Pharmacokinetic (PK) Modeling of Efavirenz, Atazanavir, Lamivudine, and Tenofovir in the Female Genital Tract of HIV-Infected Pre-Menopausal Women

Julie B. Dumond, Melanie R. Nicol, Racheal N. Kendrick, Samira M. Garonzik, Kristine B. Patterson, Myron S. Cohen, Alan Forrest, Angela D.M. Kashuba

13th International Workshop on Clinical Pharmacology of HIV Therapy
Barcelona, Spain
April 16-18, 2012
Abstract O_14
PK Modeling and Prevention

• Antiretrovirals (ARVs) developed for HIV therapy

• New applications:
  – Treatment as prevention
  – Pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP)
  – Cure

• Genital tract is a protected compartment
  – Need a way to predict ARV behavior

• Design ARV regimens to:
  – Suppress genital tract RNA in the infected
  – Protect mucosal surfaces in the uninfected
Systemic PrEP For Women

Female Genital Tract Exposure
(median percent of blood plasma)

GT exposure within 2 hrs of dosing

N(t)RTIs | NNRTI | PI | Entry Inhibitors | Integrate Inhibitors

600%
500%
400%
300%
200%
100%
75%
50%
25%
0%

3TC (400%)
FTC (395%)
ZDV (235%)
TDF (110%)
NVP (80%)

IDV (200%)
ETR (130%)
DRV (150%)

APV (50%)
DLV (20%)
ATV (18%)

Patterson et al. IDSA 2009
Jones et al. IPWCPH 2009
Dumond et al. AIDS 2008
Min et al. JAIDS 2005

GT AUC = BP AUC

Patterson et al. IDSA 2009
Jones et al. IPWCPH 2009
Dumond et al. AIDS 2008
Min et al. JAIDS 2005
Methods: Drug Selection

CVF:BP AUC$_{0-t}$ Ratio %

Lamivudine (3TC)
- High penetration
- 40% protein bound

Tenofovir (TFV)
- Neutral penetration
- Negligible protein binding

Atazanavir (ATV)
- Moderate penetration
- 86% protein bound

Efavirenz (EFV)
- Low penetration
- 99.9% protein bound

Dumond et al, AIDS 2007
Sustiva®, Reyataz®, Epivir®, Viread® Full U.S. Prescribing Information

Presented at the 13th Int. Workshop on Clin. Pharmacology of HIV Pharmacology – 2012, Barcelona Spain
Methods: Data Collection

First Dose PK Visit

Day 1

BP and CVF

Multiple Dose PK Visit

Day 30

Sampling schedule (hrs)

0 2 4 6 12 24

BP: blood plasma
CVF: cervicovaginal fluid

Dumond et al, AIDS 2007

LC-UV or MS
NCA for CVF:BP AUC_{0-\tau}
Methods: Model Development

- ADAPT5
- MAP
- Bayesian estimation

- Beal M3 Method
- log-normal probability distribution for parameters
- additive + proportional error variance

Iterative 2-stage analysis

Model discrimination:
AIC, visual inspection of overall goodness of fit & individual subject model fits

Collapse parameters varying between visits
Likelihood Ratio Test, $\alpha = 0.05$


Presented at the 13th Int. Workshop on Clin. Pharmacology of HIV Pharmacology – 2012, Barcelona Spain
Results:
Structural Models for Efavirenz & Atazanavir

\[ \tau \cdot (C1 \cdot f_{ub}) \]
Results:
Structural Models for Lamivudine & Tenofovir

CLt•C1
Visual Predictive Check: EFV and ATV

EFAVIREN Z BLOOD- MULTIPLE DOSE

EFAVIREN Z CVF- MULTIPLE DOSE

ATAZANAVIR BLOOD- MULTIPLE DOSE

ATAZANAVIR CVF- MULTIPLE DOSE

>90% observed data within CI
4/9 parameters with IIV >100%
3/4 associated with multiple dose

>90% observed data within CI
8/9 parameters with IIV >100%
Visual Predictive Check: 3TC and TFV

LAMIVUDINE BLOOD- MULTIPLE DOSE

75% observed data in CI

LAMIVUDINE CVF- MULTIPLE DOSE

85% observed data in CI

5/14 parameters with IIV >100%
All describe drug movement in genital tract

TENOFOVIR BLOOD- MULTIPLE DOSE

90% observed data in CI
9/14 parameters with IIV >100%
1 specific to multiple dosing

TENOFOVIR CVF- MULTIPLE DOSE
Results: Multiple Dose Model-Predicted AUC$_{0-\tau}$ Ratios

<table>
<thead>
<tr>
<th></th>
<th>CVF AUC$<em>{0-\tau}$: Blood AUC$</em>{0-\tau}$ Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFAVIRENZ</td>
<td>0.655% (0.0744, 1.25)</td>
</tr>
<tr>
<td>ATAZANAVIR</td>
<td>17.3% (7.19, 59.6)</td>
</tr>
<tr>
<td>LAMIVUDINE</td>
<td>281% (53.0, 997)</td>
</tr>
<tr>
<td>TENOFOVIR</td>
<td>79.8% (66.4, 779)</td>
</tr>
</tbody>
</table>

Median AUC$_{0-\tau}$ Ratio, Dumond et al, AIDS 2007

<table>
<thead>
<tr>
<th></th>
<th>CVF AUC$<em>{0-\tau}$: Blood fAUC$</em>{0-\tau}$ Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFAVIRENZ</td>
<td>65.5% (7.44, 125)</td>
</tr>
<tr>
<td>ATAZANAVIR</td>
<td>124% (51.4, 1240)</td>
</tr>
<tr>
<td>LAMIVUDINE</td>
<td>467% (87.8, 1660)</td>
</tr>
<tr>
<td>TENOFOVIR</td>
<td>85.8% (71.4, 838)</td>
</tr>
</tbody>
</table>

Presented at the 13th Int. Workshop on Clin. Pharmacology of HIV Pharmacology – 2012, Barcelona Spain
Limitations

• Small sample size, sparse sampling

• High variability
  – Inherent to ARVs
  – CVF more variable than BP
  – Drug-drug interactions
    • Efavirenz co-administered with protease inhibitors
    • Atazanavir + tenofovir
    • Boosted vs. unboosted atazanavir

• Covariates
  • Similar subjects except for body weight
Conclusions

• PK models can describe BP and CVF disposition for ARVs
• Differences between models for drugs with differing penetration
  – Unbound concentration vs. total concentration in the CVF
• Future directions
  – Incorporation of tissue concentrations
  – Ex vivo pharmacodynamics
    • Sterilize the genital tract
    • Protect mucosal surfaces
Acknowledgements

• Funding Sources:
  – NIH/NIAID
    • K23AI093156-JBD  K23AI077355-KBP
    • K23AI54980-ADMK  U01AI095031-ADMK
  – UNC Center for AIDS Research
    • 5P30AI050410-13- JBD, ADMK
  – NC TraCS Institute
    • UL1RR025747- JBD

• University at Buffalo-Affiliated Colleagues
  – Donald Mager, PharmD, PhD
  – Jurgen Bulitta, PhD
  – Olanre Okusanya, PharmD, MS