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Physiologically Based Pharmacokinetic Models to Predict Maternal Pharmacokinetics and Fetal Exposure to Emtricitabine and Acyclovir

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Abstract

Pregnancy is associated with physiological changes that may impact drug pharmacokinetics (PK). The goals of this study were to build maternal-fetal physiologically based pharmacokinetic (PBPK) models for acyclovir and emtricitabine, 2 anti(retro)viral drugs with active renal net secretion, and to (1) evaluate the predicted maternal PK at different stages of pregnancy; (2) predict the changes in PK target parameters following the current dosing regimen of these drugs throughout pregnancy; (3) evaluate the predicted concentrations of these drugs in the umbilical vein at delivery; (4) compare the model performance for predicting maternal PK of emtricitabine in the third trimester with that of previously published PBPK models; and (5) compare different previously published approaches for estimating the placental permeability of these 2 drugs. Results showed that the pregnancy PBPK model for acyclovir predicted all maternal concentrations within a 2-fold error range, whereas the model for emtricitabine predicted 79% of the maternal concentrations values within that range. Extrapolation of these models to earlier stages of pregnancy indicated that the change in the median PK target parameters remained well above the target threshold. Concentrations of acyclovir and emtricitabine in the umbilical vein were overall adequately predicted. The comparison of different emtricitabine PBPK models suggested an overall similar predictive performance in the third trimester, but the comparison of different approaches for estimating placental drug permeability revealed large differences. These models can enhance the understanding of the PK behavior of renally excreted drugs, which may ultimately inform pharmacotherapeutic decision making in pregnant women and their fetuses.

Keywords

pregnancy, PBPK modeling, emtricitabine, acyclovir, drug development

Medication use during pregnancy is common and increasing. In a prospective, longitudinal cohort study of prescription drugs and other medication use in pregnancy, 97.1% women took at least 1 medication during pregnancy, and 30.5% women took 5 or more medications.[1] Although the physiologic effects occurring during pregnancy can have a significant effect on drug disposition, pregnant women are generally not included in clinical studies. As a result, clinicians often have to prescribe drugs in pregnancy without having pregnancy-specific information on pharmacokinetics (PK) and safety at hand.

Antiviral medications are often used during pregnancy both for treatment of the mother and for prophylaxis to prevent perinatal viral transmission. Acyclovir is an antiviral drug effective against herpes simplex virus, one of the most common sexually transmitted infections that can lead to neonatal death or long-term disabilities if neonatal infection is not prevented or treated.[2] Emtricitabine is an antiretroviral drug effective against human immunodeficiency virus

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(HIV) infection. As of 2016, 19.5 million people living with HIV are on antiviral treatment.[3] Both drugs are primarily excreted unchanged in the urine by a combination of glomerular filtration and tubular secretion; the fractions excreted unchanged in urine as measured in mass balance studies (corrected for the amount of radioactivity lost) are ~0.71 and ~0.90 for emtricitabine[4] and acyclovir,[5] respectively.

With the accumulation of increasingly detailed knowledge on anatomical and physiological changes during pregnancy, physiologically based pharmacokinetic (PBPK) models for pregnant women can now be applied to available PK data as a means of increasing the confidence in these models. Due to their mechanistic nature, PBPK models may generate important insights into the physiological mechanisms governing PK changes. PK changes in special populations such as pregnant women may also be predicted before the initiation of clinical trials, facilitating the design and performance of clinical studies. However, the prerequisite for such an application is a sufficiently high confidence in the established PBPK model. The initial establishment of various PBPK models for pregnancy has been accomplished.[6] Yet, although many pregnancy PBPK models focus on maternal PK, drug exposure of the fetus is rarely accounted for.[7]

This study presents the development of 2 maternal-fetal PBPK models for acyclovir and emtricitabine. The objectives of this study were to (1) evaluate the model predictions of the PK in the mother at different stages of pregnancy, (2) predict the changes in PK target parameters following the current dosing regimen of these drugs throughout pregnancy, (3) evaluate the predicted concentrations of these drugs in the umbilical vein at delivery, (4) compare the predictive performance of the emtricitabine PBPK model presented herein in the third trimester with previously published models,[8,9] and (5) compare different previously published approaches for estimating the placental permeability of these 2 drugs.

Materials and Methods

Software

The nonpregnancy and pregnancy PBPK models were developed using Open Systems Pharmacology software package version 7.2.0 (http://www.open-systems-pharmacology.org/). The Open Systems Pharmacology suite makes formerly commercial software PK-Sim and MoBi available as freeware under the GPLv2 license. All source code and the models developed herein will be made publicly available on GitHub (accessible via www.open-systems-pharmacology.org). WebPlotDigitizer (http://automeris.io/WebPlotDigitizer/) was used to extract data from published figures and convert them into digital format. The software R (version 3.4.1, R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org) was used for noncompartmental analysis and graphics creation.

General Workflow

The workflow for the development of a PBPK pregnancy model (Figure 1) has been previously described in detail[10] and is schematically shown in Figure S1. The workflow can be briefly summarized as follows: Initially, a PBPK model was developed for a virtual nonpregnant population that matched the demographic characteristics of the healthy volunteer groups in the comparison studies taken from the literature. The model was evaluated by comparing simulation results with the observed in vivo PK data of the comparison studies. Thereafter, the nonpregnant PBPK model was translated to pregnancy by replacing the standard model structure with the pregnancy structure, which includes 9 additional compartments, and by changing the values of system-specific model parameters according to the observed changes during pregnancy. In addition, drug transport of emtricitabine and acyclovir across the placenta was informed on the basis of various data collected from the literature. Finally, PK predictions were conducted in virtual populations of pregnant women who matched the demographic characteristics of the in vivo pregnant women in the comparison studies. PK predictions were evaluated by comparison with in vivo PK data obtained from clinical trials and from the literature.

Development of PBPK Models

Acyclovir. After intravenous administration, 61% to 91% of the radioactively labeled dose is excreted unchanged in urine (corrected for the amount of radioactivity lost), and 8.5% to 14.1% is metabolized to CMMG (9-carboxy methoxymethylguanine).[5] OAT (organic anion transporter) 2 has been suggested to be the main transporter involved in renal secretion.[11] CMMG is formed in a 2-step reaction involving a reversible oxidation catalyzed by alcohol dehydrogenase[12] and subsequent irreversible transformation to CMMG via aldehyde dehydrogenase 2.[13] The input data used in the PBPK model for acyclovir are detailed in Table 1. Additional information can be found in the Supplemental Material.

Pharmacokinetic profiles in nonpregnant subjects were obtained from a study by Laskin et al,[14] who investigated acyclovir disposition after intravenous administration of different doses, and additionally from another study[15] that investigated acyclovir PK after oral administration of 400 mg acyclovir as either a suspension or a tablet. Two studies involving pregnant women close to term reported maternal plasma

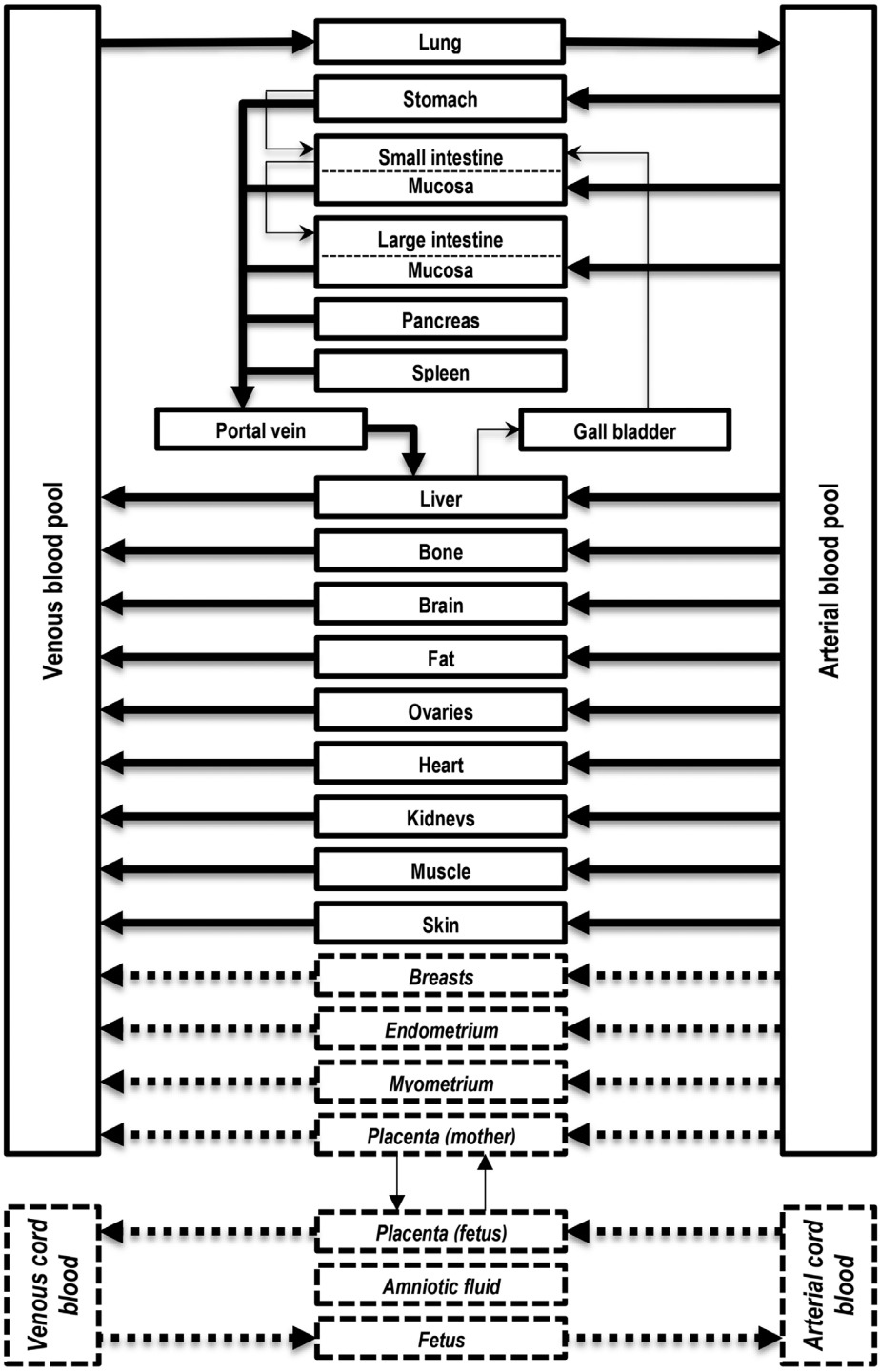

Figure 1. Pregnancy PBPK model structure. Thick arrows represent drug transport via blood flow, and thin arrows via other pathways (eg, via passage in the gastrointestinal tract, biliary excretion through the gallbladder, and diffusive transfer in the placenta). Compartments that are exclusively part of the pregnancy PBPK model structure are shown in italics with dashed borders and dashed arrows for drug transfer via the blood flow.

concentration-time data after administration of 400 mg acyclovir following single and multiple doses[16,17] and were used for evaluating the predicted maternal plasma concentrations. Although the studies also include a valacyclovir group in addition to the acyclovir group, the acyclovir data from the latter group were then applied to verify the model. Another study reported paired concentration measurements in the maternal plasma and in the umbilical vein obtained at delivery,[18] which were used for evaluating the predicted concentrations in the umbilical vein blood compartment of the model.

Table 1. Summary of Input Data for PBPK Models in Nonpregnant Subjects

	Acyclovir		Emtricitabine	
Parameter [Unit]	Value	Reference	Value	Reference
Molecular weight [g/mol]	225	PK-Sim template[64,65]	247.25	Drugbank
Lipophilicity [log units]	−0.887	Fitted	–0.43	US FDA[4]
pK_a (acid)	9.20	PK-Sim template[64,65]	2.65	Drugbank
pK_a (basic)	2.20	PK-Sim template[64,65]	NA	NA
Fraction unbound	0.85	PK-Sim template[64,65]	0.96	Drugbank
Major binding protein	Albumin	PK-Sim template[64,65]	Albumin	Drugbank
Solubility in water [mg/mL]	34.0	PK-Sim template[64,65]	112	Drugbank
Intestinal permeability (transcellular) [cm/min]	$2.27 \bullet 10^{-7}$[a]	Fitted	$3.98 \bullet 10^{-6}$[c]	Fitted
Model for estimating organ-to-plasma partition coefficients	PK-Sim standard	OSP Manual [66]	Rogers and Rowland	OSP Manual[66]
GFR fraction	1.0	PK-Sim template[64,65]	1.0	...
Specific tubular secretion [min^{-1}]	0.703[b]	Fitted	0.570[b]	Fitted
Specific hepatic plasma clearance [min^{-1}]	0.0229[b]	Fitted	0.0362[b]	Fitted
Dose fractions excreted unchanged in urine (f_e) and metabolized (f_m)				
f_m	0.10	De Miranda et al[5]	0.29	NA
f_e	0.90	De Miranda et al[5]	0.71	US FDA,[4] Zong et al[21]

GFR indicates glomerular filtration rate; PBPK, physiologically based pharmacokinetic.
[a]Value fitted to in vivo pharmacokinetic data of nonpregnant women following oral administration.
[b]Value simultaneously fitted to in vivo plasma concentration-time profiles of nonpregnant subjects and to the dose fraction excreted unchanged in urine.
[c]Value fitted to in vivo pharmacokinetic data of nonpregnant women following oral administration.

Emtricitabine. Emtricitabine is a nucleoside reverse transcriptase inhibitor with a daily oral dose of 200 mg in both pregnant and nonpregnant adult populations.[4,19] Emtricitabine is primarily eliminated unchanged via renal excretion through a combination of glomerular filtration and tubular secretion (~71% of the radioactive dose, corrected for the amount of radioactivity lost).[4,20] The input parameters and their values for the emtricitabine PBPK model are listed in Table 1. Additional information can be found in the Supplemental Material.

PK simulations in the nonpregnant population were evaluated by comparison with in vivo data obtained from 5 different studies that investigated the PK of emtricitabine in nonpregnant subjects after single and multiple oral administration of 200 mg.[20–22] In pregnant women the PK was predicted in different populations, namely in 3 different gestational age groups of nonlaboring pregnant women (23-30, 31-35, and 36-42 gestational weeks) and in women in labor between 34 and 39 weeks of gestation. Drug concentrations in the umbilical vein were predicted in the latter group. PK predictions in pregnant populations were evaluated through comparison with some hitherto unpublished and published in vivo data.[23] The clinical in vivo data were from the IMPAACT (International Maternal Pediatric and Adolescent AIDS Clinical Trials) Network study P1026s.[23] In this clinical study steady-state PK samples were collected at 0, 1, 2, 4, 6, 8, 12, and 24 hours after dosing. The protocol for this study was approved by the responsible institutional review boards. These data were completed by previously published data in the umbilical vein obtained at delivery.[24]

Parameterization of Placental Transfer of Acyclovir

Analogous to previous studies,[24,25] the placental transfer of acyclovir was estimated from ex vivo cotyledon perfusion experiments. Briefly, a 4-compartment model with a slightly modified ordinary equation system was built in MoBi and used to describe the observed data reported in a previous study.[26] No metabolism of acyclovir in the placenta was assumed. The following ordinary differential equation system was used to describe the time-dependent change of the molar drug amount in each of the 4 compartments, namely the maternal reservoir, maternal cotyledon, fetal cotyledon, and fetal reservoir ($N_{\{m,mp,fp,f\}}$) [µmol]:

$$d_t \begin{bmatrix} N_m \\ N_{mp} \\ N_{fp} \\ N_f \end{bmatrix} = f_{u\_exp} \begin{bmatrix} C_m \\ C_{mp} \\ C_{fp} \\ C_f \end{bmatrix} \times \begin{bmatrix} -Q_m & \frac{Q_m}{K_{ppl}} & 0 & 0 \\ Q_m & -\frac{Q_m}{K_{ppl}} - D_{cot\_mf} & D_{cot\_fm} & 0 \\ 0 & D_{cot\_mf} & -\frac{Q_f}{K_{ppl}} - D_{cot\_fm} & Q_f \\ 0 & 0 & \frac{Q_f}{K_{ppl}} & -Q_f \end{bmatrix} \quad (1)$$

Here, f_{u_exp} denotes the fraction unbound of acyclovir in the experiment; $C_{\{m,mp,fp,f\}}$ the drug concentration

in each of the 4 compartments [μmol/L]; Q_m and Q_f the flow rates on the maternal and fetal sides, respectively [L/h]; K_{ppl} the placental partition coefficient, and D_{cot_mf} and D_{cot_fm} the transfer coefficient parameter from maternal to fetal side and vice-versa, respectively [L/h]. f_{u_exp} was predicted from the reported albumin concentration used in the experiment and by using a previously described scaling approach.[27] Q_m and Q_f were reported (1.2 and 0.24 L/h, respectively) as well as the volumes of the maternal and fetal reservoirs (0.2 and 0.1 L, respectively), which were used to convert molar drug amount into molar concentrations.[26] K_{ppl}, D_{cot_mf}, and D_{cot_fm} were fitted to the observed data using the Levenberg-Marquardt algorithm implemented in MoBi. To reduce model complexity, D_{cot_mf} and D_{cot_fm} were assumed to be equal, as has been done in previous studies.[25] Thereafter, D_{cot_mf} and D_{cot_fm} were scaled as described below and integrated together with K_{ppl} in the maternal-fetal PBPK model.

Parameterization of Placental Transfer of Emtricitabine

Previously, the transfer of emtricitabine over the placenta barrier in ex vivo human placentas has been quantified in terms of the cotyledon transfer parameter D_{cot} [L/h], which was assumed to be equal in both directions, a minor elimination rate constant in the cotyledon and K_{ppl}.[24] The reported mean value for D_{cot} was 0.104 L/h, 1.49 h^{-1} for the elimination rate constant and 3.94 for K_{ppl}; these values were also applied in the maternal-fetal PBPK model presented here to predict fetal exposure. D_{cot} was scaled to the whole placental transfer parameter D_{pl} using the following equation:

$$D_{pl} = D_{cot} \cdot \frac{V_{pl}}{V_{cot}} \quad (2)$$

where V_{pl} and V_{cot} are the volumes of the placenta and cotyledon, respectively. For V_{pl}, a value of 642 mL was calculated,[28] and for V_{cot} a value of 58 mL was used.[24]

Comparison of Different Approaches for Estimating Placental Permeability

In addition to estimating the placental permeability rate (D_{pl}) from the ex vivo cotyledon perfusion experiment as described above, other methods have also been reported. Specifically, Zhang et al reported an approach to estimate the intrinsic transfer clearance across the placenta from the apparent permeability measured across, eg, Caco-2 cell lines in vitro.[29] Another method is per default implemented in the Open Systems Pharmacology (OSP) software, which estimates the permeability across organ membranes from the physicochemical descriptors lipophilicity and molecular weight.[27] The permeability rates calculated for acyclovir and emtricitabine according to these 2 approaches were compared with those obtained from the ex vivo cotyledon perfusion experiment as described above.

Prediction of PK Target Changes of Acyclovir and Emtricitabine Throughout Pregnancy

Serum trough levels (C_{min}) and area under the concentration-time curve (AUC) at steady state were used as measures for PK target parameters. These parameters were predicted for each gestational week in a virtual population of 2000 individuals and compared with the reported half-maximal inhibitory concentration (IC_{50}) of acyclovir and emtricitabine, the reported 90% maximal inhibitory concentration of emtricitabine, and the reported target AUC of acyclovir and emtricitabine in the non-pregnant population. Due to the low protein binding of both drugs, C_{min} referring to total plasma concentrations was used here. For acyclovir, an IC_{50} of 0.01 mg/L was reported,[30] whereas for emtricitabine the IC_{50} and 90% maximal inhibitory concentration were reported to be 0.004 mg/L and 0.07 mg/L, respectively.[31] In nonpregnant populations, the average $AUC_{0\text{-}24,\,ss}$ of acyclovir 400 mg from several studies is 3.4 mg · h/L with a range from 2.4 to 4.6[15,32–37] mg · h/L, and the minimum target $AUC_{0\text{-}24,\,ss}$ of emtricitabine in pregnant women is ≥7 mg · h/L (30% lower than the typical $AUC_{0\text{-}24,\,ss}$).[23,38,39]

Evaluation of PBPK Models. The PBPK models were evaluated through visual comparison of observed in vivo plasma concentration-time profiles with the concentrations simulated in nonpregnant women or predicted in pregnant women. Other visual predictive checks included goodness-of-fit (GOF) plots, in which individual in vivo concentration values, if available, were combined at each time point to geometric mean values. Additionally, simulated or predicted PK parameters were compared with observed PK parameters obtained from the mean in vivo plasma concentration-time profiles. Ratios of simulated or predicted to observed PK parameters were also estimated. Table S1 provides an overview of the clinical studies conducted in pregnant women that were used herein for model evaluation.

Results

PBPK Models for Nonpregnant Subjects

The results described in the following refer exclusively to nonpregnant subjects. Simulated plasma concentration-time profiles of acyclovir following intravenous administration are shown in Figure S2. Simulated plasma concentration-time profiles following oral administration of acyclovir and emtricitabine in nonpregnant populations are depicted in Figure S3 and Figure S4, respectively. Figure 2 presents GOF plots for

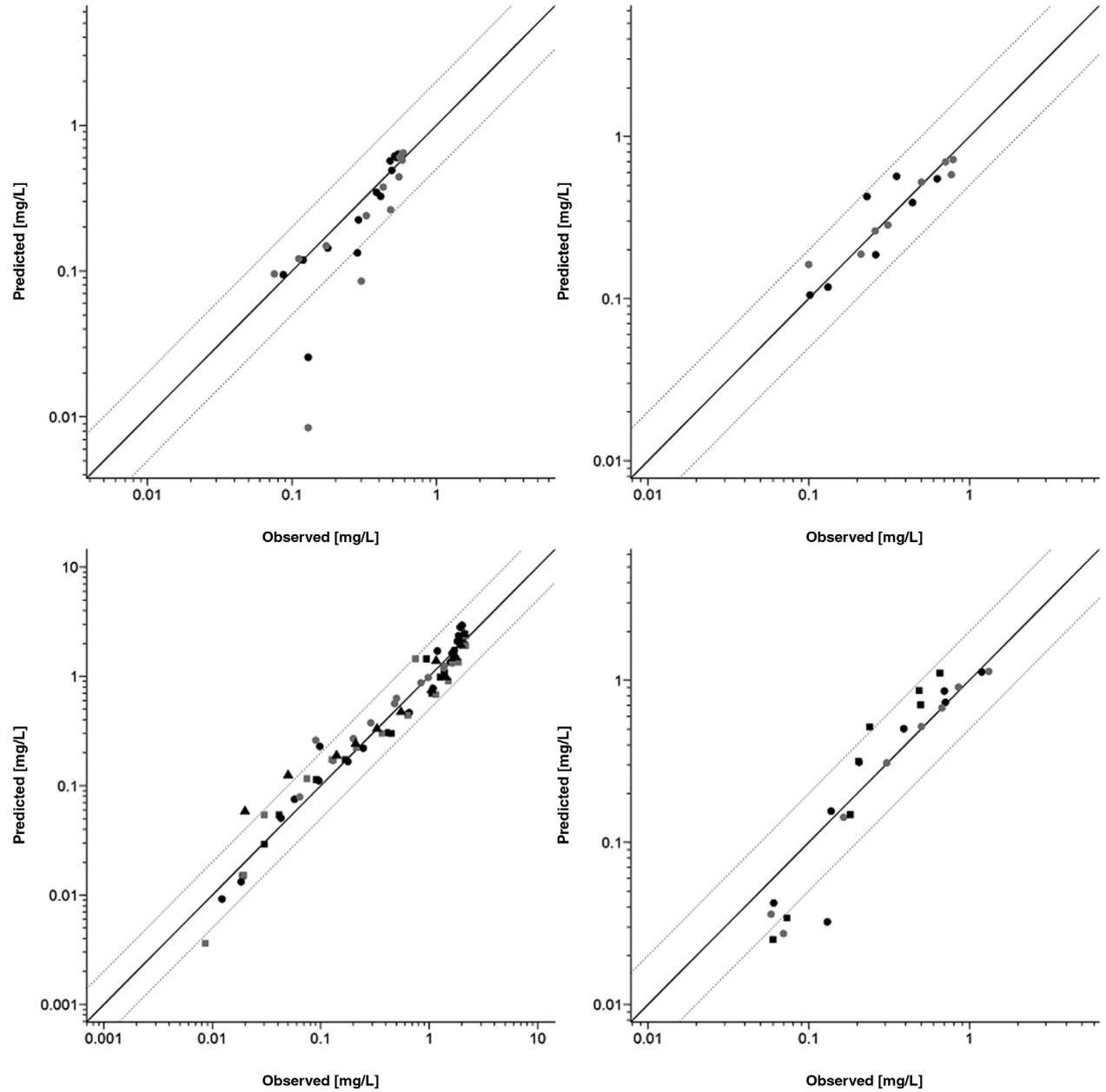

Figure 2. Goodness-of-fit plot for plasma concentrations of acyclovir (upper panels) and emtricitabine (lower panels) in nonpregnant subjects (left panels) and pregnant women (right panels). The solid line represents the line of identity, and the dotted lines the 2-fold error range. Upper left panel: Acyclovir plasma concentrations in nonpregnant subjects; black circles indicate concentrations for the suspension,[15] and gray circles indicate concentrations in steady state for the suspension.[15] Upper right panel: Acyclovir plasma concentrations in pregnant women[16,17]; black circles indicate concentrations after a single dose, and gray circles indicate concentrations in steady state.[16,17] Lower left panel: Emtricitabine plasma concentrations in nonpregnant subjects; black circles indicate the concentrations after a single dose,[22] gray circles indicate concentrations at steady state,[20] gray squares indicate concentrations after a single dose,[21] black squares indicate concentrations after a single dose,[21] and black triangles indicate concentrations at steady state.[21] Lower right panel: Emtricitabine plasma concentrations in pregnant women; black circles indicate concentrations in women at gestational age 23-30 weeks,[23] gray circles indicate concentrations in women at gestational age 31-35 weeks,[23] and black squares indicate concentrations in women at gestational age 36-42 weeks.[23]

the simulated mean plasma concentrations of acyclovir and emtricitabine. As shown in this figure, 84% of the simulated acyclovir concentration values fell within a 2-fold error range, and for emtricitabine, 92% of the simulated values fell within that range. A comparison of the observed in vivo PK parameters with those obtained from the simulated concentration-time profiles is given in Table 2. For emtricitabine all PK parameters except 1 peak concentration (C_{max}) value, were simulated within a 25% error range (ie, 0.8 < simulated/observed < 1.25),

Table 2. Comparison of Simulated or Predicted and Observed PK Parameters

	AUC_{0-t} [mg·h/L] Simulated or Predicted/Observed (Ratio)	C_{max} [mg/L] Simulated or Predicted/Observed (Ratio)	t_{max} [h] Simulated or Predicted/Observed (Ratio)
Emtricitabine			
Nonpregnant women			
Bapuji et al[22]	10.60/11.20 (0.95)	3.00/2.01 (1.49)	0.90/0.78 (1.15)
Zong et al, study 1[21]	9.67/11.20 (0.86)	2.46/2.13 (1.16)	0.95/1.01 (0.94)
Zong et al, study 2[21]	9.62/11.11 (0.87)	2.36/2.17 (1.09)	0.95/1.25 (0.76)
Blum et al[20] (steady state)	10.70/10.33(1.04)	1.33/1.64 (0.81)	3.00/3.07 (0.98)
Zong et al, study 3[21] (steady state)	9.62/9.67 (0.99)	2.44/2.11 (1.16)	1.00/1.02 (0.98)
Pregnant women			
GA 23-30 weeks[23] (steady state)	7.41/7.50 (0.99)	1.14/1.19 (0.96)	2.25/2.00 (1.13)
GA 31-35 weeks[23] (steady state)	7.35/6.45 (1.14)	1.17/1.32 (0.89)	2.50/2.00 (1.25)
GA 36-42 weeks[23] (steady state)	7.27/4.15 (1.75)[a]	1.12/0.66 (1.70)[a]	2.25/2.00 (1.13)[a]
Acyclovir			
Nonpregnant women			
Intravenous injection[14]			
Study group A (2.5 mg/kg)	13.7/11.5 (1.19)		
Study group B (5.0 mg/kg)	22.8/23.3 (0.98)		
Study group C (10 mg/kg)	38.8/37.6 (1.03)		
Study group D (15 mg/kg)	56.9/44.9 (1.27)		
Oral administration[15]			
Suspension	2.98/2.51 (1.19)	0.640/0.543 (1.18)	1.60/1.50 (1.07)
Tablet	3.09/2.50 (1.24)	0.669/0.590 (1.13)	1.65/1.75 (0.94)
Pregnant women			
GA 36 weeks[16]	2.00/2.11 (0.95)	0.574/0.630 (0.91)	1.65/2.00 (0.83)
GA 38 weeks[16,17] (steady state)	2.84/3.05 (0.93)	0.726/0.791 (0.92)	1.65/1.50 (1.10)

AUC_{0-t} indicates area under the concentration-time curve from 0 to the time point of the last observed plasma concentration (in case of multiple dose studies, time refers to the time after last dose); C_{max}, peak plasma concentration; GA, gestational age; PK, pharmacokinetic; t_{max}, time at which peak plasma concentration is reached.

For emtricitabine, observed data were available as geometric mean values, whereas for acyclovir observed data were only available as arithmetic mean values. Therefore, the values in the table are given as geometric mean values for emtricitabine and as arithmetic mean values for acyclovir. Note that the listed C_{max} values do not refer to the mean of the reported individual C_{max} values, but to the C_{max} value of the mean PK curve.

[a]Two of 7 patients had extremely low plasma concentrations. Excluding those 2 patients as outliers resulted in observed geometric mean values of 8.23 mg·h/L 1.31 mg/L, 2 h, and 24.30 L/h for AUC_{0-t}, C_{max}, and t_{max}, respectively, and in predicted-to-observed ratios of 0.88, 0.85, and 1.13 for AUC_{0-t}, C_{max}, and t_{max}, respectively.

and for acyclovir all PK parameters except 1 AUC_{0-t} value were within this error range.

Evaluation of Predicted Drug Pharmacokinetics for Pregnant Women

The results described in the following refer exclusively to pregnant women. Figure 3 (panels A and B) and Figure 4 (panels A, B, and C) show the predicted maternal plasma concentration-time profiles of acyclovir and emtricitabine. All predictions were in good agreement with the observed in vivo data. Figure 2 presents the predicted mean concentration values in a GOF plot and indicates that all maternal concentrations of acyclovir were predicted within a 2-fold error range, whereas for emtricitabine 79% of the concentration values were predicted within that range. PK parameters calculated from the predicted emtricitabine and acyclovir plasma concentration-time profiles are compared with the observed in vivo PK parameters in Table 2. For acyclovir, the ratios of predicted to observed PK parameters were all within a 25% error range, whereas for emtricitabine most of these ratios were within that range. Of note, 2 patients between gestational weeks 36 and 43 had extremely low plasma concentrations, suggesting nonadherence. Exclusion of these 2 patients from the analysis substantially improved the results, reducing all predicted-to-observed PK ratios below the 25% error limit.

Prediction of Changes in Maternal PK Target Parameters During Pregnancy

The predicted acyclovir median C_{min} was consistently decreased during pregnancy, ranging from 0.12 to 0.19 mg/L with a nadir value of 0.12 mg/L at 27 weeks of gestation. Despite this decrease, all C_{min} values, including those at the lower 5th percentile, were well above the reported IC_{50} of 0.01 mg/L (Figure 5A). The predicted acyclovir median AUC was also consistently decreased during pregnancy. Compared with the average AUC of 3.4 mg · h/L (the pooled mean value from several studies) in nonpregnant subjects, the greatest reduction during pregnancy (–36%) occurred

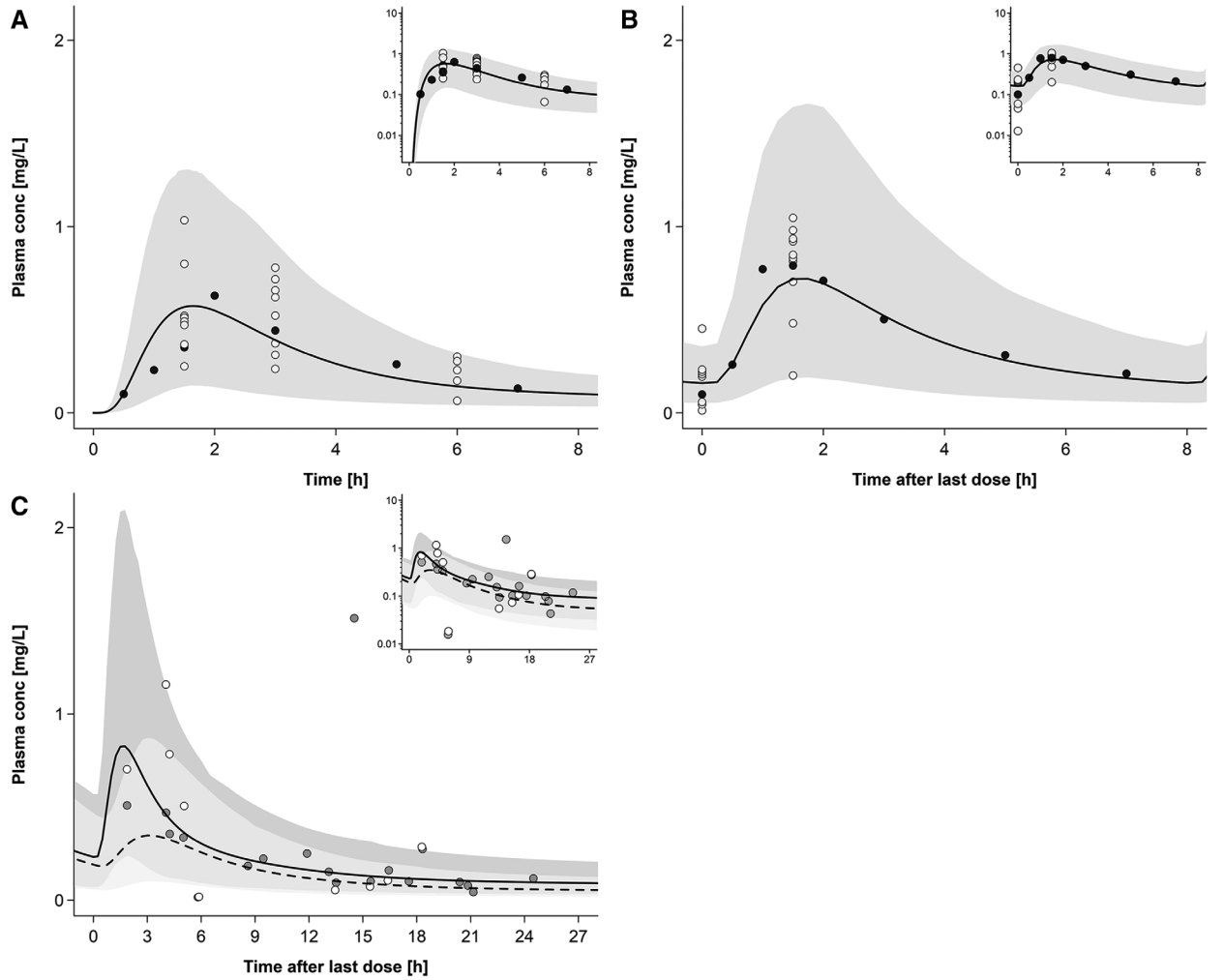

Figure 3. Plasma concentration-time profiles of acyclovir following oral administration of 400 mg in pregnant women. Semi-log scale figures are given as inset figures in the top right corners. Observed in vivo data were taken from published studies.[16–18] **A**, Single dose in pregnant women with an average gestational age of 36 weeks. Empty circles represent individual concentrations taken from Frenkel et al,[16] and closed circles represent mean concentrations in the maternal plasma taken from Kimberlin et al[17]; the solid line represents the predicted mean concentration, and the shaded area the predicted 5th to 95th percentile range. **B,** Multiple doses in steady state in pregnant women with an average gestational age of 38 weeks. Empty circles represent individual concentrations taken from Frenkel et al,[16] and closed circles represent mean concentrations in the maternal plasma taken from Kimberlin et al[17]; the solid line represents the predicted mean concentration, and the shaded area the predicted 5th to 95th percentile range. **C,** Multiple doses in steady state in pregnant women with an average gestational age of 40 weeks. Empty circles represent individual concentration data in the maternal plasma, and closed circles individual concentration data in the umbilical vein taken from Leung et al[18]; the solid and dashed lines represent the predicted mean concentration in the maternal plasma and umbilical vein, respectively, and the shaded areas the predicted 5th to 95th percentile ranges.

at 30 weeks of gestation, where a median AUC of 2.19 mg·h/L was predicted (Figure 5B).

For emtricitabine, the median C_{min} was predicted to decrease during pregnancy, reaching a trough value of 0.034 mg/L at 26 weeks of gestation. Despite this decrease, the median C_{min} was above the IC_{50} of 0.004 mg/L at all gestational weeks. However, the predicted C_{min} of patients in the very low percentiles fell slightly below the IC_{50} (Figure 5C). The predicted emtricitabine median AUC was also consistently decreased during pregnancy. Starting at a prepregnant value of 10.5 mg · h/L, the median AUC was predicted to decrease to a nadir value of 7.59 mg · h/L at 30 weeks of gestation. Despite this decrease, all median AUC values were above the desired AUC of ≥7 mg · h/L. Yet, the predicted AUC of patients in the lower percentiles fell also below the desired AUC (Figure 5D).

Evaluation of Predicted Drug Concentrations in the Umbilical Vein

Figure S5 in the supplement depicts the observed and simulated acyclovir concentrations measured in the ex vivo cotyledon perfusion experiment. The fitted D_{cot} was 0.056 L/h (95%CI 0.043-0.069 L/h), and the fitted K_{ppl} was 0.49 (95%CI 0.39-0.59). The

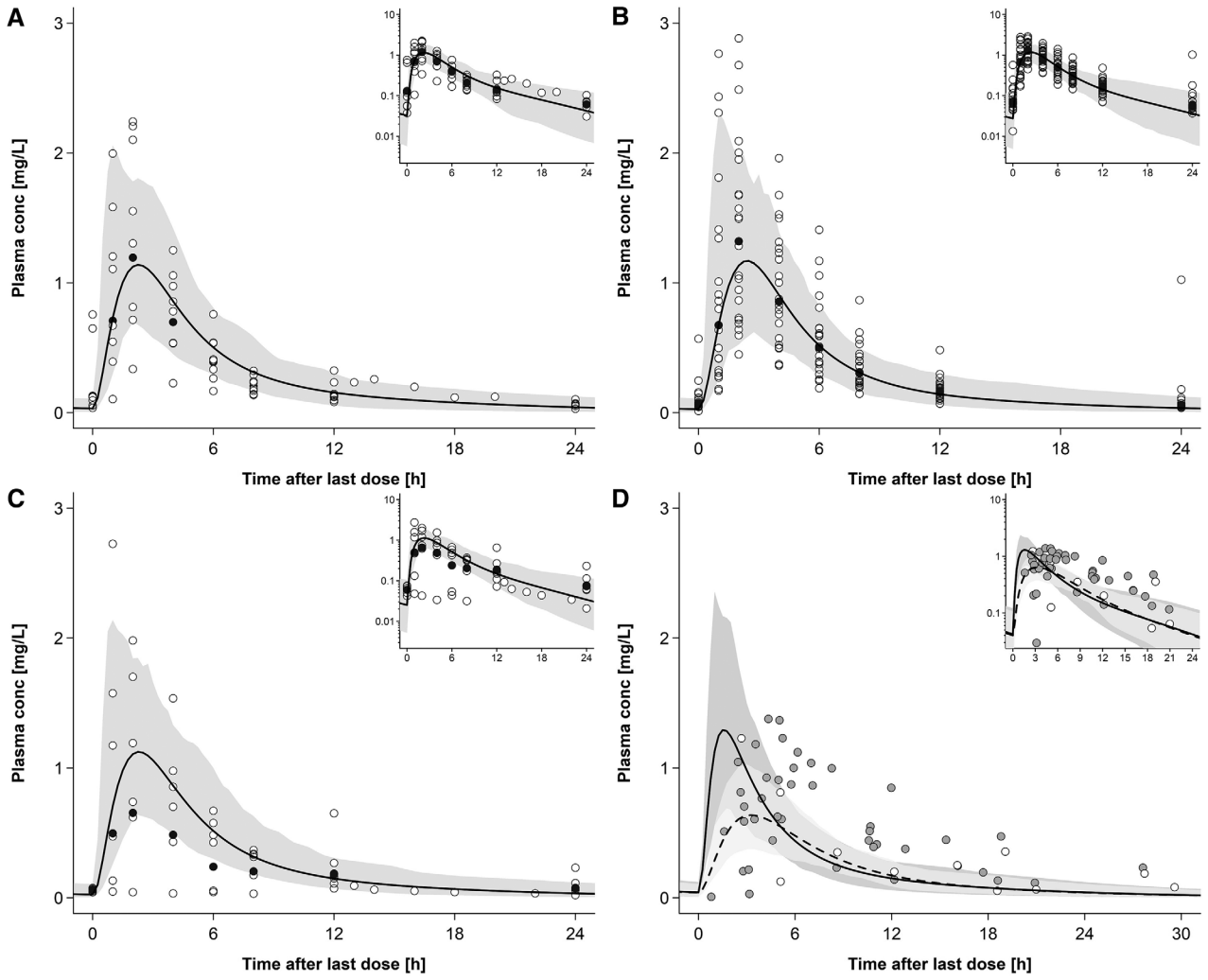

Figure 4. Plasma concentration-time profiles of emtricitabine following oral administration of 200 mg in pregnant women in steady state. Semi-log scale figures are given as inset figures in the top right corners. Observed in vivo data were taken from the described clinical study[23] and from another study published in the literature.[24] **A**, Pregnant women with a gestational age of 23-30 weeks; empty circles represent individual concentrations, and closed circles the geometric concentrations in the maternal plasma; the green line represents the predicted geometric mean concentration, and the shaded area the predicted 5th to 95th percentile range. **B**, Pregnant women with a gestational age of 31-35 weeks; empty circles represent individual concentrations, and closed circles the geometric concentrations in the maternal plasma; the green line represents the predicted geometric mean concentration, and the shaded area the predicted 5th to 95th percentile range. **C,** Pregnant women with a gestational age of 36-42 weeks; empty circles represent individual concentrations, and closed circles the geometric concentrations in the maternal plasma; the green line represents the predicted geometric mean concentration, and the shaded area the predicted 5th to 95th percentile range. **D**, Empty circles represent individual concentration data in the maternal plasma, and gray circles individual concentration data in the umbilical vein; the solid and dashed lines represent the predicted mean concentration in the maternal plasma and umbilical vein, respectively, and the shaded areas the predicted 5th to 95th percentile ranges.

scaled D_{pl} for acyclovir was 0.62 L/h. These values were integrated in the maternal-fetal PBPK model for acyclovir.

Figure 3C shows the observed and predicted concentrations of acyclovir in the umbilical vein and additionally those measured at the same time in the maternal plasma. As can be seen in this figure, umbilical vein concentrations were slightly underestimated. The predicted ratio between acyclovir concentrations in the umbilical vein plasma and the maternal plasma was between 0.30 and 0.85, whereas the observed ratios were slightly higher ranging from 0.61 to 1.1 in vivo.[16]

For emtricitabine, a total of 11 pairs of maternal plasma and umbilical cord concentrations were available from the clinical study, and an additional 33 concentration values in the umbilical vein were taken from the literature.[24] Figure 4D shows the observed and predicted concentrations of emtricitabine in the

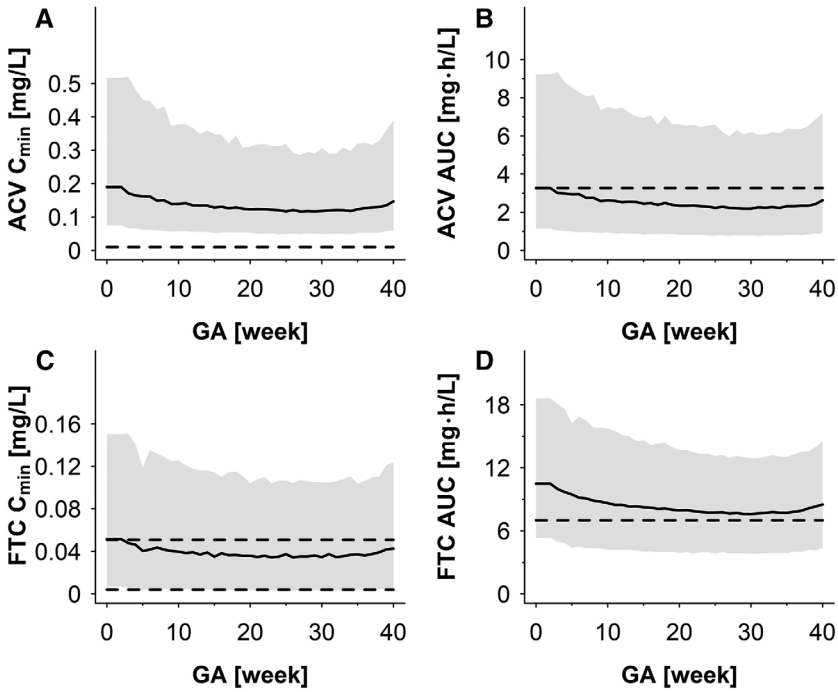

Figure 5. Predicted changes in PK target parameters of acyclovir (upper panels) and emtricitabine (lower panels) during pregnancy. **A,** The dashed line represents the reported half-maximal inhibitory concentration (IC_{50}),[30] the solid line the predicted median trough level (C_{min}), and the shaded area the predicted 5th to 95th percentile range. **B,** The dashed line represents the reported average exposure (AUC) in nonpregnant subjects,[15,32–37] the solid line the predicted AUC, and the shaded area the predicted 5th to 95th percentile range. **C,** The upper and lower dashed lines represent the reported IC_{50} and 90% of maximal inhibitory concentration (IC_{90}),[31] respectively, the solid line the predicted C_{min}, and the shaded area the predicted 5th to 95th percentile range. **D,** The dashed line represents the reported target AUC in pregnant subjects,[23,38,39] the solid line the predicted AUC, and the shaded area the predicted 5th to 95th percentile range. ACV indicates acyclovir; AUC, area under the concentration-time curve; C_{min}, trough drug concentration; FTC, emtricitabine; GA, gestational age; IC_{50}, drug concentration that produced 50% inhibition; PK, pharmacokinetics.

umbilical vein and maternal blood plasma. As can be seen from this figure, the predicted maternal and umbilical cord concentrations were in adequate agreement with the observed data, although the umbilical vein concentrations in the terminal phase were slightly underestimated. The observed geometric mean value of the paired concentrations in umbilical vein and maternal plasma was 1.1 and ranged from 0.66 to 1.80 in vivo. The predicted ratio of these concentrations was 0.99 (range 0.44-1.20).

Comparison of the Predictive Performance of Different Emtricitabine PBPK Models in the Third Trimester

Previously, 2 different pregnancy PBPK models for predicting emtricitabine PK around gestational week 33 have been published.[8,9] In these models, tubular net secretion was increased by 40% and 37%, whereas it was increased by 52% in the model presented here according to a previously discussed rationale,[6] which is also discussed further below. Figure 6 shows the observed emtricitabine plasma concentrations in the maternal plasma around gestational week 33 together with the predictions by the 3 different models. All 3 models appeared to describe maternal plasma concentration similarly well. Slight differences were observed among

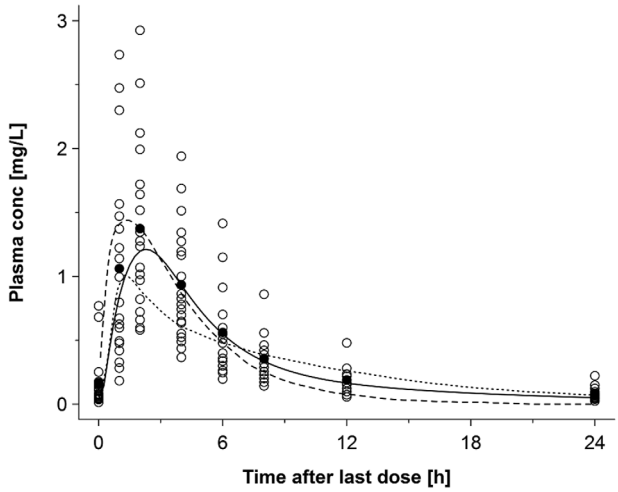

Figure 6. Emtricitabine plasma concentration-time profile in pregnant women around gestational week 33 following oral administration of 200 mg in steady state. Empty circles indicate individual observed plasma concentration data obtained from the publication of Mendes et al,[9] black circles indicate the mean values of these data; the dashed line indicates mean plasma concentrations predicted by Mendes et al,[9] the dotted line indicates mean plasma concentrations predicted by Xia et al,[8] and the solid line indicates mean plasma concentrations predicted by the model presented here. Data from Mendes et al[9] and Xia et al[8] were extracted from the published figures.

predicted C_{max}, time to C_{max} (t_{max}), and concentrations in the terminal phase.

Comparison of Different Approaches for Estimating Placental Permeability

The results of the different approaches for estimating the placental permeability of acyclovir were as follows: (1) 10.3 mL/min according to the ex vivo cotyledon perfusion experiment[25] (scaled from the cotyledon permeability to placental permeability according to Equation 2); (2) 5.37 mL/min according to the approach suggested by Zhang et al[29]; and (3) 3.10 mL/min according to the default method implemented in the OSP software. For emtricitabine, the results were (1) 18.8 mL/min according to the ex vivo cotyledon perfusion experiment[24] (scaled from the cotyledon permeability to placental permeability according to Equation 2); (2) 10.8 mL/min according to the approach suggested by Zhang et al[29]; and (3) 7.8 mL/min according to the default method implemented in the OSP software. To illustrate the effect of these differences on the predicted concentrations in the fetus, Figure S6 presents the predicted PK profiles in the umbilical vein together with the observed data.

Discussion

In the current study maternal-fetal PBPK models for emtricitabine and acyclovir were developed and evaluated by using in vivo data including both maternal and fetal concentration data obtained at different stages of pregnancy. In general, maternal PK was well predicted by the presented models as indicated by the fact that the observed values for C_{max}, t_{max} and $AUC_{0\text{-}tlast}$ were predicted within a 25% error range (Table 2). However, the description of interindividual variability was less adequate, especially for acyclovir, which is a general limitation in current PBPK models.[27,40]

However, several weaknesses of the models and analysis presented here are important to note. The presented PBPK models did not account for potential pregnancy-induced changes in the gastrointestinal tract, and hence the predicted absorption profile is similar to that simulated in nonpregnant women. Still, it is debatable whether pregnancy affects drug absorption or not; for example, although there is no consensus yet, some authors reported changes in drug absorption during pregnancy due to altered gastric acid secretion and small intestine motility,[41] and for other antiretroviral drugs such as elvitagravir boosted with cobicistat, bioavailability appears to be decreased in pregnant women.[42]

In the presented models, changes in drug distribution were preliminarily driven by increases in the volume of the blood plasma and other tissues (eg, fat tissue)[27] and in the drug's fraction unbound. Unfortunately, no PK data following intravenous administration of the herein modeled drugs were reported, complicating an evaluation of the predicted drug distribution. However, results from previously developed pregnancy PBPK models for different intravenously administered drugs (namely, cefazolin, cefradine, cefuroxime, and acetaminophen) indicated that disposition kinetics at various stages of pregnancy were adequately predicted.[27,43] Specifically, the mean volume of distribution for all 4 drugs was predicted within a 15% error range, which increases the confidence that the aforementioned physiological changes are correctly implemented in the model and the drug distribution adequately captured.

There are some data showing that women have a higher ganciclovir clearance after correction for individual body surface area and estimated glomerular filtration rate compared with men.[44] Unfortunately, no PK data following intravenous administration of acyclovir in nonpregnant women were available. The presented nonpregnant model for intravenous administration was developed on the basis of PK data from men, which might have led to an underestimation of acyclovir clearance when extrapolated to pregnant women. Further research is needed to clarify these points during pregnancy.

Previous studies reported conflicting findings on a potential effect of food on emtricitabine absorption.[4,45,46] In 1 study, administration of emtricitabine under fasting conditions resulted in a higher mean plasma concentration as compared with fed conditions.[4,45] Under fasting conditions, observed emtricitabine C_{max} was reached within 1.25 hours postdose, whereas under fed conditions C_{max} was reached after 3 hours postdose.[4,45] In most of the nonpregnant PK studies used herein for model evaluation, emtricitabine was administered in the fasted state. However, the clinical study in pregnant women did not strictly control the prandial state at the study visits. According to the study protocol, concomitantly administered atazanavir in 11 patients was administered following intake of a light meal (~360 kilocalories), suggesting that at least in these patients emtricitabine was taken in the fed state. Consequently, a light meal intake was incorporated in all maternal-fetal PBPK models, which resulted in a decrease in C_{max} and increase in t_{max} compared with that simulated in nonpregnant women. $AUC_{0\text{-}t}$ was not affected, and was virtually identical between fasted and fed state predictions in pregnant populations. These findings suggest that there may be a negative food effect on emtricitabine PK; however, because exposure is unaffected, this food effect is probably of no clinical significance.

Both drugs investigated herein are not exclusively cleared via the kidneys but are metabolized to a minor extent. A small dose fraction of acyclovir (8.5% to 14.1%[5]) is metabolized via aldehyde dehydrogenase 2 (ALDH2). Currently, no information is available from in vivo studies investigating the effect of pregnancy on the expression or activity of ALDH2. Transcription of *ALDH2* in vitro has been observed to be under the control of hepatocyte nuclear factor 4.[47] In pregnant mice expression of hepatocyte nuclear factor 4 was found to be unchanged in the third trimester.[48] This finding provides some evidence that ALDH2 may be unchanged during pregnancy, although further studies are needed to confirm this point. A similar conclusion may be drawn for emtricitabine, for which the enzyme involved in metabolism is unknown. Emtricitabine is metabolized by oxidation of the thiol moiety to form the 3′-sulfoxide diastereomers and by conjugation with glucuronic acid to form 2′-O-glucuronide. These reactions do not appear to be catalyzed by the cytochrome P450 enzyme system.[23] In the PBPK models presented, metabolic clearance of both acyclovir and emtricitabine was unchanged during pregnancy. Although the small dose fractions metabolized via these pathways may mask slight changes, the fact that clearance was adequately predicted during pregnancy suggests that no substantial changes can be expected. Yet, more research is clearly needed to confirm this hypothesis.

Both emtricitabine and acyclovir are substrates of renal drug transporters. Emtricitabine is a substrate for the efflux transporters MATE1[49,50] and MRP1.[51] The influx transporter for emtricitabine has not yet been identified. Acyclovir is a substrate for multiple transporters including influx transporters OAT1,[52,53] OAT2,[11] OAT3,[53] and organic cation transporter 1 (OCT1),[52] and the efflux transporters MATE1[49,50] and MATE2.[49,50] To date, clear evidence of the effect of pregnancy on the expression of these transporters is lacking. In the maternal-fetal PBPK models presented, the predicted increase in total renal clearance could be attributed to multiple factors, especially the rise in glomerular filtration rate, kidney volume, renal blood flow, and fraction unbound. Similarly to a previous study,[27] a univariate sensitivity analysis of these parameters was conducted. Specifically, the plasma concentration-time profile for acyclovir and emtricitabine was simulated while these factors in the model were either kept constant (fixed to the nonpregnant value) or changed to the pregnant value (Figure S7). This analysis demonstrated that the rise in glomerular filtration rate, fraction unbound, and renal blood flow was not sufficient to describe the observed increase in total renal clearance. In fact, the higher kidney volume was the major factor affecting the predicted increase in tubular net secretion (leading to a directly proportional increase in tubular secretion rate) and was hence needed to correctly predict the observed increase in total renal clearance (Figure S7).

Although it is debatable whether the kidney growth observed in vivo is associated with hyperplasia, the growth is typically attributed to an increase in the intravascular and interstitial volume of the kidneys.[54] Yet, the same increase in renal clearance could also be predicted if the tubular secretion rate is increased while kidney volume remains constant, as discussed elsewhere in greater detail.[6] Currently, there is only limited information available on renal physiology and renal transporters in pregnant women, which hinders the identification of the factors underlying the observed increase in tubular net secretion clearance. In previous pregnancy PBPK models for emtricitabine,[8,9] the rise in tubular net secretion was informed either on the basis of observed increases in net secretion clearance of metformin, a well-known substrate of OCT2, or on the basis of observed increases in renal plasma flow. Accordingly, tubular net secretion in the third trimester was increased by 40%[8] or by 37%,[9] which is lower than the 52% increase applied in the current model. Although each of these factors (increase in kidney volume, metformin net secretion, and renal plasma flow) appears to be a good descriptor of the observed increase in tubular net secretion clearance during pregnancy, further in vitro and in vivo data are needed to uncover the physiological mechanism(s) behind the clearance increase.

Apart from transporter expression in the kidneys, transporters may also play an important role in drug transfer across the placenta. The presented PBPK models for both drugs do not include any transporters in the placenta that may potentially increase (influx transporters) or decrease (efflux transporters) fetal drug exposure. However, most of the abovementioned transporters (OAT1/2/3 and MATE1/2) are not or only weakly expressed in the placenta,[55,56] suggesting that they can be neglected in the model. However, MRP1 was found to be expressed in the term placenta.[57] Although not explicitly implemented in the form of transporter-mediated kinetics, the model implicitly accounts for transporters in the placenta to some extent because the partition coefficient between the maternal and fetal compartment does not equal 1. For drugs that cross the placenta exclusively through passive diffusion, a partition coefficient of 1 can be assumed.[7] In equilibrium, a partition coefficient of >1 results in concentrations in the fetal compartment that exceed those in the maternal compartment, if there is no substantial drug clearance in either of the 2 compartments (as is the case of emtricitabine). In case of acyclovir the predicted fetal concentrations were relatively insensitive

to changes in the transfer constant but sensitive toward changes in the partition coefficient (data not shown). Specifically, fetal concentrations were slightly underestimated by the PBPK model because the partition coefficient, which was identified on the basis of data from the ex vivo cotyledon perfusion experiment,[26] was smaller than 1, resulting at equilibrium in higher concentrations on the maternal side compared with the fetal side of the placenta. It is questionable whether the in vivo partition coefficient for acyclovir is smaller than 1. Further research is needed to elucidate this point.

The comparison of different approaches for estimating the placental permeability of acyclovir and emtricitabine revealed interesting results. Whereas the ex vivo cotyledon perfusion experiment is considered the gold standard for placental transfer,[58] the approach suggested by Zhang and Unadkat[29] appeared to perform similarly well. The default method implemented in OSP assumes that placental permeability can be approximated by the membrane permeability for other tissues (eg, muscle). Figure S6 reveals that this approach performed poorly, suggesting that the permeability across the placenta is much higher than the permeability across the membrane of other tissues. The active drug transport across the placenta can implicitly be factored into the permeability rate, but further studies should address the deconvolution of passive and active processes because it provides a greater mechanistic understanding of the transfer processes that may ultimately facilitate an extrapolation to earlier stages of pregnancy or even to other compounds.

This study also investigated the pregnancy-induced alterations in PK target parameters. However, any conclusions on adequate dosing regimens necessitate considering drug pharmacodynamics in addition to its PK, which was beyond the scope of this study. It should also be noted that the patients investigated who were living with HIV took multiple antiviral drugs. The clinical study used herein for model evaluation during pregnancy coadministered emtricitabine with multiple other antiretroviral medications including atazanavir, didanosine, efavirenz, lopinavir, ritonavir, tenofovir, and zidovudine. However, none of these comedications is expected to interact with emtricitabine.[59–61] Lahiri et al reported that darunavir increases concentrations of emtricitabine in the plasma and cerebrospinal fluid,[62] but this drug combination was not taken in the current study. Even though no drug-drug interactions between emtricitabine and other antiviral drugs were expected in this study, the drug effect, ie, viral load suppression, necessarily represents a combined effect of multiple antiviral drugs, which complicates the development of a mechanistic PD model. In the current study the median C_{min} of acyclovir as well as the C_{min} in the 5th percentile was predicted to be consistently above the reported IC_{50} throughout pregnancy. For emtricitabine, the median C_{min} and AUC predicted throughout pregnancy were also above the reported target thresholds. However, for patients in the lower percentiles, both C_{min} and AUC in late second trimester and at the beginning of the third trimester were predicted to be lower than the IC_{50} and desired AUC, respectively. Further research may help to clarify the clinical significance these findings. For example, population PK models that precisely capture interindividual variability may be used to investigate combined emtricitabine/tenofovir pharmacokinetics in lower percentiles and assess whether these patients receive adequate therapy. It is noteworthy that the antiretroviral effect of tenofovir might also be compromised because this antiretroviral is also predominantly cleared via the kidneys. However, further studies are clearly needed to evaluate this finding.

The PBPK models developed herein are based on the described population and have not been adjusted for pharmacogenetic differences or ethnicity. For emtricitabine and acyclovir, however, no changes in this regard are expected.

Conclusions

In conclusion, the developed maternal-fetal PBPK models successfully predicted the PK profiles of emtricitabine and acyclovir at different stages of pregnancy. This increases the confidence in leveraging 1 of the main strengths of PBPK analyses, namely the extrapolation of drug PK from a well-characterized population of healthy adults to the special population of pregnant women. Investigations of the pregnancy-induced change in PK target parameters confirm the adequacy of the current dosing regimens for acyclovir and emtricitabine, at least for the typical pregnant patient. Compared with previously published pregnancy PBPK models for emtricitabine, the model presented here captured the observed maternal plasma concentrations similarly well. In view of previously published pregnancy PBPK models for renally cleared drugs,[6] the presented model increases confidence in such models, which is a key prerequisite if they are applied to inform the design of clinical trials for drugs with similar PK characteristics in pregnant women. Because participation of pregnant women in clinical trials is generally limited, PBPK modeling can complement the PK understanding in cases where clinical data are sparse (or even missing).[63] Although these models should not be seen as a substitute for clinical trials, they can contribute to a broader and mechanistic PK understanding that holds the potential to ultimately improve drug safety and efficacy for both the mother and her fetus.

Author Contributions

X.I.L., J.D.M., N.R., J.N.V.D.A., D.J.G., G.J.B., B.M.B., M.M., E.V.C., and A.D. wrote the manuscript. X.I.L., J.D.M., B.M.B., M.M., E.V.C., and A.D. designed the research. X.I.L., J.D.M., B.M.B., M.M., E.V.C., and A.D. performed the research. X.I.L., J.D.M., and A.D. analyzed the data.

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Data Sharing

The authors are unable to share the clinical data on emtricitabine supporting the results of this study. All other data, including the models, will be made available on GitHub (https://github.com/Open-Systems-Pharmacology) on publication of this article.

Disclaimer

The opinions expressed in this article are those of the authors and should not be interpreted as the position of the U.S. Food and Drug Administration or of the National Institutes of Health.

Conflicts of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Dr André Dallmann is an employee of Bayer AG, a company that is part of the Open Systems Pharmacology (OSP) member team and involved in OSP software development. The results from this study were presented in part at the American College of Clinical Pharmacology Annual Meeting, Washington, DC, September 2018.

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