physicians on drug related questions
  – Drug interactions
  – Therapeutic Drug Monitoring
  – Resistance interpretation
  – Paperwork to get drug supply

• Medication reconciliation
  – Comprehensive drug history

• Seamless care
  – Facilitate communication with regards to drug therapy with other health care professionals.

• Research… collaboration
SAVE THE DATE

11th International Workshop on Clinical Pharmacology of HIV Therapy

7 - 9 April 2010
Sorrento, Italy

Please visit www.virology-education.com for more information
Confirmed Speakers

Invited Lectures
Dr. Dan Roden  Pharmacology and Genetics of QTc Prolongation
Dr. Larry Lesko  Pharmacogenetic labeling
Dr. Helen McIlleron  TB-ARV interactions
Dr. Steve Taylor  Management of Influenza and HIV: What do we know
Dr. Ed Acosta  PK of Anti-Influenza Drugs and Potential for Interaction with ARV’s
Dr. Giovanni di Perri  Evolving HIV Epidemic in Italy

Round table discussions
-) Incorporating pharmacogenetic data into Drug development, approval and post-marketing labels
   Dr. Dan Roden & Dr. Larry Lesko
-) Pharmacokinetic Enhancers
   Dr. Rick Bertz & Dr. Trevor Hawkins

Registration opens 1 December

Please visit www.virology-education.com for more information
## Acknowledgements

<table>
<thead>
<tr>
<th>Patients</th>
<th>Dr Sylvie Gregoire</th>
<th>Isabelle Seguin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Volunteers</td>
<td>Dr Wayne Gold</td>
<td>Jennifer Hoffman</td>
</tr>
<tr>
<td>AIDS bureau</td>
<td>Dr Claudia Cortes</td>
<td>Danielle Tardiff</td>
</tr>
<tr>
<td>OHTN</td>
<td>Dr Marcelo Wolff</td>
<td>Nancy Lamoureux</td>
</tr>
<tr>
<td>Jeremy Zhang</td>
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<td>Dr Gary Garber</td>
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<tr>
<td>Gianni Lorello</td>
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<td>Dr Bill Cameron</td>
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<td>Pierre Giguere</td>
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<td>Dr Paul MacPherson</td>
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<td>Amanda Jacques</td>
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<td>Dr Saye Khoo</td>
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