A physiologically-based population pharmacokinetic analysis to assess a lower efavirenz dose of 400 mg once daily in HIV-positive pregnant women

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Efavirenz...

- Is a cornerstone for treatment of HIV in parts of the world where HIV is most prevalent.

- Is the WHO recommended 1\textsuperscript{st}-line treatment option for HIV-infected individuals including pregnant women.

- Is administered as 600 mg once daily and available in several fixed-dose combinations.

- Reduce the risk of mother-to-child transmission from 15-40% to less than 1%.

Guidelines for antiretroviral therapy in low and middle-income countries. WHO. 2013
Dose reduction of efavirenz

• The ENCORE1 Study Group showed non-inferiority of 400 mg compared to 600 mg once daily in adults (phase III).

• Reduction of efavirenz-associated CNS side effects.

• Cost minimization
  I. A 33 percent dose reduction may translate into three-year cost savings of up to $336 M.
  II. More global access to HIV treatment.

• Ideally a ‘one dose fits all’ regimen.

• 400 mg in pregnancy not studied.
Physiological changes during pregnancy

- **Total body water**: ↑44%
- **Plasma volume**: ↑50%
- **Total body fat**: ↑35%
- **Albumin conc.**: ↓31%
- **GFR**: ↑37%
- **gastric pH**: ↑
- **gastric emptying and intestinal motility**: ↓
- **CYP2D6 activity**: ↑48%
- **CYP3A4 activity**: ↑38%
- **CYP2B6 activity**: ??

3rd trimester

Efavirenz PK-PD relation well-established

- Concentrations (~C12) above 4.0 mg/L are associated with CNS-side effects.
- Concentration (~C12) lower than 0.7-1.0 mg/L are associated with treatment failure.
- Small PK studies in pregnancy with 600 mg efavirenz once daily indicate lower exposure during pregnancy.

Knowledge gap

Based on these PK studies with 600 mg and knowledge of pregnancy-related physiology, a lower exposure during pregnancy can be expected.

It is unknown whether the 400mg dose is appropriate for pregnant women.

We aim:
1.) To develop a mechanistic population pharmacokinetic model to describe the pharmacokinetics of efavirenz in pregnant and non-pregnant women
2.) To simulate efavirenz exposure using 400mg once daily during pregnancy
Approach

- Review of literature
- Plan of analysis
- Gather and compile PK data on efavirenz
- Develop popPK model
- Investigate exposure with an EFV 400 mg dose
Methods: efavirenz protein binding

• >99% protein binding (mainly albumin)

• Relation between plasma albumin concentration and time of gestation described by Abduljalil et al. 2012

• Relation free fraction efavirenz and albumin concentration described by Avery et al. 2013

• Efavirenz dissociation constant ($K_{diss}$) = 2.05 µM

\[ f_u = \frac{K_{diss}}{K_{diss} + [P]} \]
Methods: mechanistic input II

• Female total liver blood flow = 109 L/h

• Conflicting data provide no evidence for pregnancy-induced changes in total liver blood flow

\[ Q_{\text{hep,plasma}} = (1 - H_t) \times Q_{\text{hep}} \]

• Relation between hematocrit and time of gestation described by Abduljalil et al. 2012

• To account for the relation between hepatic systemic and first-pass metabolism, a well-stirred liver model was implemented.

\[ CL_{\text{hep}} = \frac{Q_{\text{hep,plasma}} \cdot CL_{\text{int,hep}} \cdot f_u}{Q_{\text{hep,plasma}} + CL_{\text{int,hep}} \cdot f_u} \]
Methods: general

• No evidence for *a priori* pregnancy-induced alterations in CYP2B6 expression

• Pregnancy-induced PK alterations were incorporated as time-dependent effects

• Allometric scaling of flow parameters (^0.75) and volumes (^1) to non-pregnant total body weight.

• Pregnancy was tested as covariate on all PK parameters. Effects retained when $\Delta$OFV$\geq$3.84, clinically relevant (>10% change), and physiologically plausible.

• Patients using potentially interacting concomitant medicines (e.g. rifampicin or isoniazid) were excluded.

• NONMEM v7.3 & R

Methods: pharmacogenetics

We assumed three subpopulations (phenotypes) based on known CYP2B6 pharmacogenetics:
1. Poor metabolizers (PM)
2. Intermediate metabolizers (IM)
3. Extensive metabolizers (EM)

$\text{MIXTURE subroutine:}$
Subjects with missing genotype (84%) were assigned to the mixture (subpopulation) with the highest individual probability

Results: datasets

- Published and unpublished data from 9 studies were gathered and compiled.

- Largest EFV PK dataset in women to date.

<table>
<thead>
<tr>
<th>Study</th>
<th>HIV+♀</th>
<th>Population</th>
<th>Sampling</th>
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<tbody>
<tr>
<td>1</td>
<td>129</td>
<td>International</td>
<td>Sparse</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>100% Asian</td>
<td>Intensive</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>100% Caucasian</td>
<td>Intensive</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>100% Black</td>
<td>Intensive</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>Mainly Caucasian</td>
<td>Sparse</td>
</tr>
<tr>
<td>6</td>
<td>25 (pregnant)</td>
<td>84% Thai</td>
<td>Intensive</td>
</tr>
<tr>
<td>7</td>
<td>8 (pregnant)</td>
<td>100% Black</td>
<td>Intensive</td>
</tr>
<tr>
<td>8</td>
<td>42 (pregnant)</td>
<td>100% Black</td>
<td>Sparse</td>
</tr>
<tr>
<td>9</td>
<td>11 (pregnant)</td>
<td>100% Black</td>
<td>Intensive</td>
</tr>
<tr>
<td>Total</td>
<td>249</td>
<td></td>
<td>1697</td>
</tr>
</tbody>
</table>

Demographics

- Median total non-pregnant BW (range): 59 (37-125) kg
- Median number of occasions (range): 2 (1-7)
- Pregnant women: 86/249 (35%)
- Median gestational age (range): 35 (25-39) weeks
- Phenotype available: 41 (16%)
  - SM: 8
  - IM: 22
  - EM: 11

Results: pharmacogenetics

• Stochastic simulation and estimation showed that the phenotypic population frequencies could not be identified.

• Population frequencies were fixed based data from our population combined with known prevalence of the CYP2B6 genotypes.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Population frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow</td>
<td>12</td>
</tr>
<tr>
<td>Intermediate</td>
<td>36</td>
</tr>
<tr>
<td>Extensive</td>
<td>52</td>
</tr>
</tbody>
</table>

Results: final PK model

K12 = K23 = K34 = K45 = K_{transit}
K50 = Q_{Hep} \times EH / V_{Hep}
K56 = Q_{Hep} \times (1-EH) / V_{Hep}
K65 = Q_{Hep} / V_{d,central}
K67 = Q / V_{d,central}
K76 = Q / V_{d,peri}
E_{Hep} = (CL_{INT} \times F_U) / (Q_{Hep} + (CL_{INT} \times F_U))

Parameter | Estimate | RSE |
--- | --- | --- |
K_{transit} (h^{-1}) | 1.65 | 8.4% |
CL_{INT} SM (L/h) | 1320 | 7.5% |
CL_{INT} IM (L/h) | 3070 | 7.8% |
CL_{INT} EM (L/h) | 4410 | 6% |
V_d central (L) | 117 | 7.9% |
V_d peripheral (L) | 393 | 5.6% |
Q (L/h) | 34.9 | 7.5% |
IIV CL_{INT} (%) | 31.9 | 18.4% |
IIV K_{tr} (%) | 52.6 | 19.5% |
IOV F (%) | 27.4 | 6.3% |
Prop error (%) | 17.5 | 2.1% |

Pregnancy not identified as covariate
Results: visual predictive check

Non-Pregnant

Pregnant
Results: simulated total plasma C12

EFV C12 after 600 mg once daily in pregnant and non-pregnant women by phenotype

EFV C12 after 400 mg once daily in pregnant and non-pregnant women by phenotype

Simulated 500x/condition
Total plasma concentration versus the unbound plasma concentration

Distribution

Effects

Elimination

Measured total concentration

F

Bmax

Kd

Alb.
The lower threshold for antiviral effect of 1.0 mg/L was corrected for the fraction unbound predicted in non-pregnant women.
Conclusions

• Pregnancy decreases total efavirenz concentrations, however:
  • No effect of pregnancy on other PK parameters → unbound concentration unchanged

• Although this finding warrants *in vivo* confirmation, it indicates that a dose reduction to 400mg may be feasible in pregnancy.

• This would help to make substantial cost-savings that are especially important in countries that need more access to HIV-treatment.
Discussion

• Largest dataset of efavirenz PK data from pregnant and non-pregnant HIV-infected women.

• The mechanistic approach based on physiological data enabled us to account for pregnancy-induced alterations in pharmacokinetics a priori.

• No data on actual free concentrations, albumin concentrations or variability in unbound fraction were available and therefore assumptions on protein binding had to be made.

• Simulation results therefore did not account for variability in protein binding.

• This approach allows for extrapolation based on mechanism and physiology.

• The findings from this analysis may have been missed with standard empirical modeling.
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