First report of dolutegravir unbound plasma concentrations during pregnancy in HIV-positive women

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19th International Workshop on Clinical Pharmacology of Antiviral Therapy
22-24 May 2018 in Baltimore, USA.

Institute for Health Sciences
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Disclosures - partners PANNA

- NEAT/PENTA
- Merck
- BMS
- Janssen
- ViiV Healthcare
- Gilead

A European clinical pharmacology network to investigate the Pharmacokinetics of newly developed ANtiretroviral agents in HIV-infected pregNAnt women

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Dolutegravir in HIV+ pregnant women

- Antiretroviral treatment (ART) to reduce the risk of mother to child transmission and for the health of the mother

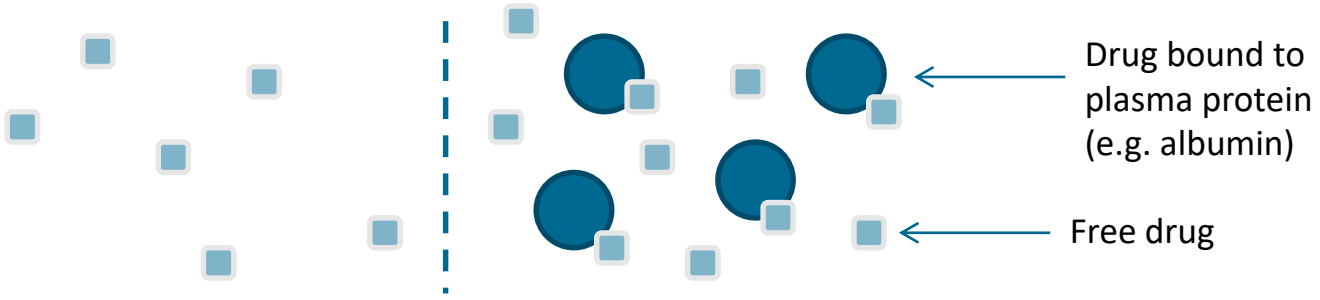
- Advice on dolutegravir (DTG) in guidelines on ART in pregnant HIV-positive women:
  - US: DTG listed a alternative agent[1]
  - EU: ART in pregnancy is the same as in non-pregnant women; women on DTG could continue their treatment[2]
  - WHO: delayed roll-out of DTG in LMIC; i.a. due to lack of data in pregnancy[3]

- Increasing data on safety and pharmacokinetics on the use of DTG in pregnancy[4]

[1] DHHS guidelines. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women. Nov 14, 2017. [2] EACS guidelines 2017, version 9.0. [3] WHO, Briefing Note 'Dolutegravir (DTG) and the fixed dose combination (FDC) of tenofovir/lamivudine/dolutegravir (TLD)', April 30, 2018. [4} Hill, A., et al., J Virus Eradication 2018; 4:66-71.

Pharmacokinetics DTG in pregnancy

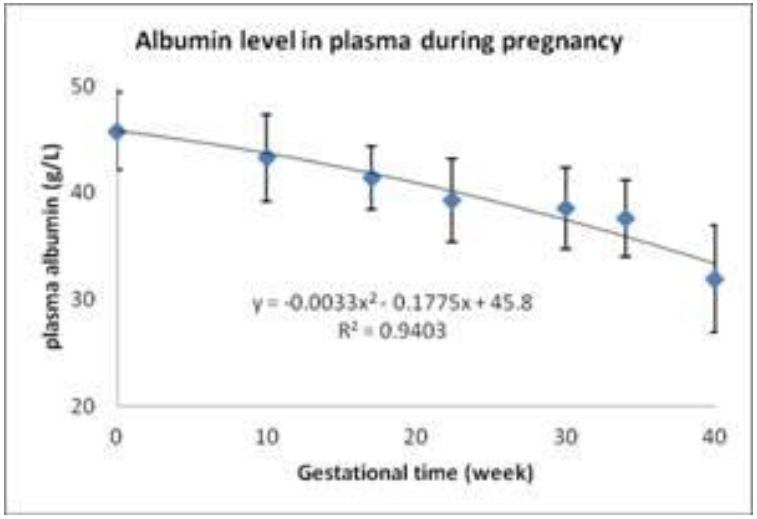
- Physiological changes in pregnancy may affect drug concentrations
- In pregnancy $AUC_{0\text{-}24h}$ and C_{24h} DTG based on total drug concentrations were 5-29% and 44% lower, respectively, in third trimester compared to post partum [1,2]
- In general only that fraction of the drug concentration that is freely circulating or unbound plasma proteins in extracellular water can penetrate cell membranes and can exert its pharmacological effect



[1] Mulligan et al., AIDS 2018, 32:729–737. [2] Bollen et al., 18th International Workshop on Clinical Pharmacology of Antiviral Therapy, July 2017, Chicago, USA. Abstract O_07.

Plasma protein binding

- Serum albumine levels decrease in pregnancy

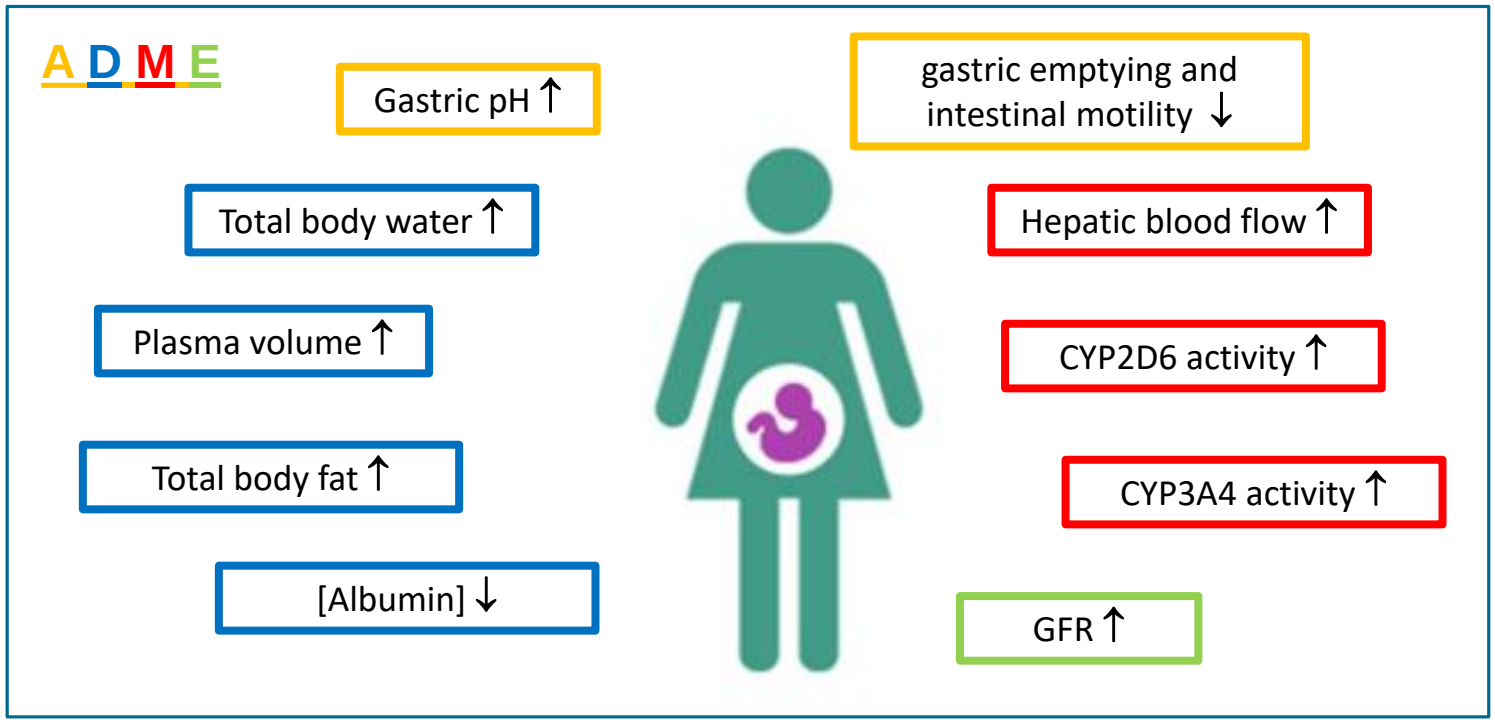


Abduljalil et al., Clin Pharmacokinet 2012; 51 (6): 365-396

- Dolutegravir:
  - DTG is highly bound to human plasma proteins (>99.3% in vitro) and exhibits a low extraction rate [1]
  - Reduction of antiviral potency with increasing percentages of human serum albumin in vitro [2]

[1] Letendre et al., Clin Infect Dis. 2014 Oct;59(7):1032-7.
[2] Kobayashi et al., AAC, Feb. 2011, p. 813–821.

Pharmacokinetics in pregnancy



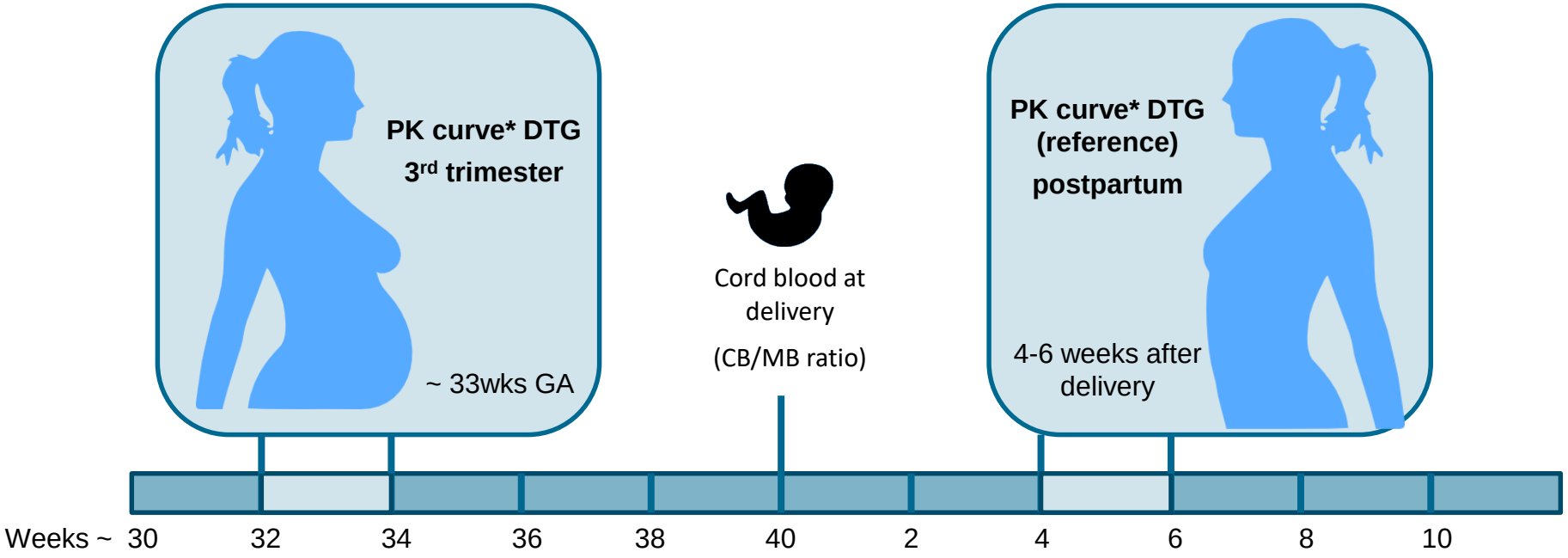
Changes in C_{Free} are not always proportional to changes in C_{Total} in case of altered pharmacokinetics >> Need to assess C_{Free} for highly protein bound drugs in pregnancy

Objectives

- To evaluate unbound DTG concentrations in pregnant HIV-positive women the 3rd trimester and postpartum

Method

- DTG arm PANNA study:



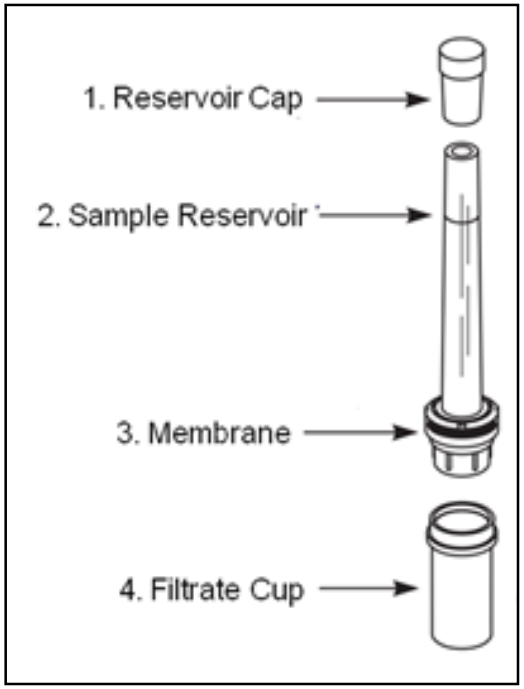
*Blood samples: predose, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24h after dosing

- Measuring unbound DTG in C_{min} and C_{max} samples selected from PK curves

Method

- Obtainment of free drug-concentrations trough ultrafiltration
  - 500 µL EDTA plasma
  - Centrifuge at 37°C; 20 min at 1650 rpm
- Quantification of DTG free drug concentrations in EDTA plasma with a validated LC-MS/MS quantification method

Ultrafiltration device



Linear range (ng/mL)	Between run precision (% CV)	Between run accuracy (% Bias)	QC levels (ng/mL)
0.5-500	≤ 13.8%	0 ≥ bias ≤ 8.2%	0.5, 2.5, 30, 250, 500

Patient characteristics

- 9 women on dolutegravir 50mg QD included in 4 European hospitals (June ‘15 - June ‘17)
  - 3 women only 3rd trimester PK

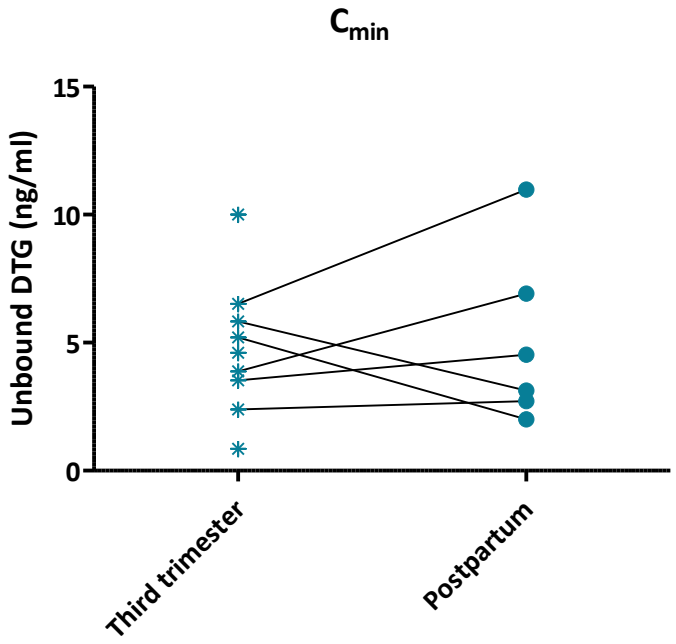
Demographics at delivery	Median (range) or n(%)
Age, *years*	30 (21-42)
Gestational age, *weeks*	38 (34-40)
HIV-1 RNA < 50 cps/mL	9 (100%)
Regimen DTG + TDF/FTC DTG/ABC/3TC DTG + DRV/r +TDF	 4 (44%) 4 (44%) 1 (12%)
DTG exposure in 1st trim	4 (44%)

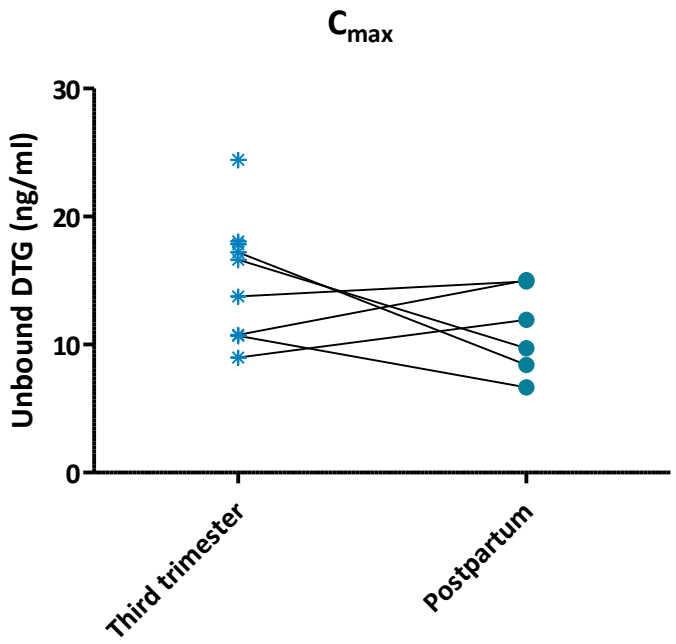
Results

		3rd Trimester	Postpartum
N		9	6
$C_{min, unbound}$	ng/mL	4.0 (80)	4.2 (70)
$C_{min, total}$	ng/mL	710 (102)	1070 (61)
Fraction unbound	%	0.63 (0.43-0.73)	0.33 (0.28-0.70)
$C_{max, unbound}$	ng/mL	15 (33)	11 (33)
$C_{max, total}$	ng/mL	3417 (31)	3350 (47)
Fraction unbound	%	0.40 (0.35-0.56)	0.29 (0.27-0.38)

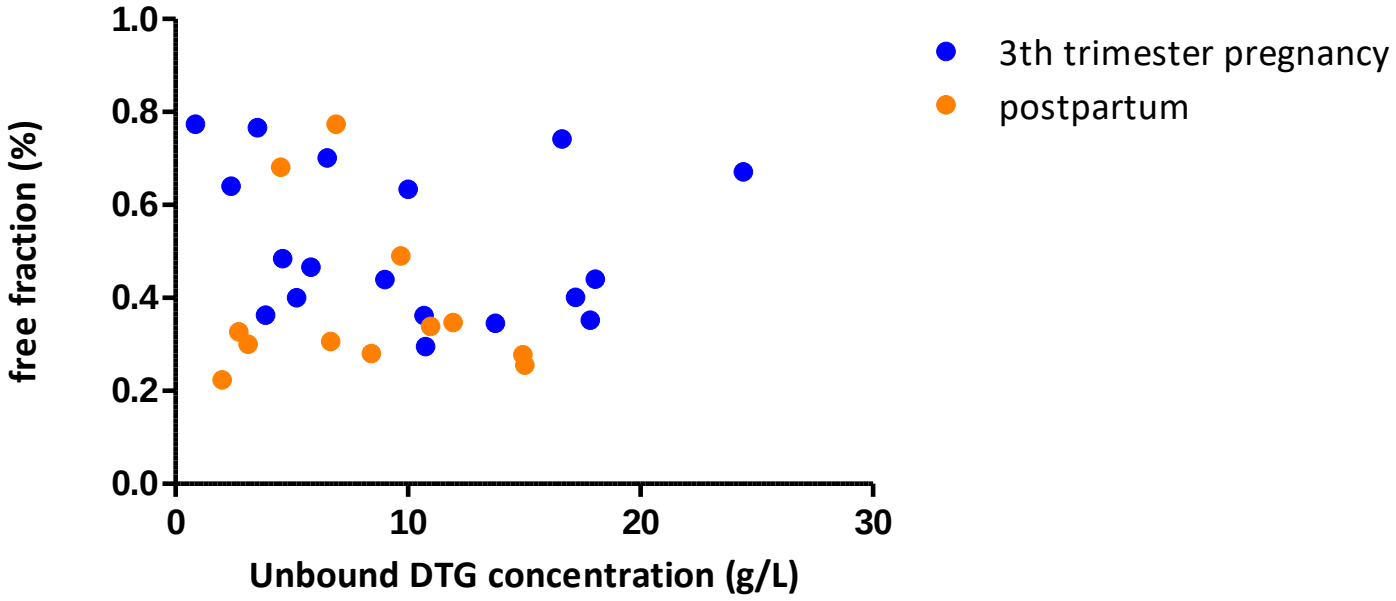
Values are expressed as geometric mean (CV%), except for fraction unbound; median (IQR).

Individual unbound concentrations

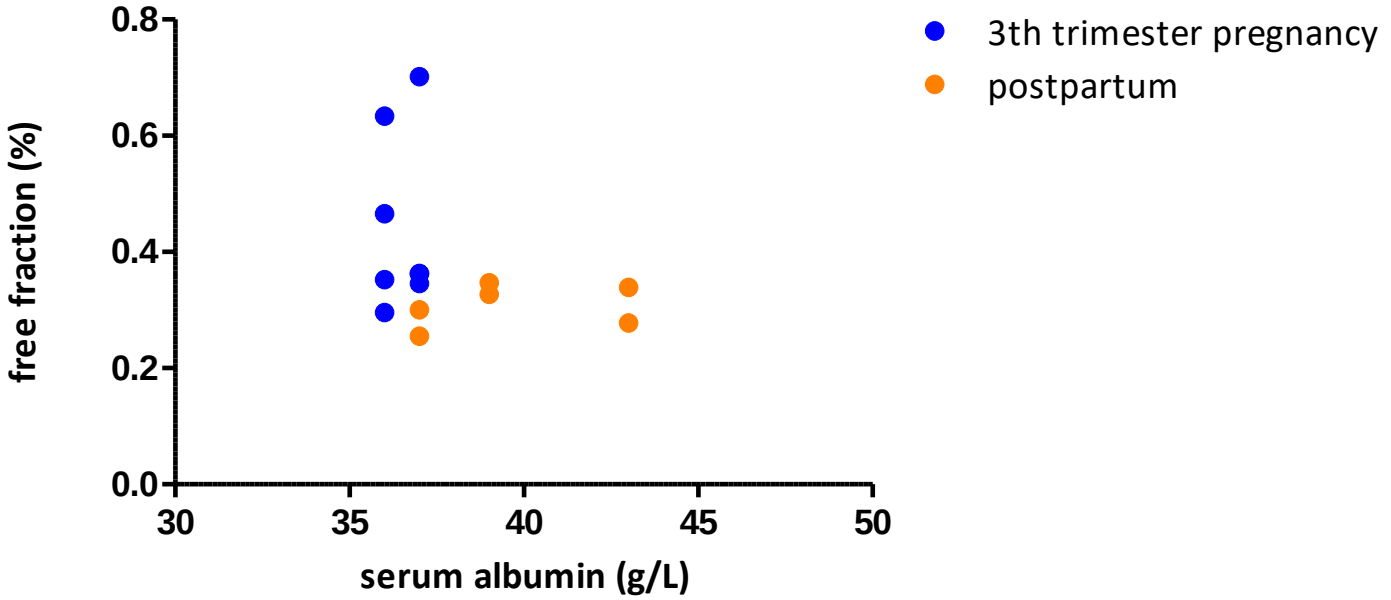




Free fraction versus C_{free}



Free fraction *vs* albumin level



[Albumin], median (IQR)	3rd trimester (n=4)	36.5 (36-37) g/L
	post-partum (n=3)	39.0 (37-43) g/L

Discussion

- For C_{min}, total DTG concentrations were lower and free DTG concentrations were comparable in 3rd trimester *vs* post-partum; this could be the result of lower serum albumin concentrations in 3rd trimester.

- DTG fraction unbound;
  - Free fraction in 3rd trimester > post-partum; 0.40-0.63% *vs* 0.29-0.33%
  - Free fraction in non-pregnant in this study < free fraction in HIV-positive subjects in literature; ~0.29-0.33% *vs* ~0.49% [1]
  - Assay differences; cross validation with dialysis membrane sample preparation method

[1] Letendre et al., Clin Infect Dis. 2014 Oct;59(7):1032-7.

Conclusion

- In late pregnancy total dolutegravir exposure is lower, however unbound dolutegravir plasma C_{min} seems unchanged in the 3rd trimester as compared to postpartum.

- Free fraction of DTG in pregnant women in the 3rd trimester in this study is ~0.4-0.63%.

- Although the sample size was small, these findings, coupled with the undetectable viral loads at delivery, suggest uncompromised efficacy of dolutegravir 50mg QD in pregnancy.

Acknowledgements

- Participants PANNA study
- Doctors and (research)nurses PANNA network
- Laboratory technicians dept. of pharmacy Radboudumc
- Stein Schalkwijk, MSc
- Dr. Angela Colbers (Projectmanager/ Investigator PANNA)
- Prof. Dr. David Burger (Principal Investigator PANNA)

Thank you for your attention