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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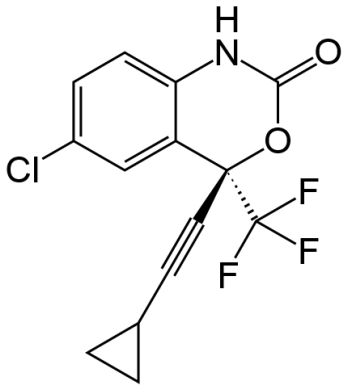
Efavirenz…



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

• Is the WHO recommended 1st-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
"WHO Model List of Essential Medicines". WHO. October 2015.
Fact sheet 2015. UNAIDS. October 2015.

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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.

Lancet Infect Dis. 2015 Jul;15(7):793-802.
Lancet. 2014 Apr 26;383(9927):1474-82.
J Acquir Immune Defic Syndr. 2015 Aug 1;69(4):422-9.
CHAI - Second Conference on Antiretroviral Drug Optimization, April 2012

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Physiological changes during pregnancy

gastric pH
↑

gastric emptying and intestinal motility
↓

Total body water
↑**44%**

Plasma volume
↑**50%**

3rd trimester

CYP2D6 activity
↑**48%**

CYP3A4 activity
↑**38%**

Total body fat
↑**35%**

CYP2B6 activity
??

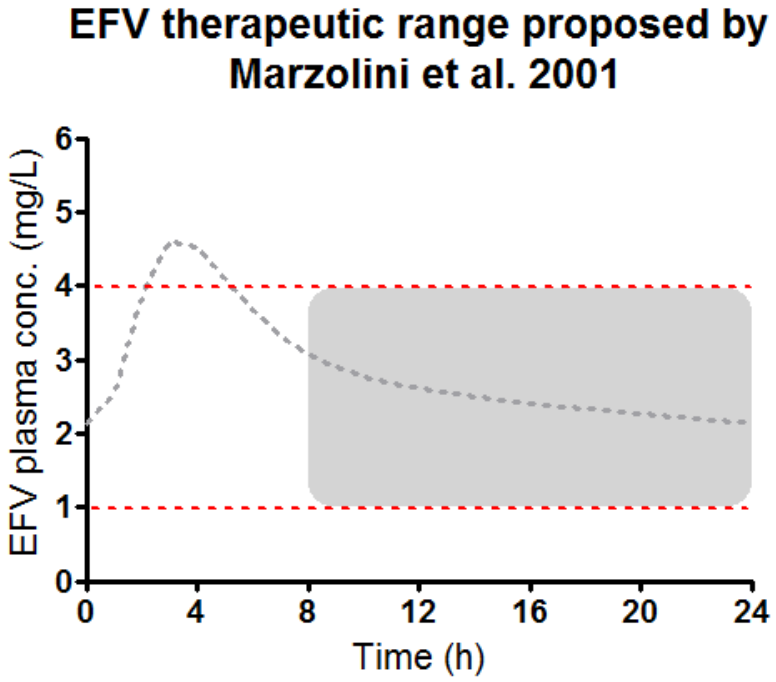
Albumin conc.
↓ **31%**

GFR
↑**37%**

Clin Pharmacokinet. 2012 Jun 1;51(6):365-96

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.



AIDS. 2001 Jan 5;15(1):71-5.
Int J Antimicrob Agents. 2016 May 4. [epub ahead of print]
Clin Pharmacol Ther. 2015 Mar;97(3):298-306.
J Acquir Immune Defic Syndr. 2012 Mar 1;59(3):245-52.
J Infect Dis. 2015 Jan 15;211(2):197-205.

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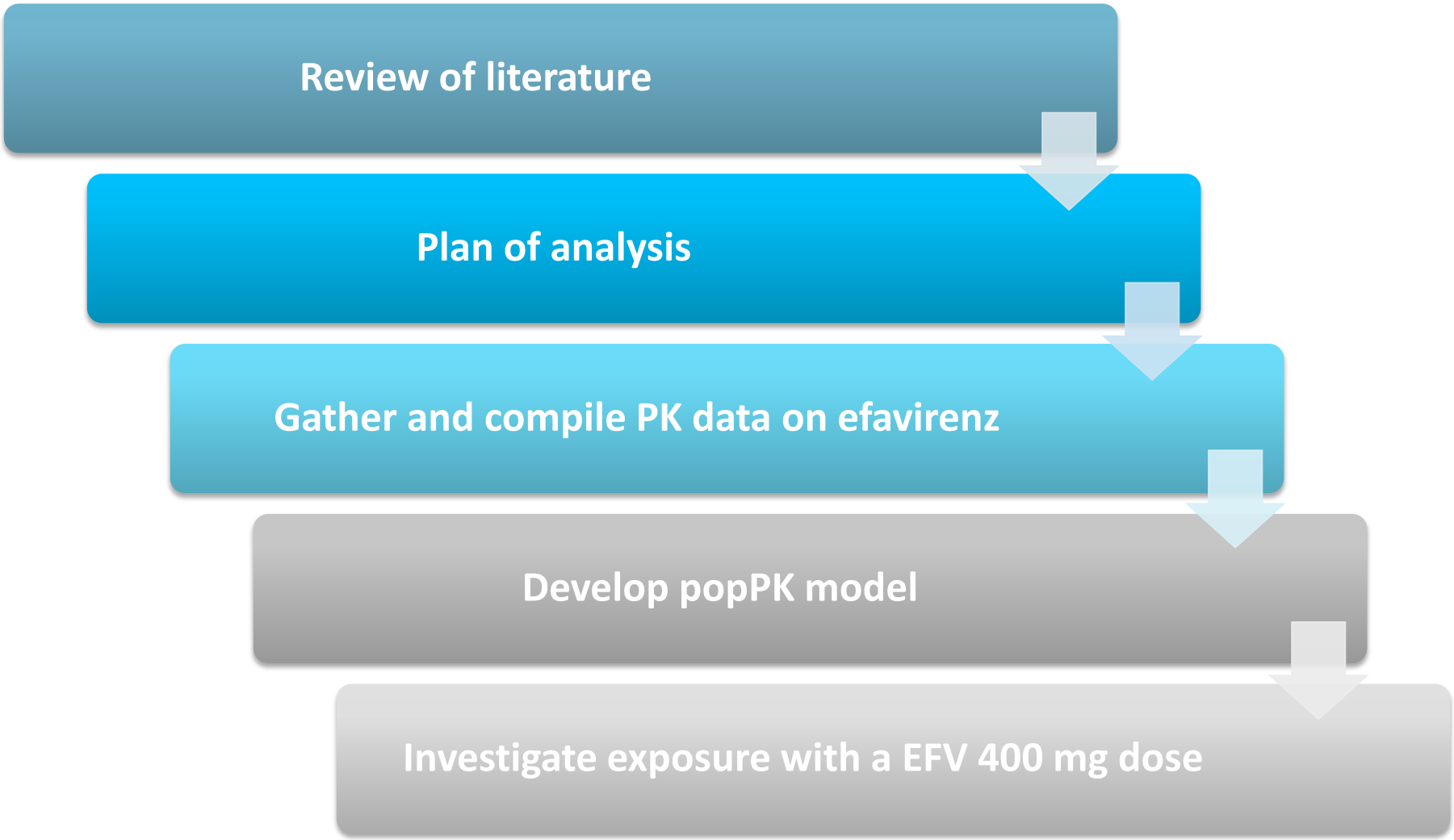
Knowledge gap

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

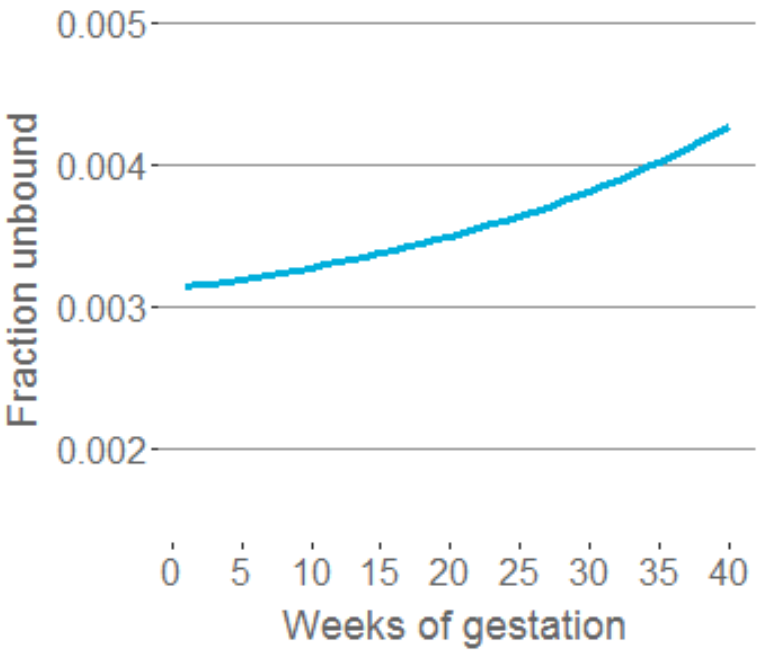
Approach


Review of literature
Plan of analysis
Gather and compile PK data on efavirenz
Develop popPK model
Investigate exposure with a 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

$$f_u = K_{diss}/(K_{diss} + [P])$$



Clin Pharmacokinet. 2012 Jun 1;51(6):365-96
Clin Pharmacol Ther. 2011 Jul;90(1):151-6
Antimicrob Agents Chemother. 2013 Mar;57(3):1409-14

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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

$$Q_{hep,plasma} = (1 - H_t) * Q_{hep}$$

- 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.

$$CL_{hep} = \frac{Q_{hep,plasma} \, CL_{int,hep} \, f_u}{Q_{hep,plasma} + CL_{int,hep} \cdot f_u}$$

Clin Pharmacokinet. 2012 Jun 1;51(6):365-96
Arch Gynecol Obstet. 2002 Jan;266(1):25-9

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 ΔOFV≥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

Clin Pharmacokinet. 2012 Jun 1;51(6):365-96
Br J Clin Pharmacol. 2005 Feb;59(2):189-98.
PAGE 2011. Poster# I-31.

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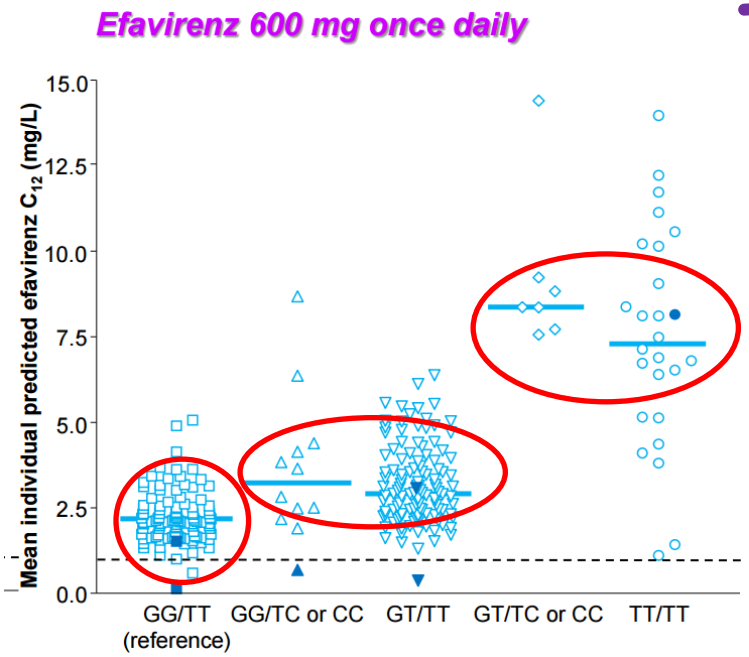
Methods: pharmacogenetics

$$CL_{hep} = \frac{Q_{hep,plasma} \cdot CL_{int,hep} \cdot f_u}{Q_{hep,plasma} + CL_{int,hep} \cdot f_u}$$



We assumed three subpopulations (phenotypes) based on known CYP2B6 pharmacogenetics:

1. Poor metabolizers (PM)
2. Intermediate metabolizers (IM)
3. Extensive metabolizers (EM)

$MIXTURE subroutine:

Subjects with missing genotype (84%) were assigned to the mixture (subpopulation) with the highest individual probability

Dickinson et al. 15th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy. May 2014
Clin Pharmacol Ther. 2015 Mar;97(3):298-306.

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Results: datasets

- Published and unpublished data from 9 studies were gathered and compiled.
- Largest EFV PK dataset in women to date.

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

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

Kappelhoff et al. 2005, Boyd et al. 2003, Aarnoutse et al. 2003, Semvua et al. 2013, Kappelhoff et al. 2005, Cressey et al. 2012, IMPAACT network (not published), Dooley et al. 2014, PANNA network (not published)

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.

Phenotype	Population frequency (%)
Slow	12
Intermediate	36
Extensive	52

Clin Pharmacol Ther. 2007;81(4):557-66.
Br J Clin Pharmacol. 2012;74(6):1005-12.

Results: final PK model

$K12=K23=K34=K45=K_{transit}$

$K50=Q_{Hep}*EH/V_{Hep}$

$K56=Q_{Hep}*(1-EH)/V_{Hep}$

$K65=Q_{Hep}/V_{d,central}$

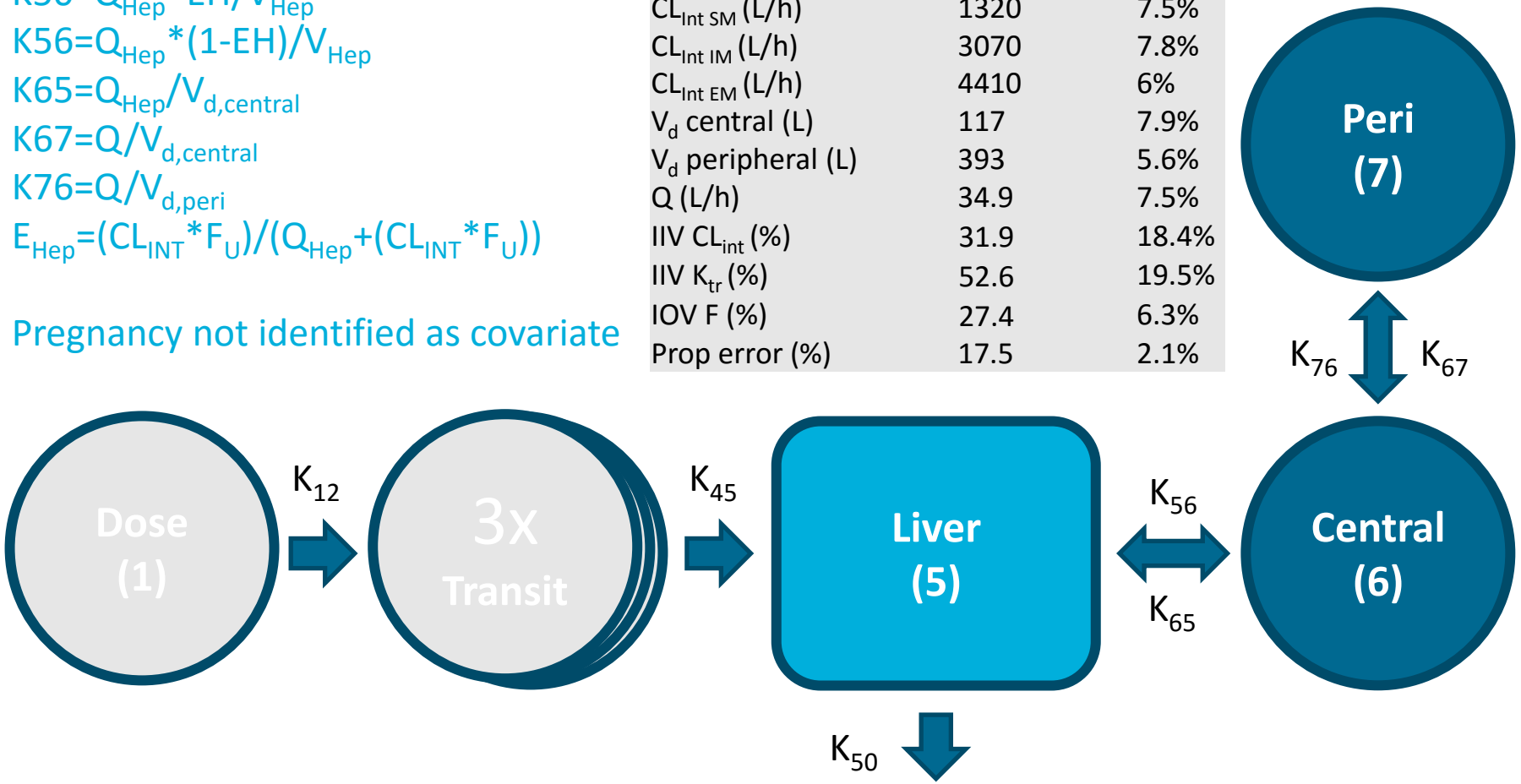
$K67=Q/V_{d,central}$

$K76=Q/V_{d,peri}$

$E_{Hep}=(CL_{INT}*F_U)/(Q_{Hep}+(CL_{INT}*F_U))$

Pregnancy not identified as covariate

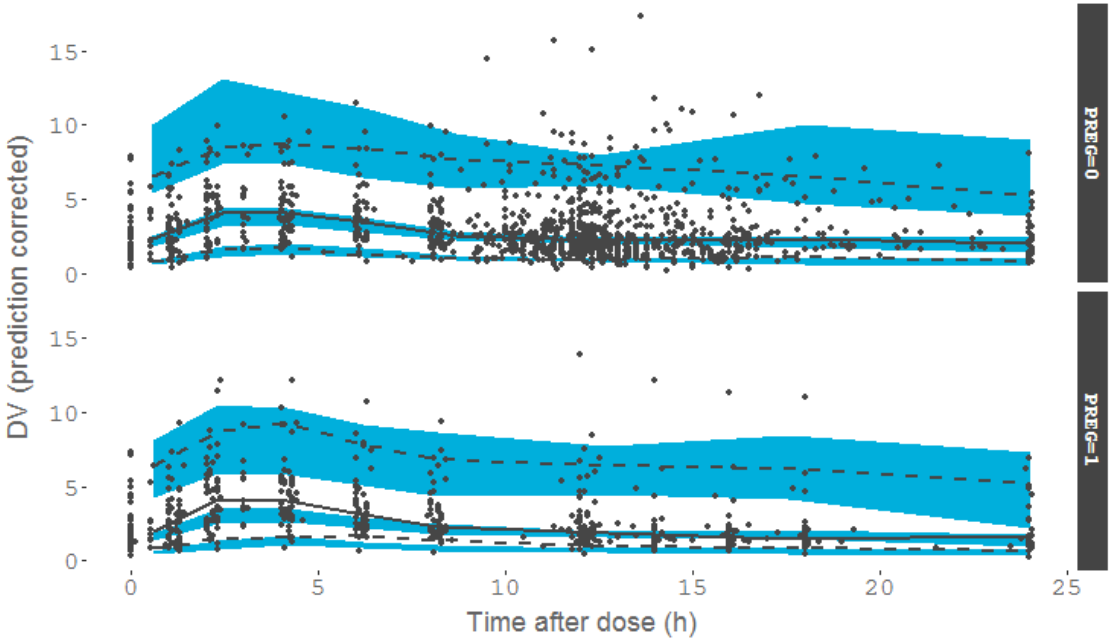
Parameter	Estimate	RSE
$K_{transit}$ (h^{-1})	1.65	8.4%
$CL_{Int\ SM}$ (L/h)	1320	7.5%
$CL_{Int\ IM}$ (L/h)	3070	7.8%
$CL_{Int\ EM}$ (L/h)	4410	6%
V_d central (L)	117	7.9%
V_d peripheral (L)	393	5.6%
Q (L/h)	34.9	7.5%
IIV CL_{int} (%)	31.9	18.4%
IIV K_{tr} (%)	52.6	19.5%
IOV F (%)	27.4	6.3%
Prop error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



Results: visual predictive check

Non- Pregnant

Pregnant



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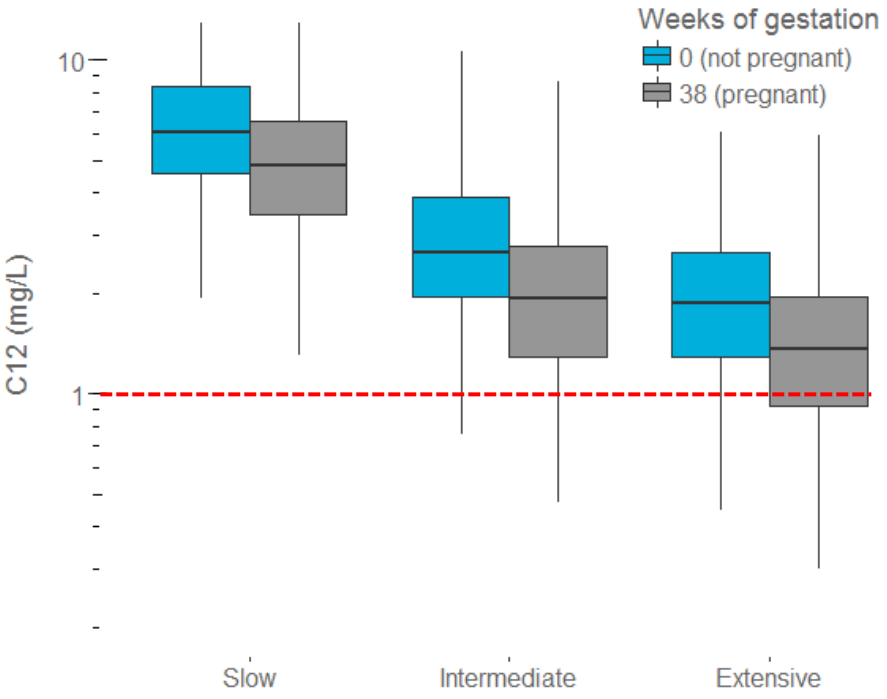
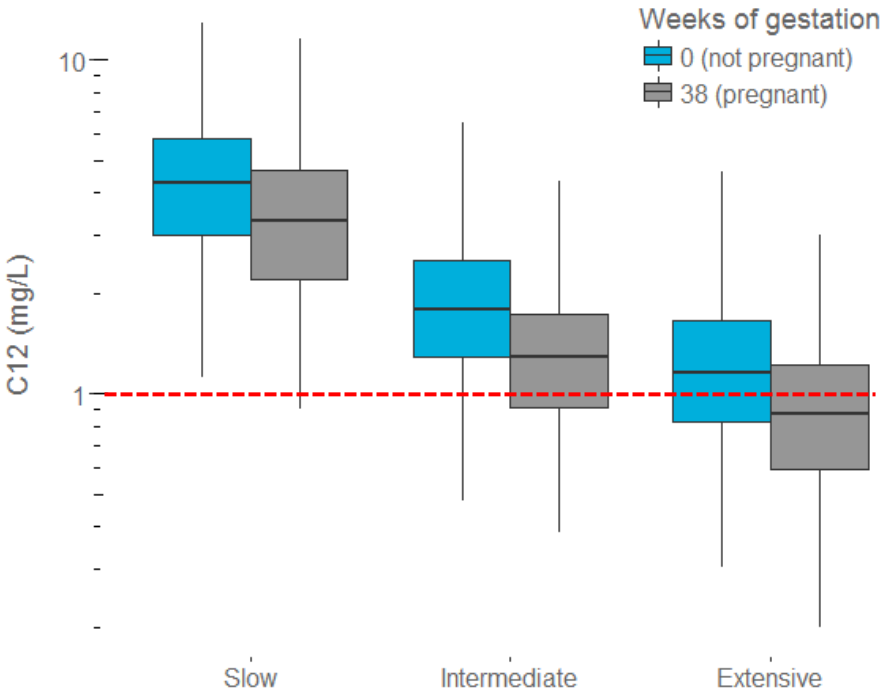
Results: simulated total plasma C12

EFV C_{12} after **600 mg** once daily in pregnant and non-pregnant women by phenotype



EFV C_{12} after 4**00 mg** once daily in pregnant and non-pregnant women by phenotype



Simulated 500x/condition

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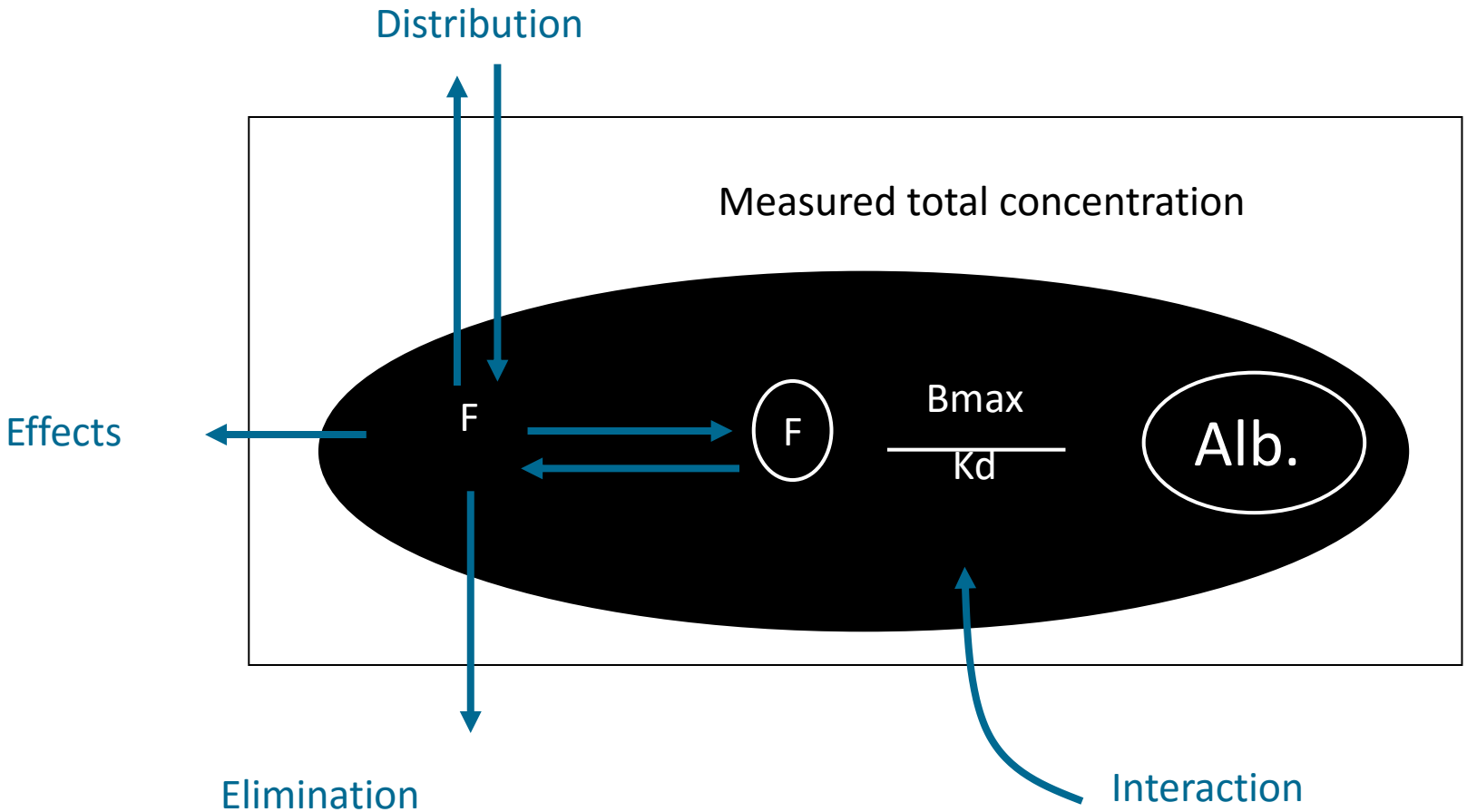
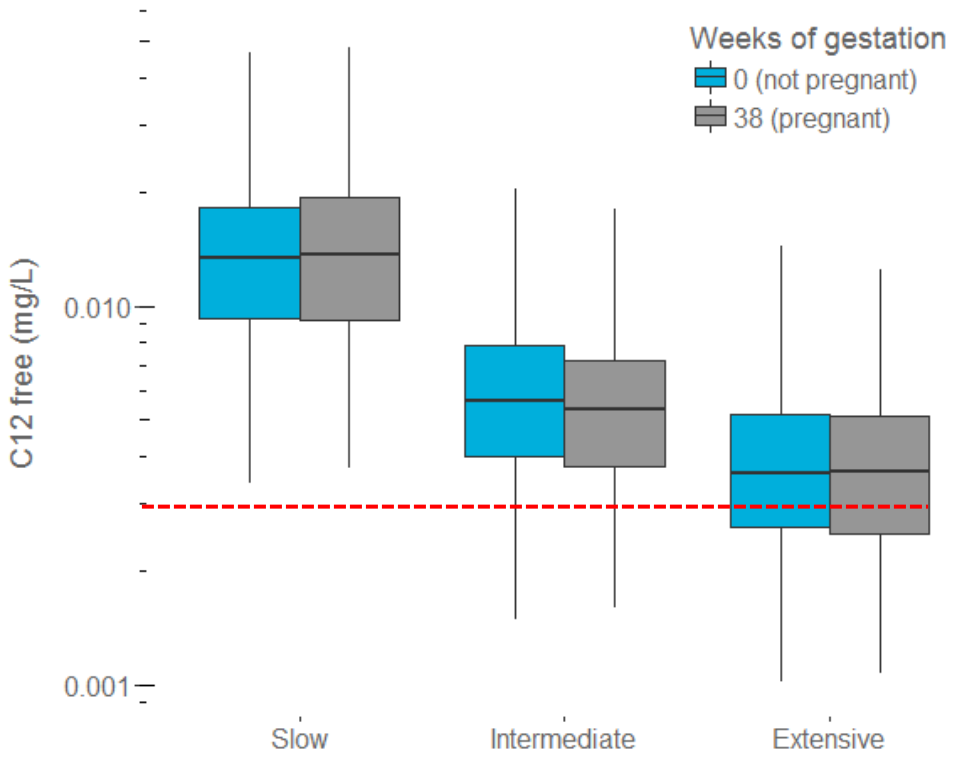
Total plasma concentration versus the unbound plasma concentration



Results: simulated free C12

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

EFV $C_{12,\ free}$ after **400 mg** once daily in pregnant and non-pregnant women by phenotype



Simulated 500x/condition

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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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