Challenges of Pharmacokinetics in Pregnancy !

… and the ways that modelling can help us address them.

Robert R Bies Pharm.D. PhD FISoP FACCP
Professor, Dept. of Pharmaceutical Sciences
School of Pharmacy, University at Buffalo

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Current Need for Clinical Studies in Pregnancy

- Pregnant women are ***rarely included*** in clinical trials for numerous practical, legal, and ethical reasons.
- Most drugs are thus prescribed to pregnant women ***off-label***, with dosage typically based on the recommended dose for men or nonpregnant women, adjusted by clinician's judgment.
- Drug exposure during early pregnancy often ***raises concerns about potential teratogenic effects***. And fetal drug exposure in later trimesters may also result in complications.
- **There is a need to make the pharmacokinetic studies in pregnancy as efficient as possible**

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Ke AB, Greupink R, Abduljalil K. CPT Pharmacometrics Syst Pharmacol. 2018 Feb;7(2):103-110.

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Agenda

- What happens during pregnancy that can change the pharmacokinetics (PK) of drugs?
- How do the PK models work?
- How can modelling improve PK studies in pregnancy (e.g., cabotegravir)?
- What about monoclonals in pregnancy?

Physiologic Change During Pregnancy

Parameter	Direction of Change	% change in first trimester T_1	% change in second trimester T_2	% change in third trimester T_3
Total body weight (kg)	↑	6%	16%	22%
Total fat mass (kg0	↑	11%	16%	32%
Total Body water (L)	↑	11%	27%	41%
Cardiac output (L))	↑	18%	28%	33%
Plasma volume (L)	↑	7%	42%	50%
Hematocrit (%)	↓	3%	8%	14%
Albumin (g/L)	↓	5%	16%	31%
a1-AGP (g/L)	↓	1%	22%	19%
Glomerular filtration rate (mL/min)	↑	19%	37%	40%
Effective plasma flow (L/h)	↑	38%	48%	31%
Creatine clearance (nL/min)	↑	28%	58%	26%
CYP P450 3A*	↑	22%	30%	18%
CYP P450 1A2*	↓	31%	50%	64%
CYP P450 2D6*	↑	19%	31%	37%
Hepatic blood flow (L/h)	↔	NA	NA	NA

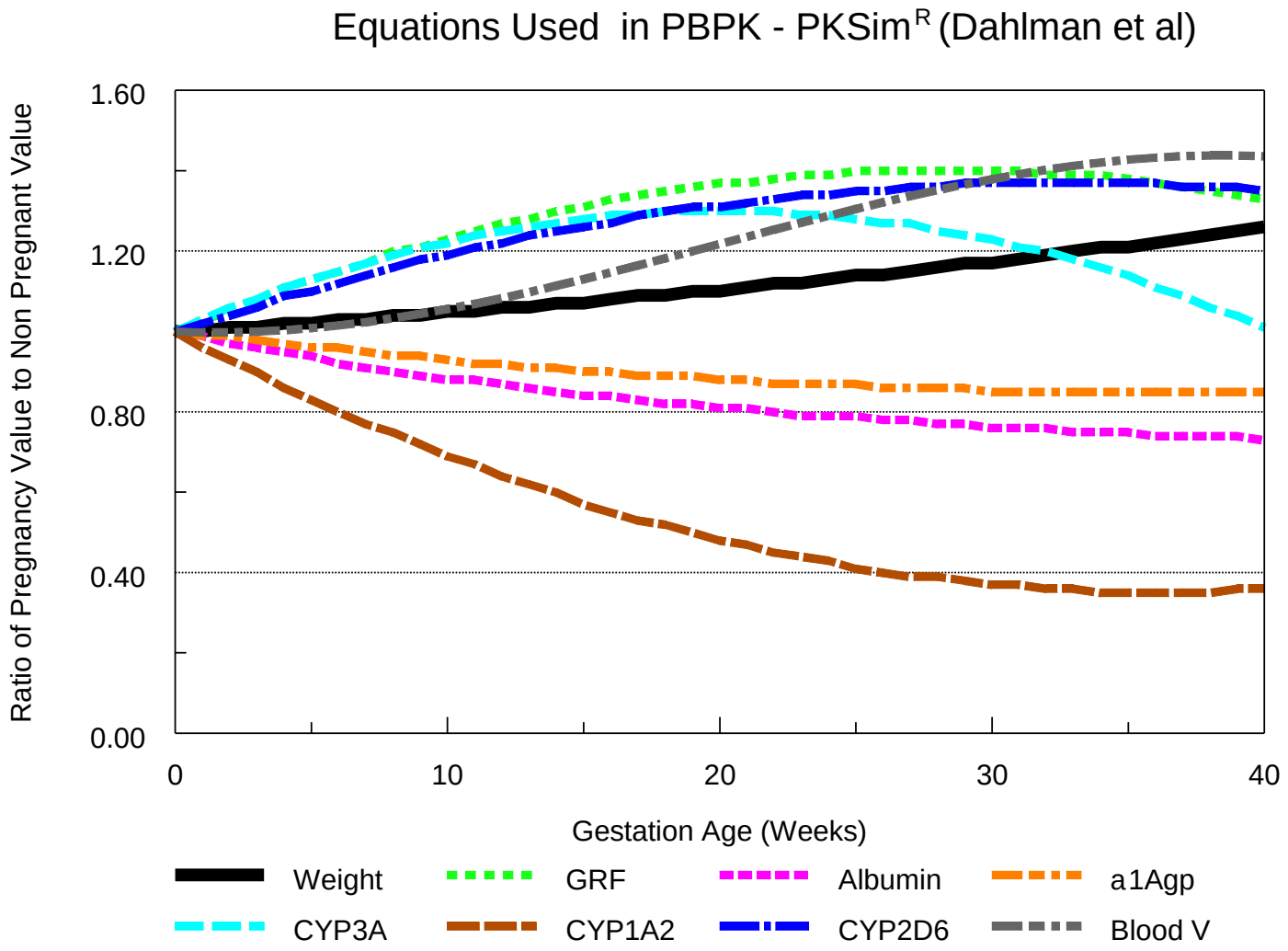
Values increasing more than 25% in red while those decreasing by more than 25% are in in blue

*For CYP 450 activity changes values estimated at 10, 20 and 34 Wks GA

Ke Ann Review Pharmacol Toxicol 2013
Abdajalil Clin PK 2012 (for enzyme activity)

- Plasma flow and clearance is altered throughout pregnancy
- Volumes of distribution can be affected dramatically in the 3rd trimester
- Metabolizing enzymes can increase (2D6), decrease (1A2) or increase then decrease (3A4)

Model Parameter Changes in Pregnancy



- Physiologic changes during pregnancy are occurring **<u>continuously, not discretely</u>**, throughout the duration of gestation

Figure courtesy of Professor Edmund Capparelli, University of California San Diego

Important PK Parameters in Pregnancy Model

- **Clearance (CL)** – Defines the total daily dose requirements
- **Volume of distribution (V)** – Defines the Cmax (single dose) and peak/trough fluctuations
- **Fraction Unbound in Plasma (fu)** – Free concentration (fu*Cp) responsible for drug action
- **Cord / Maternal blood ratio** – Important to estimate fetal drug exposure
- **Bioavailability (F)** – Needed for interpretation of CL (CL/F) and V (V/F) after PO or IM administration
- **Linear PK vs Non-linear PK** – Do changes in dose lead to proportional changes in drug concentrations
- **Absorption Rate (Ka)** – Important for IM administration of long acting or slow-release agents BPG
- Half-life ($t_{1/2}$) – Defines time to re-dose (dose interval).
  - Derived from CL and V as $t_{1/2}$=0.693*V/CL

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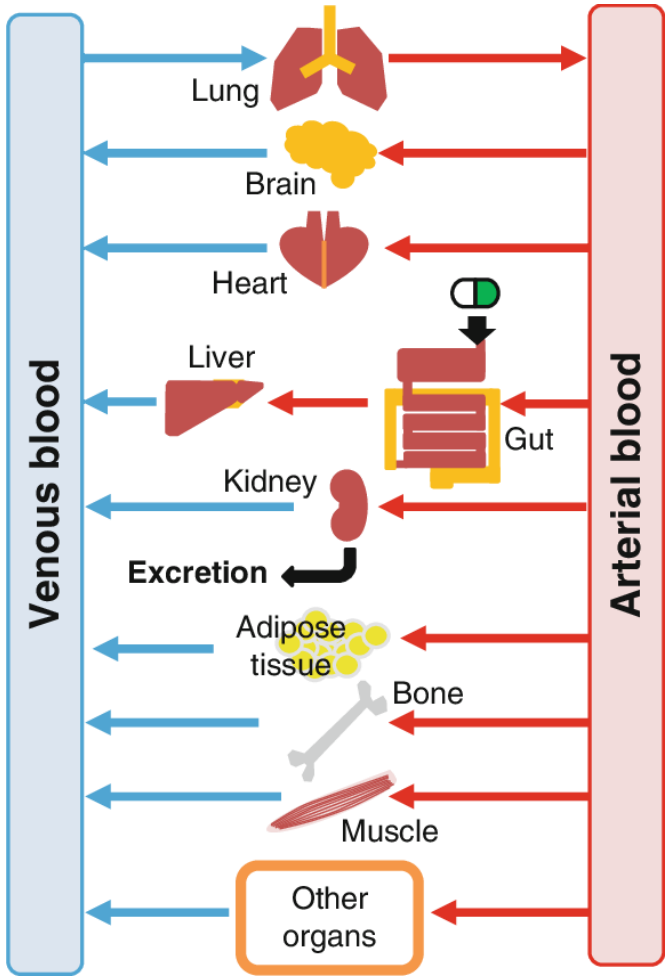
Why PK/PD Modeling and Simulation – (Pharmacometrics)

- Broadly Includes mathematical models of biology, pharmacokinetic, pharmacodynamics, pharmacology, disease, and study design to describe and quantify interactions between drugs and patients
- Leverages existing knowledge (in silico, in vitro, pre-clinical and non-pregnant adults) in a quantitative manner
- Integrate Models of Drug Characteristics with:
  - Size and Body Composition
  - Population specific activity for Drug Metabolism, Elimination and Transport
  - Disease Characteristics in Population
  - Disease progression / dynamics
- Iterative approach – new data allows updating and improvement PK/PD/DZ models

Physiologically-Based Pharmacokinetic (PBPK) Models

- Mechanistic model of drug behavior
- Incorporates information on:
  - Anatomy
  - Physiology
  - Physicochemical properties
  - In vitro performance
  - In vivo performance
- Allows for a priori predictions of drug concentration over time in tissues and systemic circulation



Shin, Hyun Kil & Kang, Young-Mook & No, Kyoung Tai. (2016). Predicting ADME Properties of Chemicals. 10.1007/978-94-007-6169-8_59-1.

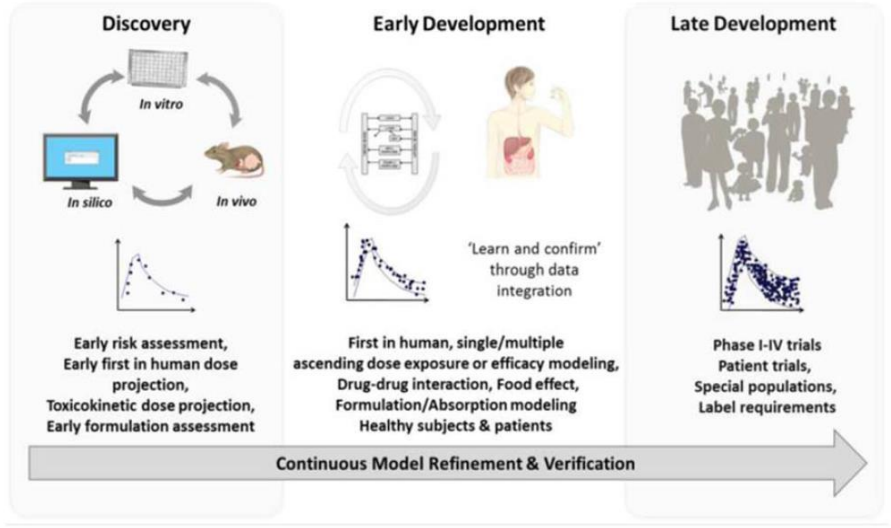
Physiologically-Based Pharmacokinetic (PBPK) Modeling

Provides a platform that reflects the constraints of physiological and anatomical characteristics.

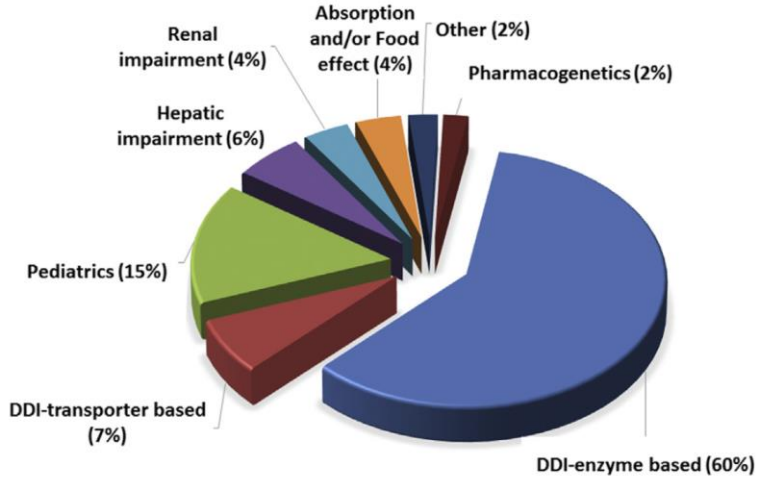
It can be used to test new compounds on the basis of their specific physiochemical properties

PBPK Modeling in New Drug Development

- Drug Development[1,2]
  - Candidate selection
  - Formulation development
  - Clinical study design
  - Dose selection
- Regulatory Decisions[3,4]
  - Potential drug-drug interactions
  - PK in special patient populations
  - Impact of disease states



Jones et al. (2015)



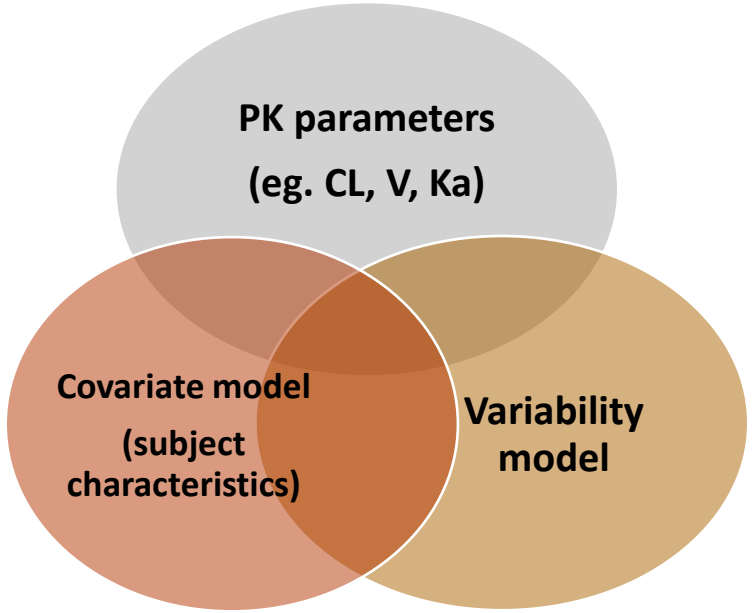
Grimstein et al. (2019)

1. Jones HM, Chen Y, Gibson C, et al. Physiologically based pharmacokinetic modeling in drug discovery and development: a pharmaceutical industry perspective. *Clin Pharmacol Ther*. 2015;97(3):247-262. doi:10.1002/cpt.37
2. Zhao P, Zhang L, Grillo JA, et al. Applications of physiologically based pharmacokinetic (PBPK) modeling and simulation during regulatory review. *Clin Pharmacol Ther.* 2011;89(2): 259-267.
3. Grimstein M, Yang Y, Zhang X, et al. Physiologically Based Pharmacokinetic Modeling in Regulatory Science: An Update From the U.S. Food and Drug Administration's Office of Clinical Pharmacology. *J Pharm Sci.* 2019;108(1): 21-25.
4. Development of Best Practices in Physiologically Based Pharmacokinetic Modeling to Support Clinical Pharmacology Regulatory Decision-Making, November 18, 2019. *U.S. Food & Drug Administration*. January, 15, 2020. Available at: https://www.fda.gov/drugs/news-events-human-drugs/development-best-practices-physiologically-based-pharmacokinetic-modeling-support-clinical. Accessed September 21, 2020.

Population PK Modeling

- Data driven (fitted to data to estimate PK parameters, variabilities, covariate effects)
- Often a nonlinear mixed effects model – fixed effects (e.g. PK parameters, covariate model) and random effects (variability model)

Provides a typical concentration time curve in a population, based on data from participants



- Explains variability predicted by subject characteristics (covariates)
- E.g., weight, age, genotype

- Variability around the PK parameters (P) and observations (O)
- Types: between-subject (P), between-occasion (P), residual (O)

Different PK Modeling Approaches – Study Design and Complexity

- Non-Compartmental (NC)
  - Intensive individual assessments
- Compartmental - Population PK (PopPK)
  - Intensive or sparse group assessments – combined study results
- Physiologic Based Pharmacokinetic Models (PBPK)
  - Predictions compared from prior models compared to observed results

Models	NC- Models	PopPK Models	PBPK Models
Generate Mean PK Parameter Values From Experimental Data	Excellent	Very Good	Poor
Estimate PK Parameter Variability	Poor	Excellent	Poor
Simulation – of new dosing regimens, study design	Poor	Very Good	Good
Incorporation existing PK from literature or in vitro studies (drug-drug interactions, new populations etc.)	Poor	Good	Very Good

When do we use these models in clinical trials?

- **PBPK modeling:**
  - ***To explore patient, formulation and molecule specific characteristics and the a priori predicted impact on the concentration time profile***

Provides a mechanistic basis for a priori exploration of anticipated/expected changes in disposition during pregnancy
Allows for prediction of concentrations in biophases not easily sampled (fetus, CNS, other target tissues)

- **Population pharmacokinetic modeling** :
  - ***To ask "what-if" questions in clinical study design with consideration of uncertainty, between subject variability, between occasion variability***

E.g. using Monte Carlo simulation strategies
Can be a priori calibrated using PBPK model prediction, and updated with observed concentration measures

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PBPK Modeling Example

PBPK Pregnancy Modules Available

- Simcyp
- PK-Sim
- Gastroplus

A Physiologically Based Pharmacokinetic Model to Predict Disposition of CYP2D6 and CYP1A2 Metabolized Drugs in Pregnant Women[S]

Alice Ban Ke, Srikanth C. Nallani, Ping Zhao, Amin Rostami-Hodjegan, Nina Isoherranen, and Jashvant D. Unadkat

Physiologically Based Pharmacokinetic Modeling of Renally Cleared Drugs in Pregnant Women

André Dallmann [1], Ibrahim Ince [2], Juri Solodenko [3], Michaela Meyer [4], Stefan Willmann [4], Thomas Eissing [5], Georg Hempel [1]

A Simplified PBPK Modeling Approach for Prediction of Pharmacokinetics of Four Primarily Renally Excreted and CYP3A Metabolized Compounds During Pregnancy

Binfeng Xia, Tycho Heimbach, Rakesh Gollen, Charvi Nanavati, and Handan He

The tested drugs covered a wide spectrum of clearance mechanisms, including several major isoforms of CYP enzymes (CYP3A4, 2D6, 1A2, 2B6, 2C9, and 2C19)and renal clearance.

Ke AB, Nallani SC, Zhao P, et al. Drug Metab Dispos. 2013 Apr;41(4):801-13. doi: 10.1124/dmd.112.050161.
Dallmann A, Ince I, Solodenko J, et al. Clin Pharmacokinet. 2017 Dec;56(12):1525-1541.
Xia B, Heimbach T, Gollen R, et al. AAPS J. 2013 Oct;15(4):1012-24.
Ke AB, Greupink R, Abduljalil K. CPT Pharmacometrics Syst Pharmacol. 2018 Feb;7(2):103-110.

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Parameter Changes: Published PBPK Models of PK in Pregnancy

Drug name	Main changes (except physiological factors)
Dolutegravir[1]	1. Increased concentration of UGT1A1 and CYP3A4 2. Increased albumin unbound fraction
Raltegravir[1]	1. Increased albumin unbound fraction
Metronidazole[2]	1. Increased CYP3A4 and CYP2D6 activity 2. Increased intrinsic hepatic clearance 3. Increased absolute renal clearance 4. Increased protein unbound fraction
Acetaminophen[3]	1. Increased UGT1A1 and CYP2E1 activity
Risperidone[4]	1. Increased CYP2D6 and CYP3A4 activity 2. Increased renal clearance
Labetalol[5]	1. Increased UGT1A1 activity 2. Decreased CYP2C9 activity

1. Liu XI, Momper JD, Rakhmanina NY et al. Clin Pharmacokinet. 2020 Nov;59(11):1433-1450.
2. Mian P, van den Anker JN, van Calsteren K, Annaert P et al. Clin Pharmacokinet. 2020 Jan; 59(1):97-110.
3. Mian P, van den Anker JN, van Calsteren K et al. Clin Pharmacokinet. 2020 Jan;59(1):97-110.
4. Mahdy WYB, Yamamoto K, Ito T, Fujiwara N et al. Clin Transl Sci. 2023 Apr;16(4):618-630.
5. Song Y, Wang W, Liu X et al. Pharm Res. 2023 Jul;40(7):1765-1775.

Models Implementation Example Cabotegravir

- **Objectives:**
  - **To predict concentration of Cabotegravir (CAB) after long-acting injection (LAI) in nonpregnant cisgender women during their 2nd and 3rd trimesters of pregnancy**
  - This model is adapted from a published maternal-fetal PBPK model by Dallmann et. al. which focuses on Dolutegravir and Raltegravir
  - We obtained drug specific parameters for CAB from the published literature and used published clinical PK data for CAB (oral and IM) in nonpregnant, cisgender women to validate the nonpregnant PBPK model
  - We then extended the validated model to pregnancy and the PBPK model was utilized to simulate dose sequences in nonpregnant and pregnant individuals, including a loading dose paradigm, with monthly dosing up to 6 months

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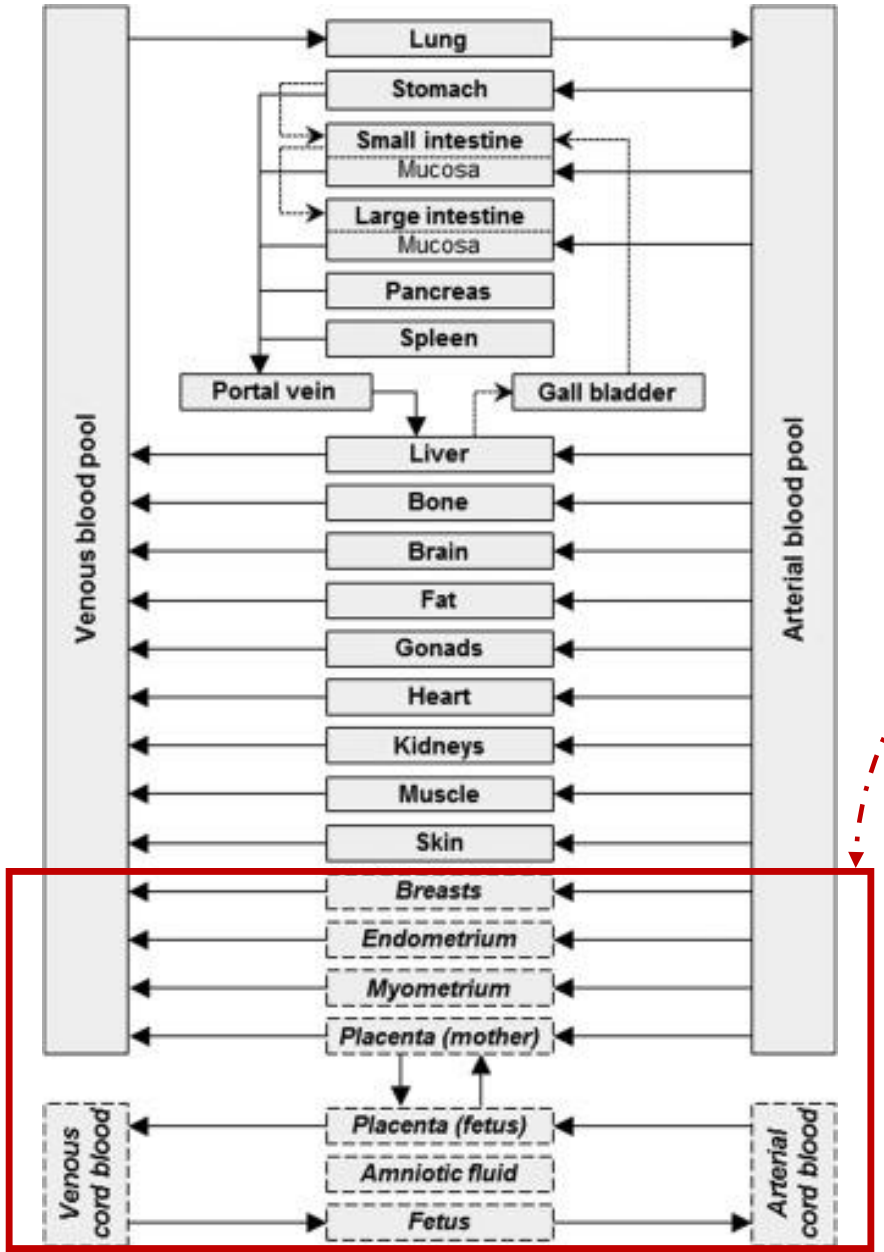
Yu Y, et al. PBPK Model Prediction of Long-acting CAB and RPV Concentrations in Pregnancy [CROI 2023 Abstract 782].

Pregnancy Model Structure Example



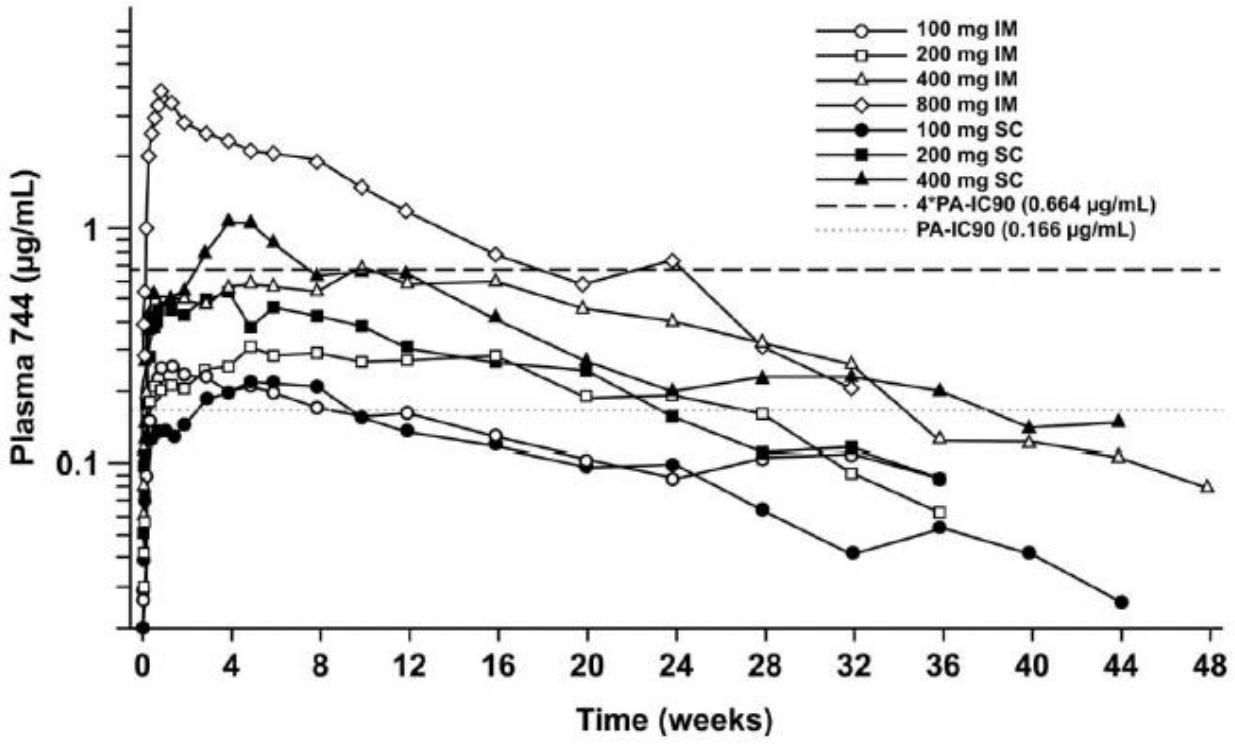
PBPK model structure for nonpregnant adults and pregnant women implemented in the Open Systems Pharmacology software suite.

Italics and dashed border compartments are exclusively parts of the pregnancy PBPK model structure.

The amniotic fluid was included as a separate compartment **without** intercompartmental exchange to facilitate future considerations, such as fetal excretion in the amniotic fluid, and to obtain a representative body weight when summing all organ weights.

Mian P, van den Anker JN, van Calsteren K, Annaert P et al. Clin Pharmacokinet. 2020 Jan;59(1):97-110.

Pre-existing Non-Pregnant PK Data



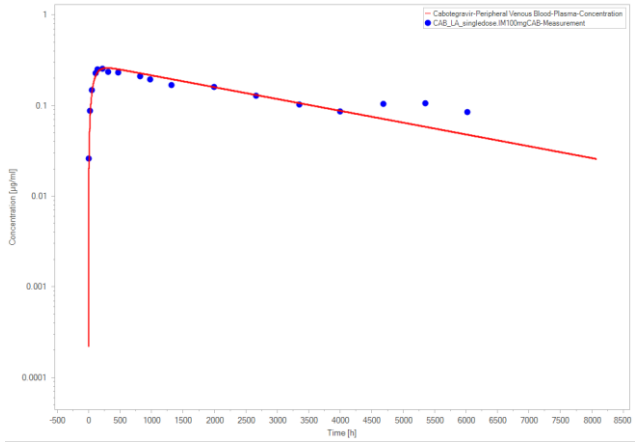
- 100-800 mg IM suspension injection in gluteal muscle
- The data was digitized and compared with PBPK simulation in non-pregnant patients

Spreen-J AcquirImmune DeficSyndr, 2014, 67(5):481

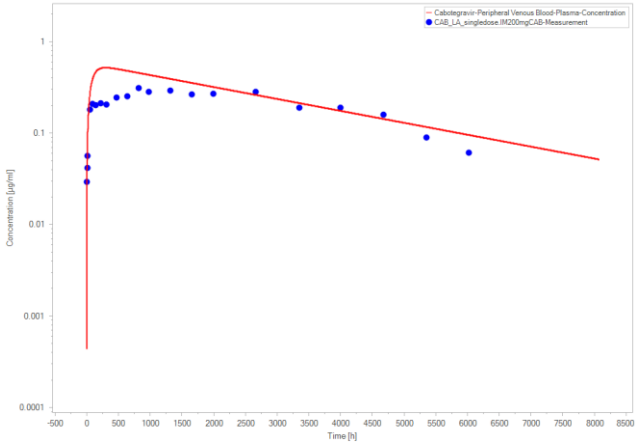
Non-Pregnant PBPK Simulation

Good predictions of data from non-pregnant Individuals across four dosage magnitudes

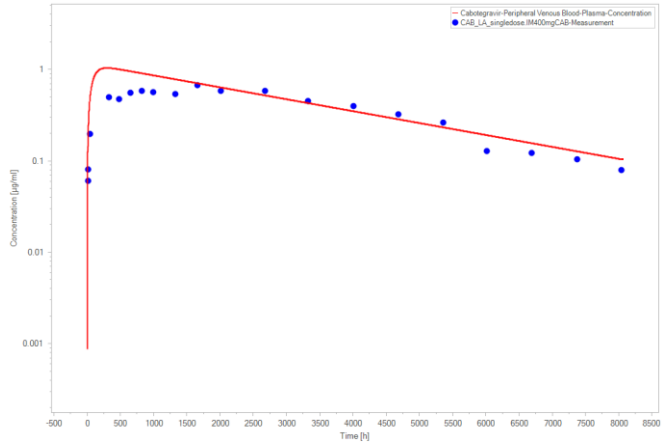
100 mg IM injection



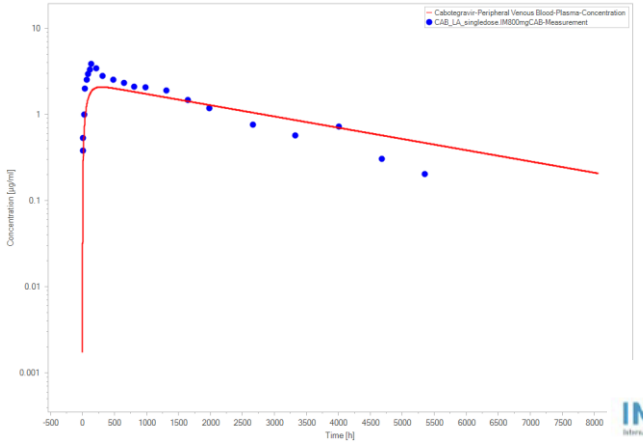
200 mg IM injection



400 mg IM injection



800 mg IM injection



Scaling of the Fraction Unbound in Pregnancy

- *Assuming Ka (equilibrium association constant) and number of binding site won't be affected by pregnancy.*

$$f_u = \frac{1}{1 + K_A \cdot [P]}$$

- **Cabotegravir is highly bound to albumin**

Time	Mean albumin concentration	Estimated CAB fraction unbound
Second trimester	34.4 g/L	0.0084
Third trimester	32.8 g/L	0.0088
6-12 weeks postpartum	41.4 g/L	

Dallmann A, Ince I, Solodenko J, Meyer M, Willmann S, Eissing T, Hempel G. Physiologically Based Pharmacokinetic Modeling of Renally Cleared Drugs in Pregnant Women. Clin Pharmacokinet. 2017 Dec;56(12):1525-1541.

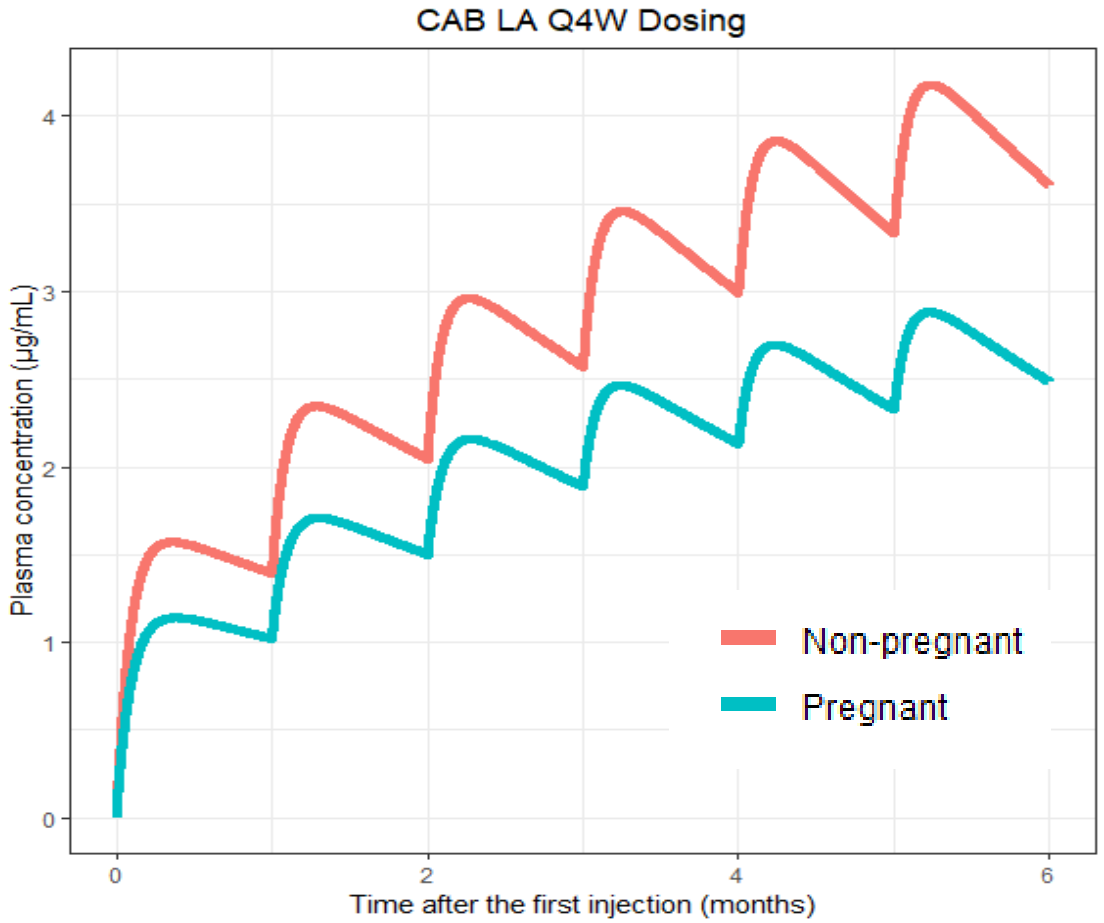
Enzyme Induction

- According to the paper, **UGT1A1** was assumed to be induced by a factor of 1.75 in the second trimester and 1.92 in the third trimester

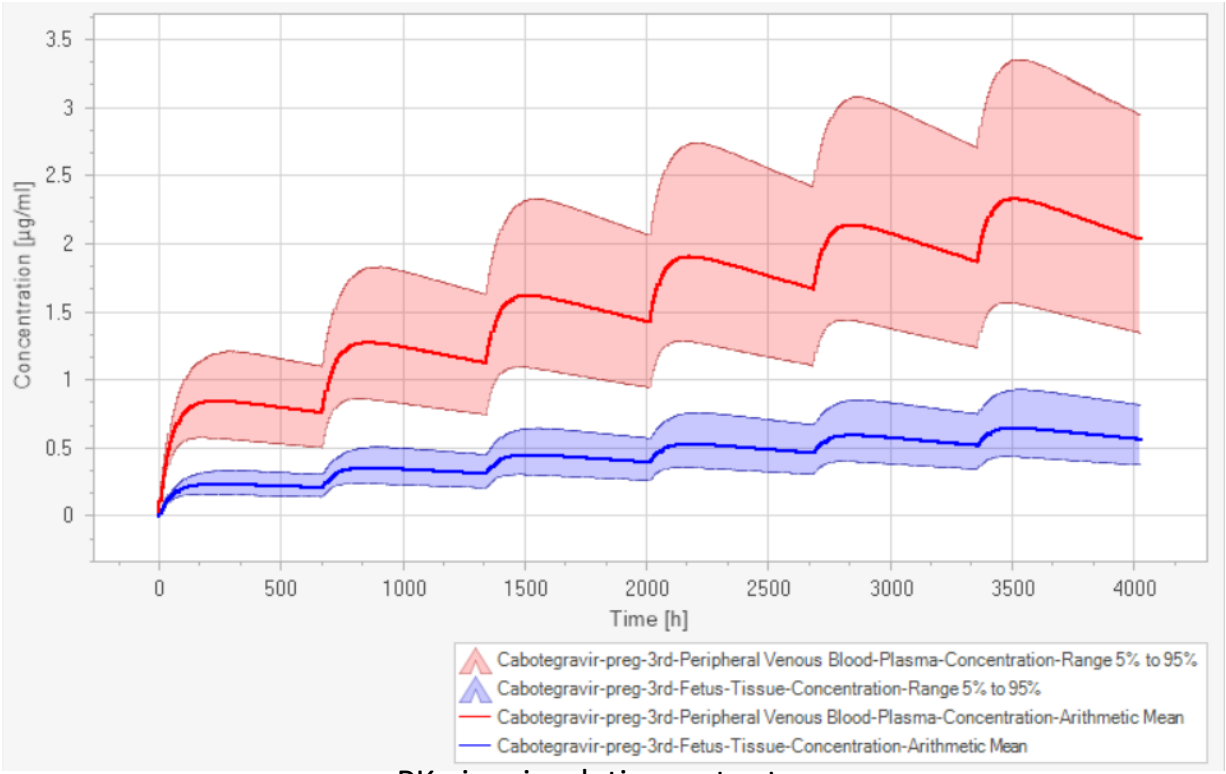
- *As no information on the effect of pregnancy on UGT1A9 could be found, this enzyme was not induced in the model*

Dallmann A, Solodenko J, Ince I, Eissing T. Applied Concepts in PBPK Modeling: How to Extend an Open Systems Pharmacology Model to the Special Population of Pregnant Women. CPT Pharmacometrics Syst Pharmacol. 2018 Jul;7(7):419-431.

Pregnancy Population Simulation in PK-sim



Simulated median PK profiles in non-pregnant cisgender women and pregnant cisgender women



PK-sim simulation output

According to the simulation results, the trough concentrations after the 1st injection (loading dose) were 29.5% lower during pregnancy compared to outside of pregnancy for CAB LA. The trough concentrations after the 6th injection were decreased 31.1% for CAB LA compared to non-pregnant cisgender women.

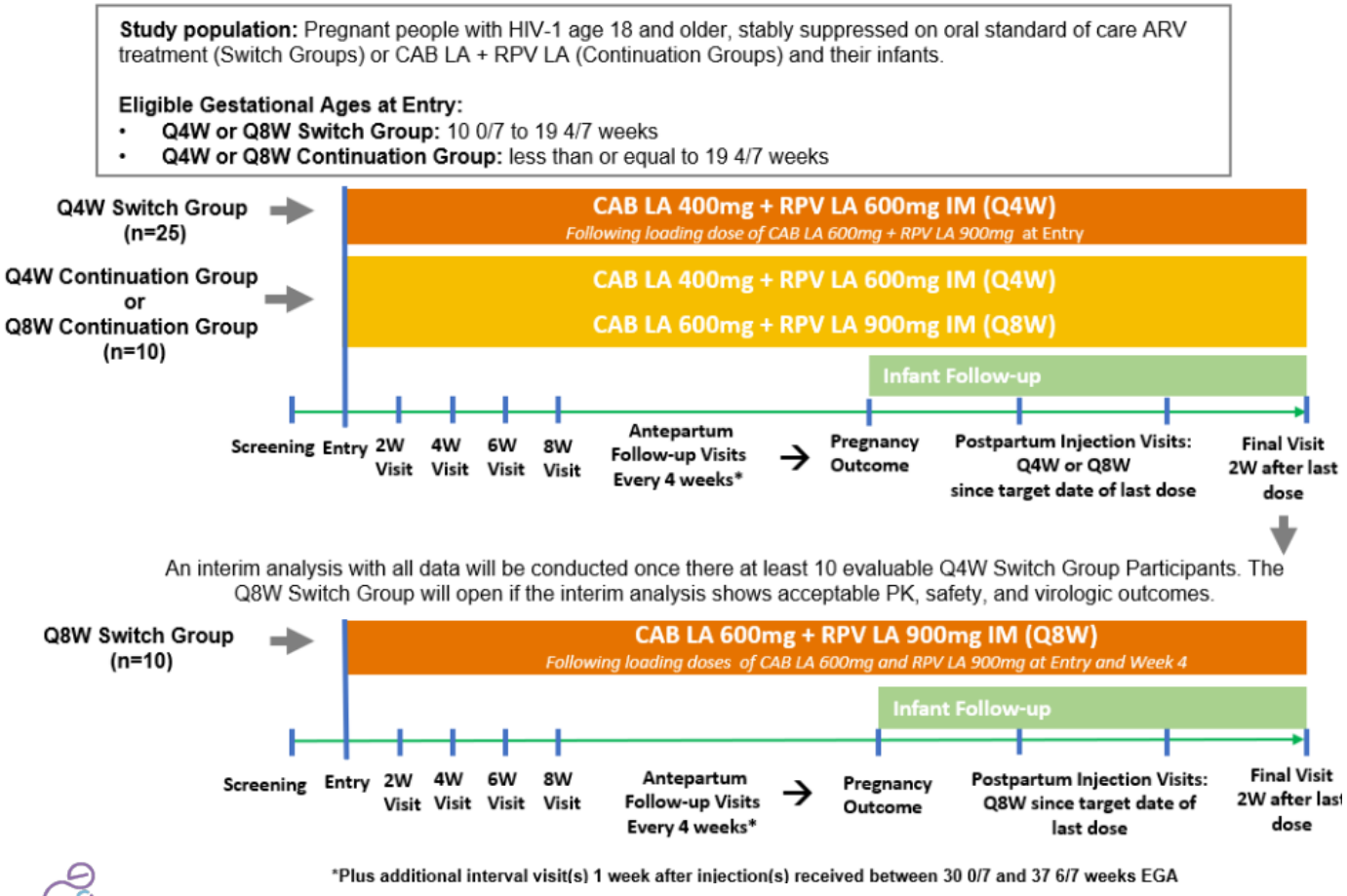
Yu Y, et al. PBPK Model Prediction of Long-acting CAB and RPV Concentrations in Pregnancy [CROI 2023 Abstract 782].

Published PBPK Models of Pregnancy

- Less than 50 published PBPK models in pregnant people
- Nine published models with code
- Diseases studied include HIV, COVID-19, schizophrenia, depression, respiratory distress syndrome, HSV-1&2, hypertension, spontaneous abortion, infectious disease, explorations of probe substrates/victim drug by enzyme, depression, epilepsy etc.

Application of Population Pharmacokinetics Long Acting Cabotegravir Injection

Injection Protocol



Entry at early pregnancy = more trough pk samples?

Then the “worst scenario” will be:

All the participants entered the study at GA of 20 weeks (minimum numbers of PK samples)

CAB LA Simulation

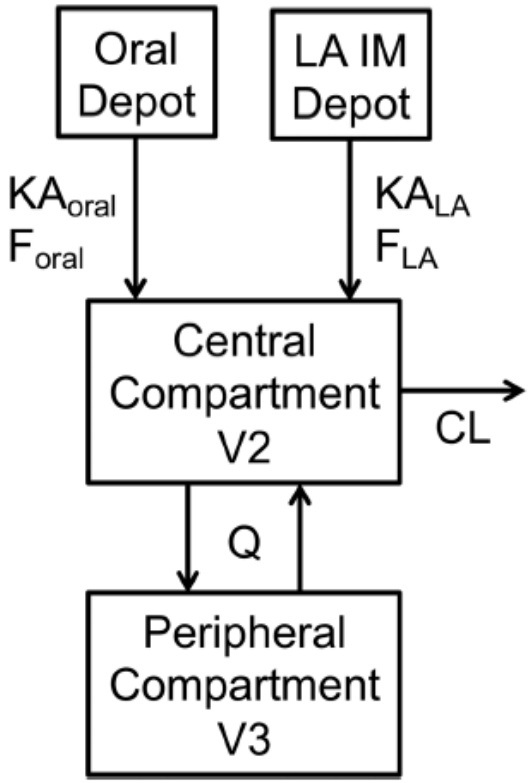


TABLE 3 Parameter estimates of the base model and final model

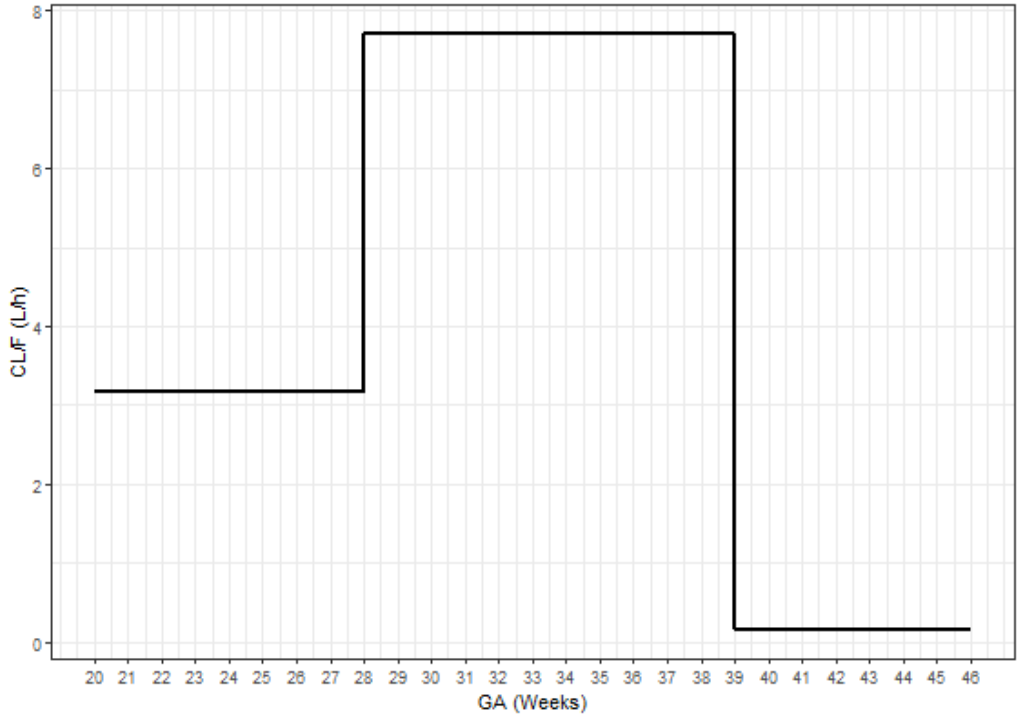
	Base model					Final model					
Parameter	Estimate	RSE (%)	IIV (%)	RSE of IIV (%)	Shrinkage (%)	Estimate	RSE (%)	90% CI (bootstrap)	IIV (%)	RSE of IIV (%)	Shrinkage (%)
KA_{oral} (h^{-1})	1.12	5.9	61.4	7.7	67.9	1.41	4	1.23,1.52	89.4	4.34	69.1
KA_{LA} (h^{-1})	0.000642	2.2	71.4	2	17	0.000733	2.3	0.000705, 0.000761	57.9	2.46	17.9
CL/F (L/h)	0.16	0.8	24.9	2.4	10.5	0.151	0.9	0.148, 0.153	23.3	2.58	10.3
V2/F (L)	5.5	2.5	22.6	8.9	29.9	5.27	2	5.07, 5.45	20.3	9.38	31.1
Q/F (L/h)	0.563	7.8				0.507	6.6	0.455, 0.579			
V3/F (L)	2.45	5.7				2.43	4.8	2.26, 2.66			
F1	0.746	1	17.2	5.9	42.3	75.6%	0.9	74.4%, 76.8%	17.4	5.70	40
Add err (μg/mL)	0.0405	18.3				0.0319	19.4	0.0202, 0.0496			
Prop err	27.3%	1.1				27.3%	1.1	26.7%, 27.8%			
BWT on CL/F and Q/F	0.611	5.9				0.618	5.6	0.562, 0.68			
BWT on V2/F and V3/F	0.675	7.5				0.702	7.1	0.622, 0.79			
Smoke on CL/F						17.4%	9.3	14.7%, 20%			
Female on KA_{LA}						−50.9%	4.4	−54.1%, −47.1%			
BMI exponent on KA_{LA}						−0.766	13	−0.922, −0.611			
Split on KA_{LA}						47.8%	14.2	36.9%, 60.2%			
NDL exponent on KA_{LA}						0.478	36.2	0.184, 0.747			

Han, K., Baker, M., Lovern, M., Paul, P., Xiong, Y., Patel, P., Moore, K. P., Seal, C. S., Cutrell, A. G., Benn, P. D., Landovitz, R. J., Marzinke, M. A., Spreen, W. R., & Ford, S. L. (2022). Population pharmacokinetics of cabotegravir following administration of oral tablet and long-acting intramuscular injection in adult HIV-1-infected and uninfected subjects. *British Journal of Clinical Pharmacology*, *88*(10), 4607-4622.

Potential changes on PK Parameters

- Assume a 20% and 50% increase on CL during the 2nd and 3rd trimesters for CAB LA based on the PBPK model changes in clearance using enzyme activity information directly

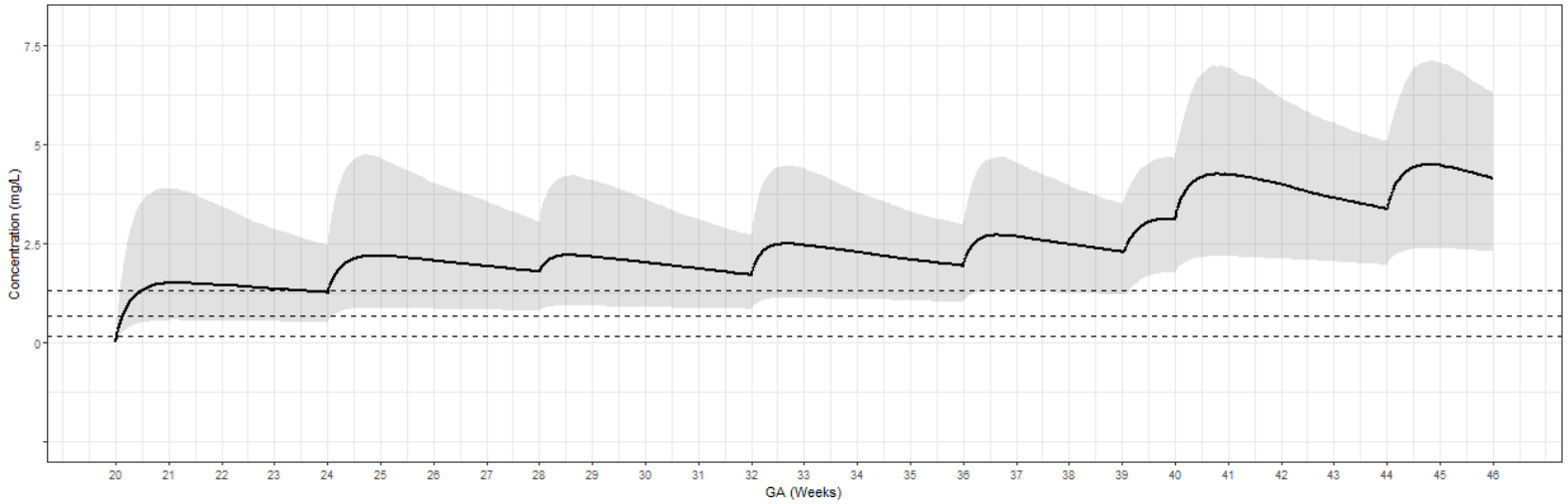
- Pop-PK CL/F assumed to change discretely at each trimester

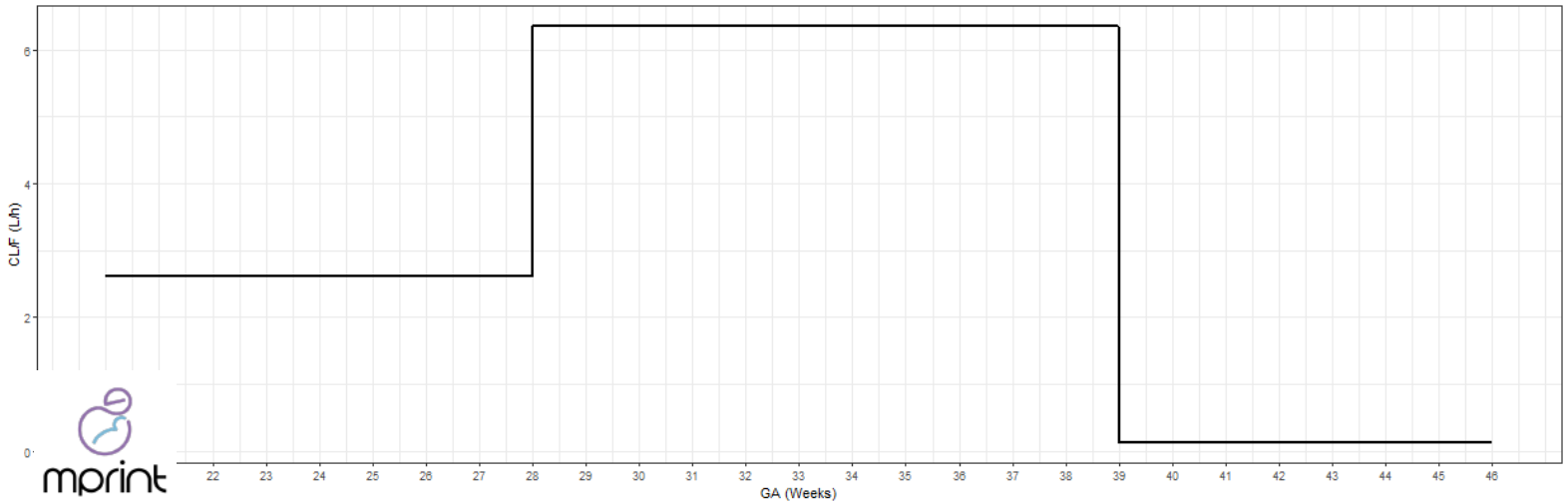


Simulation of Q4W Switch Group and Impact of BMI

Q4W Switch Group Simulation Normal Weight

Body weight: 56.0 kg
BMI: 22.4 kg/m^2 Normal weight

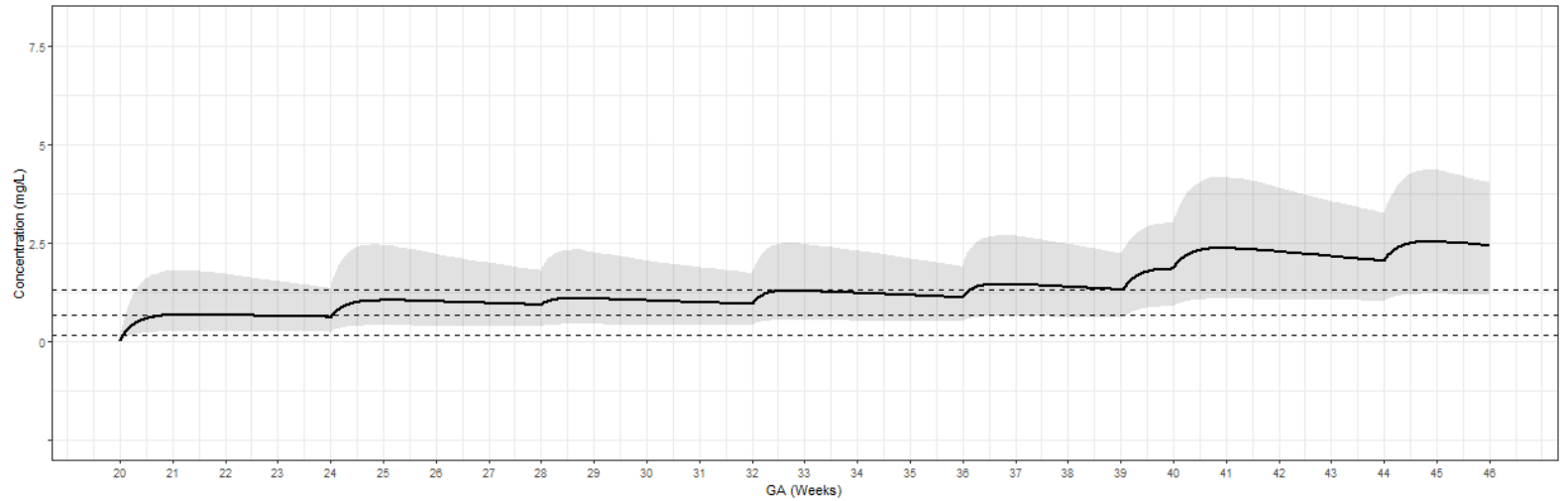


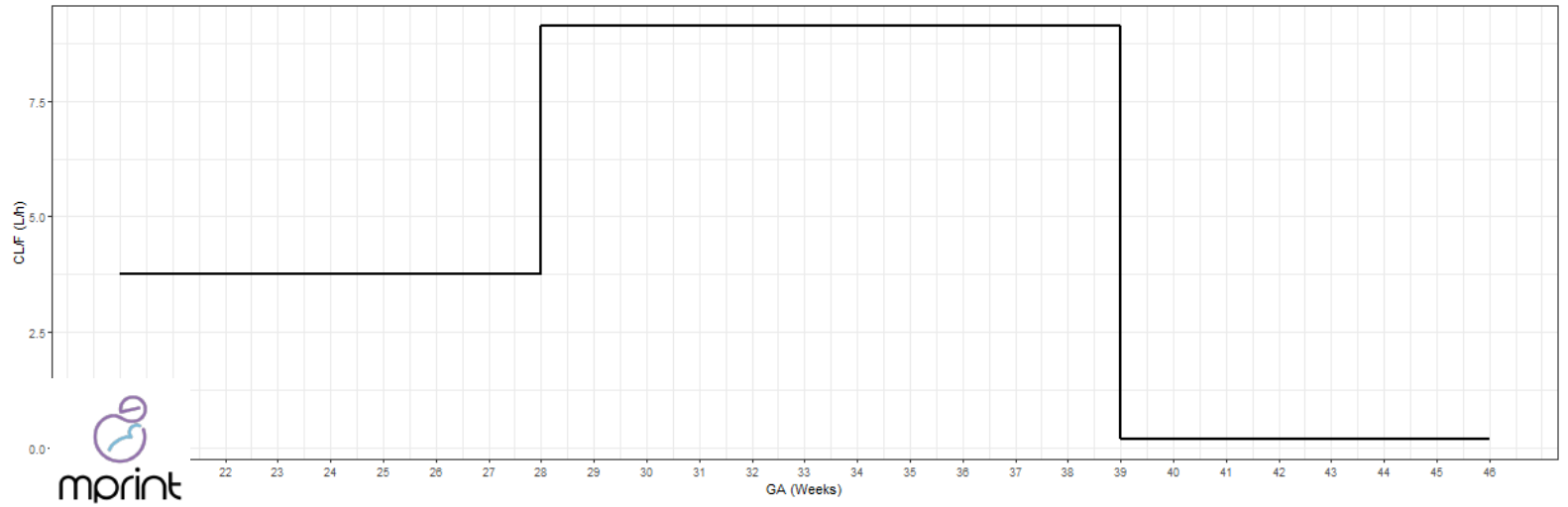


	% below PAIC90	% below 4*PAIC90	% below 8*PAIC90
1st trough	0.0	11.0	54.6
2nd trough	0.0	2.7	24.8
3rd trough	0.0	2.4	24.6
4th trough	0.0	0.9	14.0
5th trough	0.0	0.0	1.8
6th trough	0.0	0.0	0.9

Q4W Group Simulation Obesity Grade 3

Body weight: 100.8 kg
BMI: 40 kg/m^2 Obesity grade 3





	% below PAIC90	% below 4*PAIC90	% below 8*PAIC90
1st trough	1.6	55.9	94.4
2nd trough	0.2	25.1	80.4
3rd trough	0.0	22.3	82.7
4th trough	0.0	13.1	69.2
5th trough	0.0	1.8	21.2
6th trough	0.0	0.9	13.2

Simulation of Q8W Continuation Group

Virtual Clinical Trial and Population PK Model Assumptions

- First injection at GA of 0 weeks (the worst case scenario)
- Study started at GA of 20
- All the patients followed the injection protocol strictly
- All the patients delivered at GA of 39 0/7 weeks
- Assume a 20% and 50% increase on CL during the 2nd and 3rd trimesters for CAB LA
- Population PK parameter CL/F changes discretely in a step-wise fashion for each trimester

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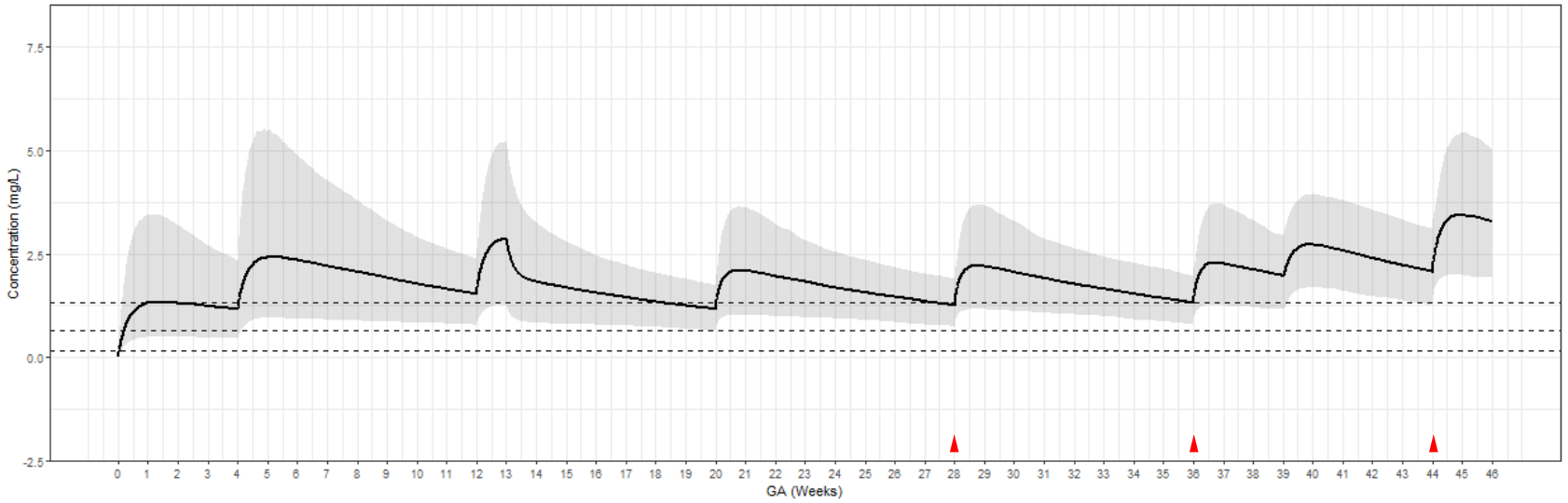
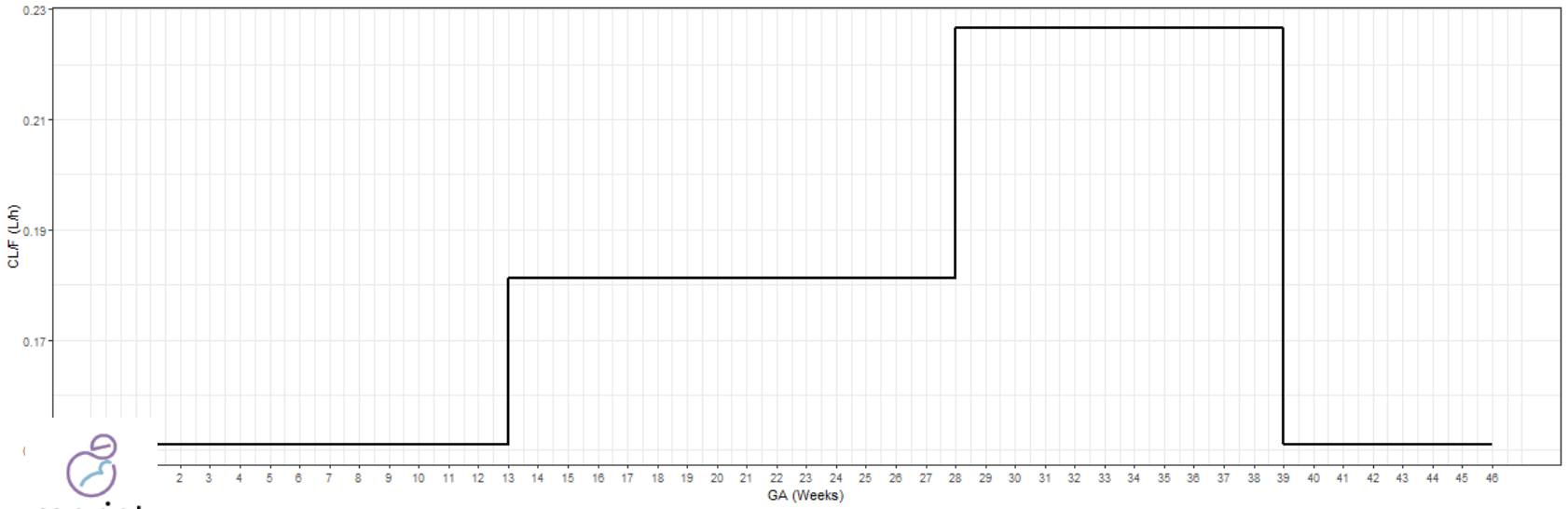
Q8W CAB LA





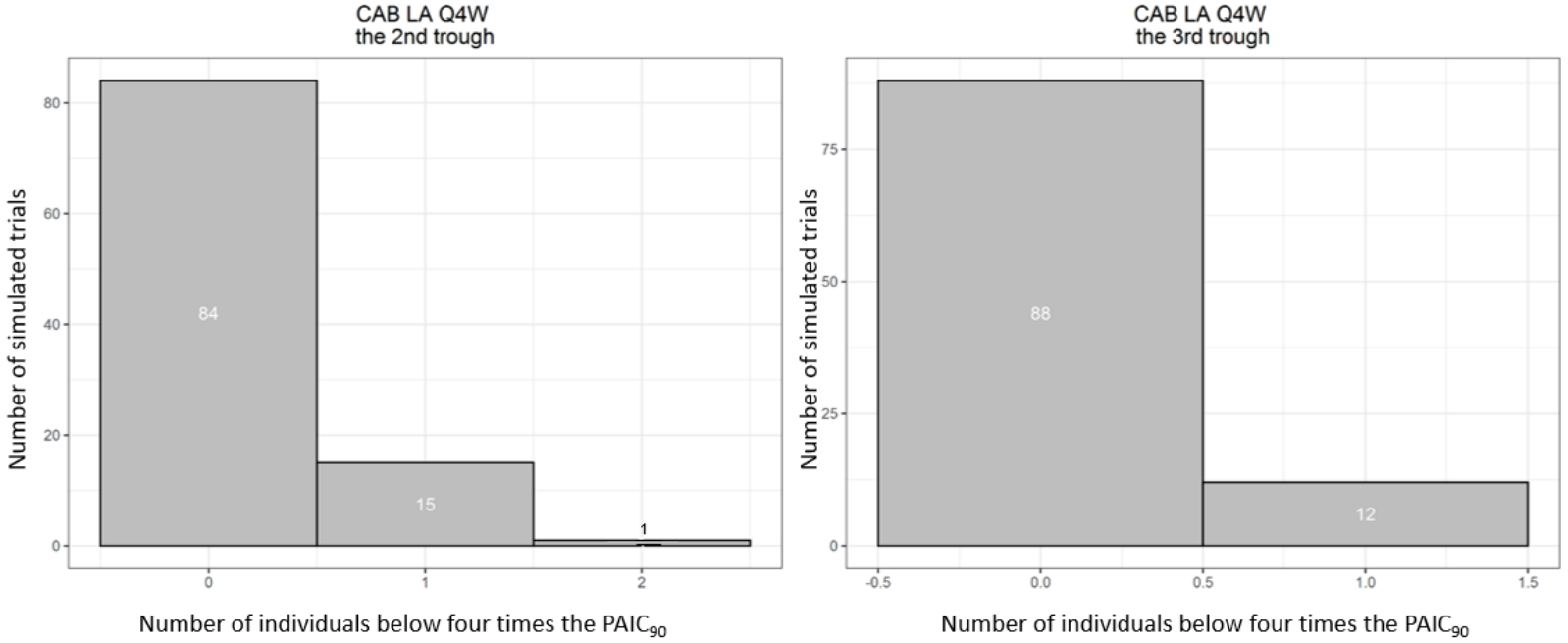
	% participants observed trough conc below PAIC90	% participants observed trough conc below 4*PAIC90	% participants observed trough conc below 8*PAIC90
1st trough	0	**3.3**	58.2
2nd trough	0	**2.2**	50
3rd trough	0	**0.5**	7.3

Interim Analysis: *Support of Decision making*

- Will use previously developed population PK models to assess the adequacy of Q8W Switch Group once there are 10 evaluable Q4W Switch Group adult-participants (modeling and simulations are summarized on the following two slides for independent review)

- Evaluable participants will have completed follow-up visits, received the expected number of CAB injections, with no oral bridging, and have no more than one missing PK sample for each agent

Simulations of Study Design - Cabotegravir



- Utilized Han et al model to simulate 100 instances of the n=10 individual for the interim analysis
- For each simulated study
  - Determined the number of individuals below particular threshold concentrations at each protocol specified trough measurement
  - Illustrates what expected number of below threshold concentrations are expected across studies
  - Defines extreme findings, i.e., if at the second trough measurement more than two individuals were observed with trough cabotegravir concentrations the below 4x PAIC, this may be of concern as zero trials were predicted to have three individuals below that threshold (left panel) and one trial (out of 100) were predicted to have two individuals below this threshold

Published Population PK Models of Pregnancy

- Over 60 published population PK models in pregnant people
- Three published models with code
- Diseases studied include:
  - HIV, malaria, infectious disease, influenza, tuberculosis, oncology, epilepsy, pre-eclampsia, neonatal abstinence syndrome, sepsis, thrombosis, hypertension, pre-term birth, respiratory distress syndrome, fetal surgery, neonatal hemochromatosis, urinary tract infection, asthma

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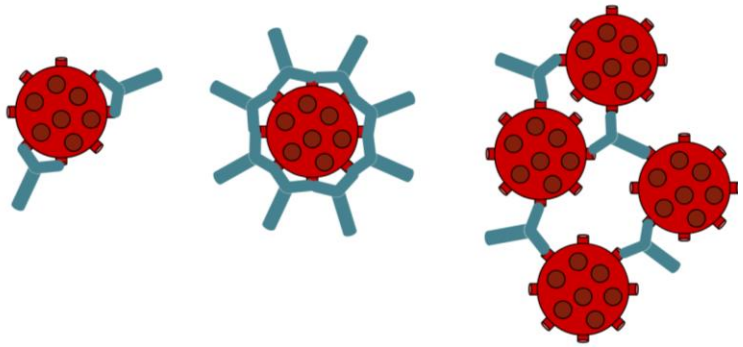
mAbs and bnAbs



- Very little information in the literature regarding disposition in pregnancy

- Additional challenges of not only changes in pregnancy, but target mediated disposition of the drug:
  - State of disease may affect clearance or other PK disposition related parameters of the drug
  - Specific biomarkers (eg. HIV viral load) affects bnAbs clearance and must be accounted for dynamically

Goga et al. BMC Infectious Diseases (2024) 24:71
https://doi.org/10.1186/s12879-024-09588-3

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Conclusions

- Population and PBPK modeling approaches can be
  - useful in trial design (e.g. predicting best starting doses, sample timing, numbers of individuals)
  - updated over the period of the study to reduce uncertainty and refine study design as well as inform important decision making when evaluating interim data.
  - employed in final data analysis (e.g. incorporation of observed data)
  - *especially useful to capture the dynamic changes in physiology affecting pharmacokinetics in pregnancy*

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