#35

Tenofovir plasma concentrations in pregnant women: comparison of hepatitis B and HIV-infected patients

Vera Bukkems,[1] Elise Smolders,[1,2] Gonzague Jourdain,[3,4] David Hawkins,[5] Jullapong Achalapong,[6] Prateep Kanjanavikai,[7] Graham Taylor,[8] Sinart Prommas,[9] David Burger,[1] Angela Colbers,[1] Tim R. Cressey,[3,4,10] for the iTAP Study Team & PANNA network

1 Department of Pharmacy, Radboud Institute for Health Sciences, Radboud university medical center, Nijmegen, The Netherlands; 2 Isala hospital, Zwolle, The Netherlands; 3 Chiang Mai University, Thailand; 4 Harvard T.H. Chan School of Public Health, MA, USA; 5 Chelsea & Westminster hospital, London, UK; 6 Chiangrai Prachanukroh Hospital, Chiang Rai, Thailand; 7 Banglamung hospital, Chonburi, Thailand; 8 St. Mary's Hospital, London, UK; 9 Bhumibol Adulyadey Hospital, Bangkok, Thailand; 10 University of Liverpool, UK..

Background

- Tenofovir disoproxil fumarate (TDF) is one of the preferred drugs to prevent mother to child transmission in both hepatitis B (HBV)- and HIV-infected pregnant women.
- Previously we found decreased exposure of approximately 20% in HBV-mono-infected pregnant women and a similar decrease was observed in HIV-mono-infected pregnant women.
- These results in HBV and HIV mono-infected women cannot be directly compared since HIV-patients may use co-medications such as ritonavir which increase tenofovir (TFV) plasma concentrations.
- This comparison is interesting as infection itself could also have an effect on the drug exposure.

Objectives

The aim of this study was to compare the effect of pregnancy on TFV exposure in women receiving TDF monotherapy for HBV mono-infection with TFV exposure in HIV-infected women on TDF with and without ritonavir boosted protease inhibitors (PI/r).

Methods

- Data from the previously published iTAP study and "Pharmacokinetics of Antiretroviral Agents in HIV-infected Pregnant Women" (PANNA) network were analyzed retrospectively. The study design of both studies is described in Table 1.
- The data was extended with 30 new TFV curves from the PANNA network.
- Descriptive statistics were used to compare the AUC and C_{trough} of HBV and HIV-mono-infected women during pregnancy and postpartum. The ratio of pregnancy/ postpartum is used to compare the pregnancy effect between HBV and HIV patients.
- The HIV-infected group was divided in patients with and without concomitant PI/r use to rule out the effect of interacting antiretroviral drugs.

Table 1: Study design of iTAP study and PANNA network

	iTAP study	PANNA network
Subjects	HBV-infected pregnant women from Thailand randomized to TDF or placebo	HIV-infected pregnant women from Europe using TDF
Pharmacokinetics	Single random blood samples during pregnancy and postpartum	Intensive 24-hour pharmacokinetic sampling during pregnancy and postpartum
Bioquantification	Validated LC-MS/MS assay	Validated RP HPLC method (old) & validated LC-MS/MS assay (new)
PK analysis	Compartmental analysis with NONMEM	Non-compartmental analysis with Phoenix 64

Results

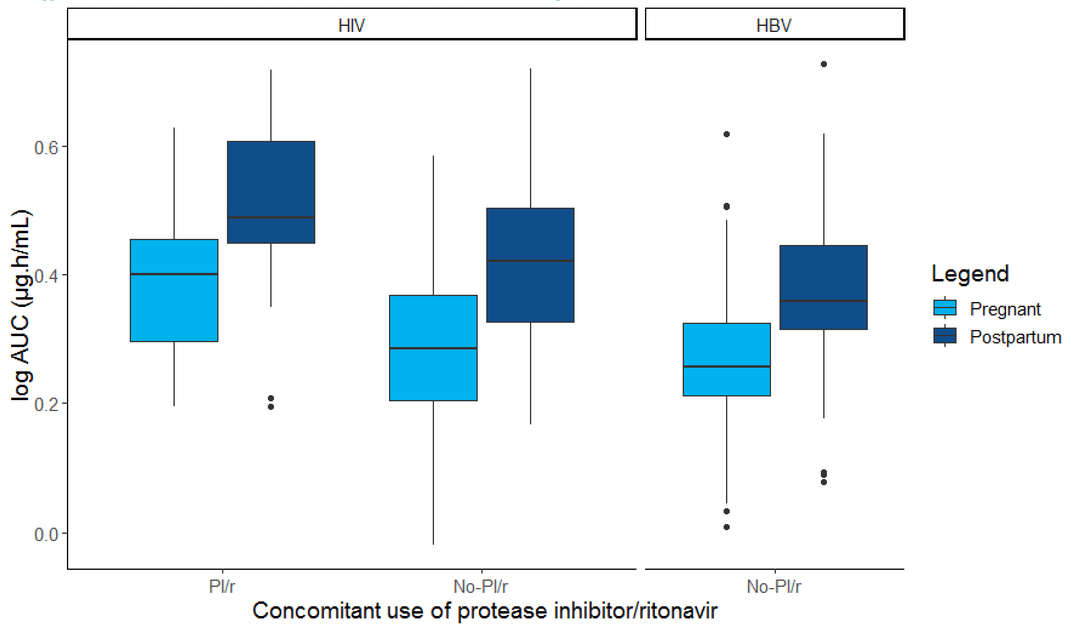
- The pharmacokinetic parameters of 64 HIV-infected patients from the PANNA network and 137 HBV-infected patients from the iTAP study were included.
- The patient characteristics are depicted in Table 2.

Table 2: Patient characteristics

	HIV (n=64)	HBV (n=137)
Maternal age, years [median (IQ range)]	32 (26-36)	26 (23-29)
PANNA: Ethnicity [n (%)] **iTAP: Country of inclusion**	Caucasian: 34% Black: 59% Asian: 3% Other: 4%	Thailand
Concomitant antiretrovirals [n (%)]	PI: 34 (53%) - Atazanavir: 17 (27%) - Darunavir: 12 (19%) - Fosamprenavir 1 (2%) - Lopinavir: 2 (3%) - Saquinavir: 2 (3%) - Ritonavir: 34 (53%) INSTI: 10 (16%) NNRTI: 22 (34%) Other antiretrovirals: 2 (3%)	-
Duration of TDF treatment at moment of first curve, months [median (IQ range)]	12 (5-34)	0.94 (0.85-1.01)
Third trimester	n=63	n=124
Gestational age, weeks [median (IQ range)]	33 (33-35)	32 (32-32)
Body weight, kg [median (IQ range)]	74 (67-83)	64 (58-73)
Creatinine concentration, µmol/L [median (IQ range)]	53 (44-58)	55 (50-60)
HIV-RNA undetectable <50 copies / ml [n (%)]	51 (82%): 2 unknown	-
Post partum	n=57	n=115
Time after delivery, weeks [median (IQ range)]	5 (5-6)	4
Body weight, kg [median (IQ range)]	70 (60-77)	56 (51-63)
Creatinine concentration, µmol/L [median (IQ range)]	66 (60-71)	73 (66-85)
HIV-RNA undetectable <50 copies / ml [n (%)]	48 (87%): 2 unknown	-
Pregnancy outcomes		
Gestational age at delivery, weeks [median (IQ range)]	39 (38-40)	39 (38-40)

Results (continued)

Figure 1: Tenofovir AUC of HIV- and HBV-infected patients



- Boxplots of the TFV log $AUC_{0\text{-}24}$ in HBV and HIV-patients are shown in Figure 1
- The descriptive statistics of TFV $AUC_{0\text{-}24}$ and C_{trough} are shown in Table 3.
- $AUC_{0\text{-}24}$ geometric mean (GM) seems to be higher in HIV-infected women overall during third trimester and postpartum compared to HBV-infected women. This effect is less clear when comparing the $AUC_{0\text{-}24}$ of HIV patients without PI/r with HBV-patients.
- $AUC_{0\text{-}24}$ geometric mean ratio (GMR) third trimester / postpartum is similar in HIV- and HBV-infected patients, with and without PI/r concomitant usage.
- C_{trough} GM seems to be higher in HIV-infected women with PI/r during third trimester and postpartum compared to HBV-infected women. GM C_{trough} of HIV-infected patients without concomitant boosted PIs is similar to HBV-infected patients during third trimester and postpartum.
- C_{trough} GMR third trimester / postpartum seems different between HIV-patients with PI/r and HBV-infected patients. However, the GMR C_{trough} of HIV-patients without PI/r is similar to HBV-patients.

Table 3: Tenofovir pharmacokinetic parameters

	Subgroup	Third trimester GM (95%CI)	Postpartum GM (95% CI)	Third trimester / postpartum GMR (90%CI)
	$AUC_{0\text{-}24}$ (ug*h/mL)			
HIV	All patients	2.18 (2.01-2.37)	2.87 (2.64-3.13)	0.75 (0.70-0.80)
	- Concomitant boosted PIs	2.44 (2.22-2.68)	3.21 (2.85-3.62)	0.75 (0.67-0.82)
	- No concomitant boosted PIs	1.92 (1.70-2.18)	2.60 (2.32-2.91)	0.74 (0.68-0.81)
HBV	No concomitant boosted PIs	1.84 (1.77-1.92)	2.35 (2.24-2.47)	0.79 (0.78-0.80)
	C_{trough} (ug/mL)			
HIV	All patients	0.044 (0.040-0.048)	0.061 (0.055-0.067)	0.72 (0.66-0.79)
	- Concomitant boosted PIs	0.049 (0.043-0.055)	0.063 (0.053-0.075)	0.79 (0.68-0.92)
	- No concomitant boosted PIs	0.039 (0.034-0.044)	0.059 (0.051-0.067)	0.67 (0.61-0.73)
HBV	No concomitant boosted PIs	0.039 (0.038-0.042)	0.058 (0.055-0.061)	0.69 (0.68-0.71)

Conclusion

- **Pregnancy had a similar effect on tenofovir pharmacokinetics in HIV-infected women as in HBV-infected women.**
- **Ritonavir boosted protease inhibitors do not seem to influence the effect of pregnancy on tenofovir pharmacokinetics**
- **Although the pregnancy effect is similar, tenofovir exposure is lower in HBV-infected women as in HIV-infected women using concomitant boosted protease inhibitors. However, the exposure is similar to HIV-infected women on a regimen without boosted protease inhibitors.**

DISCLOSURES: The PANNA network is financially supported by the "European AIDS Treatment Network (NEAT)", EC, DG Research, 6th Framework program, BMS, MSD, ViiV Health Care, Janssen Pharmaceuticals N.V. and Gilead Sciences. The iTAP study is financially supported by The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) (U01HD071889) under a cooperative agreement between NICHD, the Centers for Disease Control and Prevention, United States of America; and Institut de recherche pour le développement, France. Study drugs (TDF and matching placebo) for iTAP study are donated by Gilead Sciences Inc., CA, United States of America

Presented at the 20th International Workshop on Clinical Pharmacology of HIV, hepatitis & other antiviral drugs, 2019, Noordwijk, The Netherlands

Vera Bukkems
Department of Pharmacy
Radboud university medical center
PO Box 9101
6500 HB Nijmegen
The Netherlands
Tel: +316 50060422
Vera.Bukkems@radboudumc.nl
www.pannastudy.com

Institute for Health Sciences
Radboudumc