Case-based discussion on ARVs and DDIs in pregnancy

14th Residential Course on Clinical Pharmacology of Antiretrovirals
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Disclosures David Burger

- Research grants panna

- Janssen
- Merck
- ViiV
- Bristol-Myers Squibb
- Gilead
- PENTA

NB all payments have been invoiced by the financial department of Radboudumc

Contents

- Brief introduction
  - Pregnancy and HIV
  - Pregnancy effect on pharmacokinetics of ARVs
- Cases related to Drug-drug interactions (DDIs) of ARVs in pregnancy
- Take home message

The famous
Serie A - Dutch-soccer-players Quiz

Question 1: who was the first professional Dutch soccer player in Serie A?

A. Rudi Krol (Napoli)
B. Wim Kieft (Pisa)
C. Enzo Scifo (Torino)
D. Faas Wilkes (Inter)

Question 1: who was the first professional Dutch soccer player in Serie A?

A. Rudi Krol (Napoli)

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D. Faas Wilkes (Inter)

Question 2: who was the first Dutch soccer player for Torino in Serie A?

A. Michel van de Korput
B. Clarence Seedorf
C. Wim Kieft
D. Faas Wilkes

Question 2: who was the first Dutch soccer player for Torino in Serie A?

A. Michel van de Korput

B. Clarence Seedorf

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Question 3: Netherlands recently won 2-0 against world champion France; how many Dutchmen were playing in Serie A?

A. None
B. 1 (Marten de Roon)
C. 1 (Hans Hateboer)
D. 2 (De Roon & Hateboer)

Question 3: Netherlands recently won 2-0 against world champion France; how many Dutchmen were playing in Serie A?

A. None

B. 1 (Marten de Roon)

C. 1 (Hans Hateboer)

D. 2 (De Roon & Hatebo

Pregnancy and HIV+

Excluded from pre-marketing clinical drug trials

Widely use of ‘untested’ drugs

Knowledge gaps:
1) placental passage
2) safety for the mother and unborn child
3) pharmacokinetics in pregnancy

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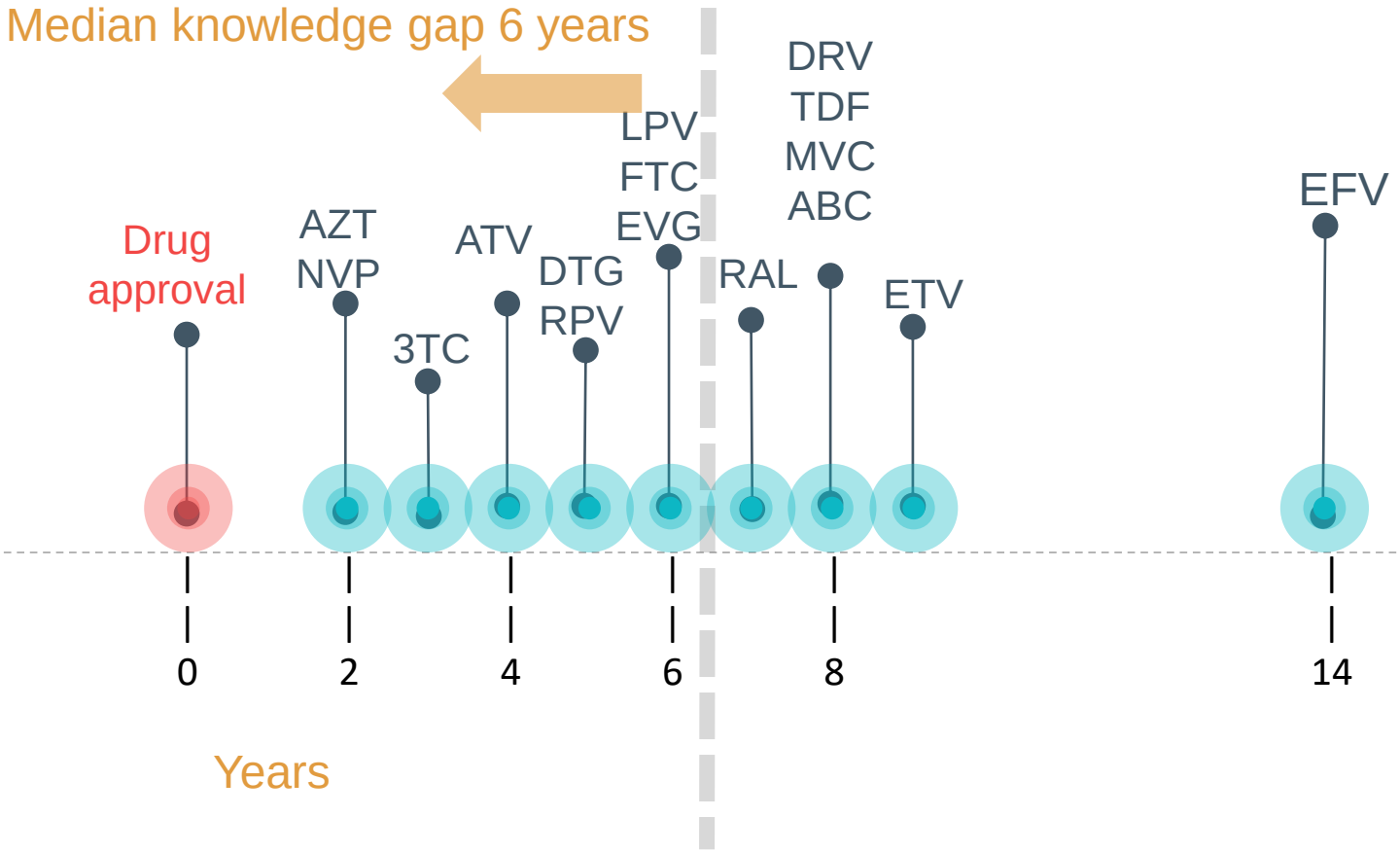
Time-to-first published (PK) data in pregnancy



https://globalhealthtrainingcentre.tghn.org/research-toolkit-paediatric-antiretroviral-drug-and-formulation-development/

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Pregnancy, Physiology & Pharmacokinetics

gastric pH ↑

gastric emptying and intestinal motility ↓

Total body water ↑

Plasma volume ↑

Total body fat ↑

Albumin conc. ↓

Cardiac output ↑

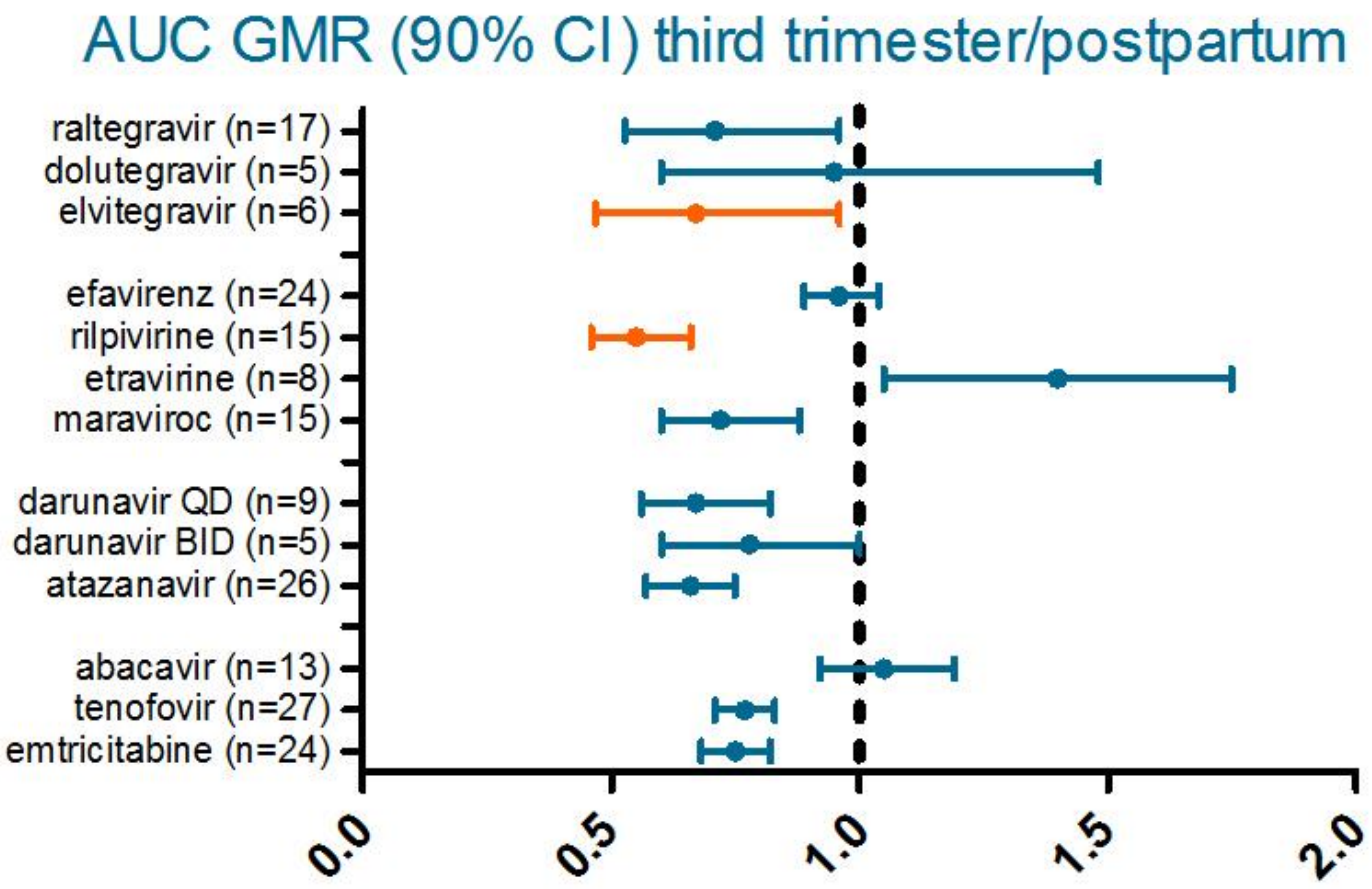
CYP2D6 activity ↑

CYP3A4 activity ↑

GFR ↑

(Abduljalil et al. 2012)

Pregnancy effect PK ARVs



PANNA study results summary
WWW.PANNAstudy.com

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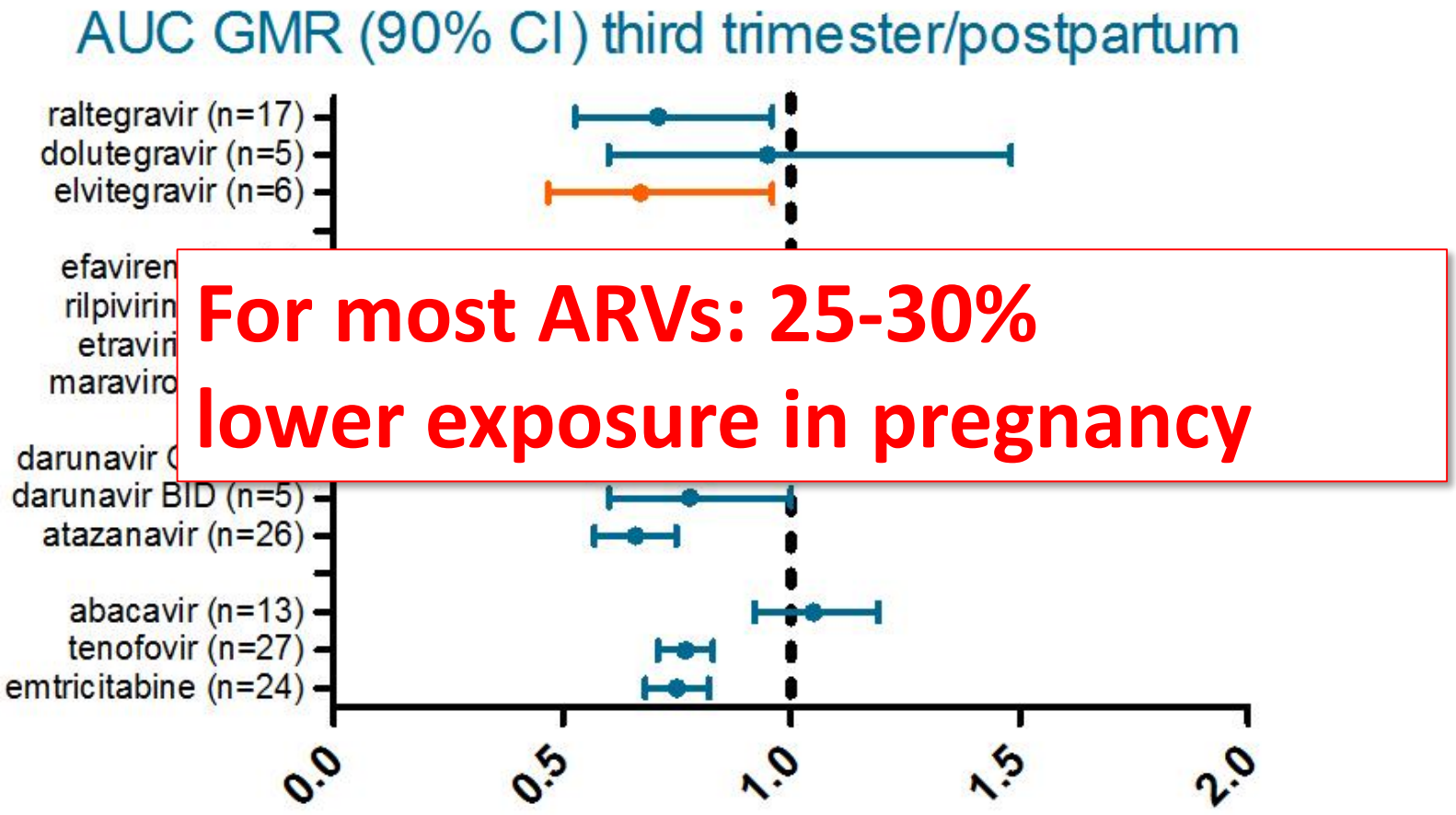
Pregnancy effect PK ARVs



For most ARVs: 25-30%
lower exposure in pregnancy

PANNA study results summary
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Case (1)

A 33-year old HIV-positive woman has been successfully treated with cART, no previous virological failure or adverse events.

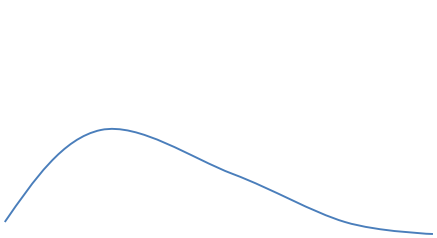
She is currently being treated with TDF/FTC (generic) + DRV/c (Rezolsta®).

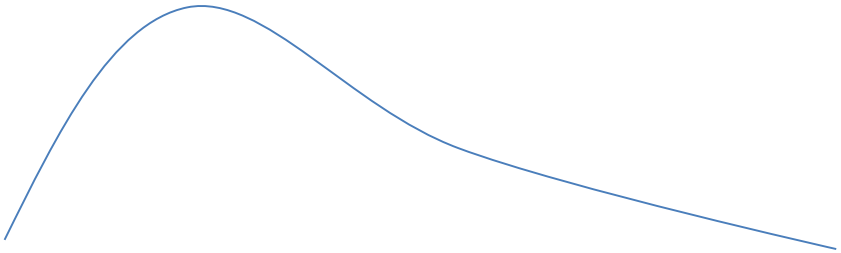
She has a stable relationship with an HIV-negative man and wants to become pregnant.

Are there any concerns?

Boosters in cART

Ritonavir and cobicistat
Potent CYP3A4 inhibitors
Also CYP3A4 substrate





Darunavir	+ ritonavir or cobicistat	AUC x 11 ↑
Elvitegravir		AUC x 20 ↑

Scientific summaryies FDA/EMA and Tseng et al. Ann Pharmacother. 2017

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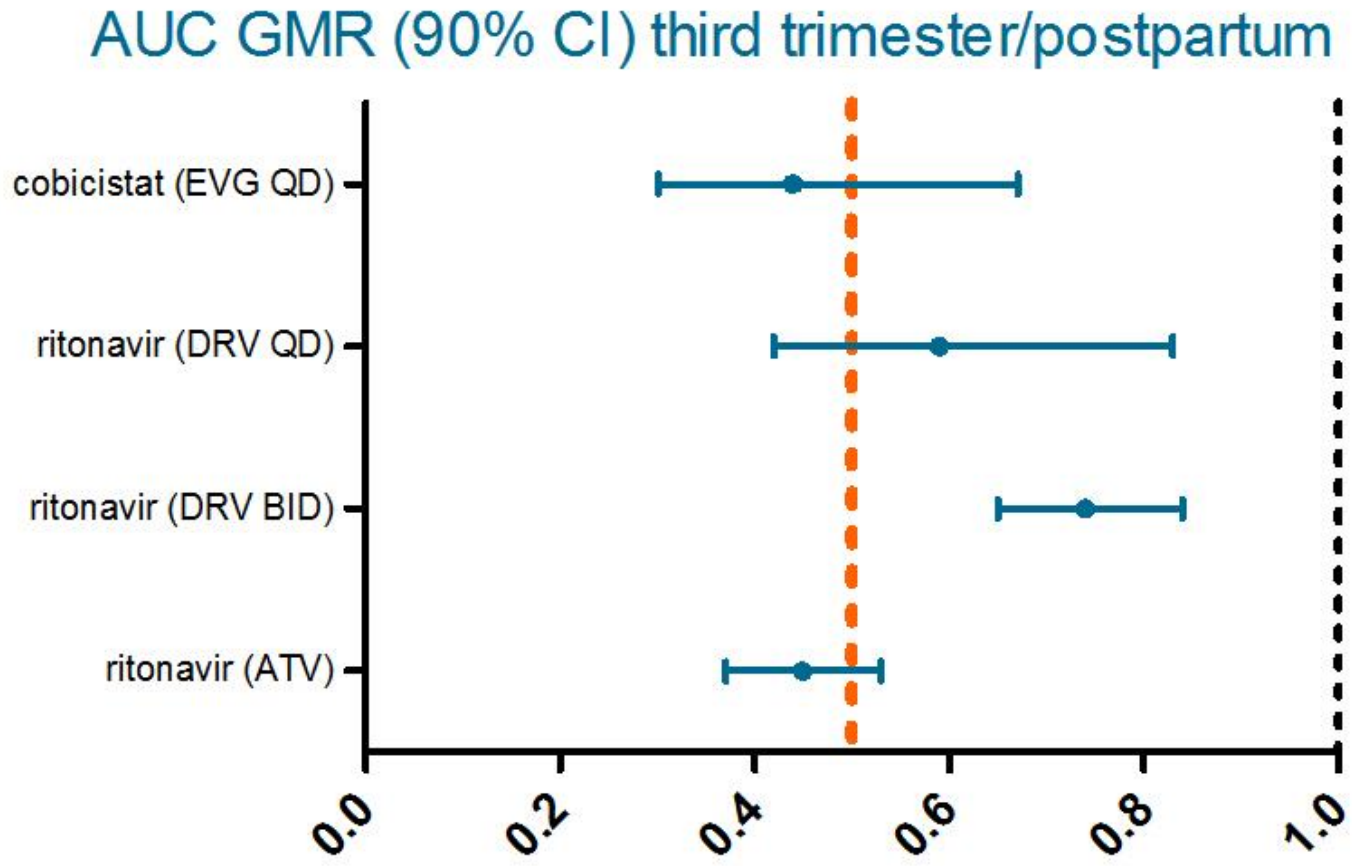
Boosters in cART: effect of pregnancy



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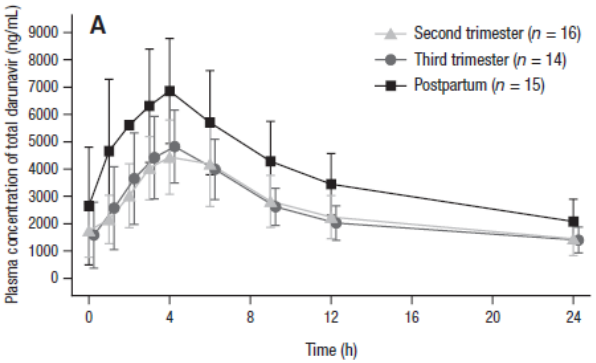
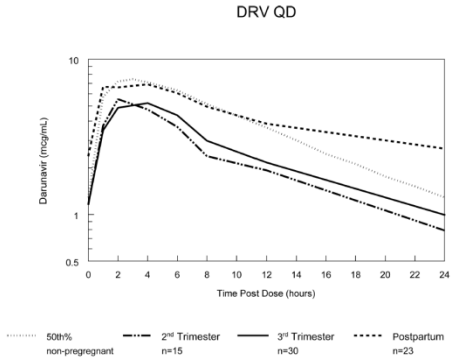
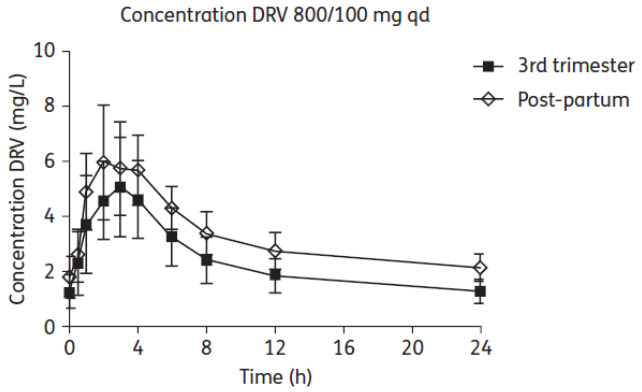
Darunavir/ritonavir 800/100mg QD



AUC total ↓ 34-35%
AUC unbound ↓ 20-34%



AUC ↓ 38-39 %



AUC ↓ 33%

8% of patients had C_{min} below target for PI resistant virus (EC_{50} of 0.55 mg/L), none below EC_{50} for wild type virus (0.055 mg/L).

Crauwels et al, HM 2016, Stek et al. JAIDS 2015, Colbers et al. JAC 2015; Boffito et al, HIV Clin Trials 2008 and AAC 2011

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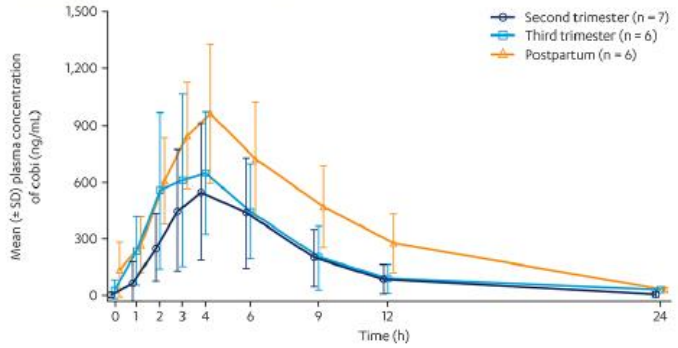
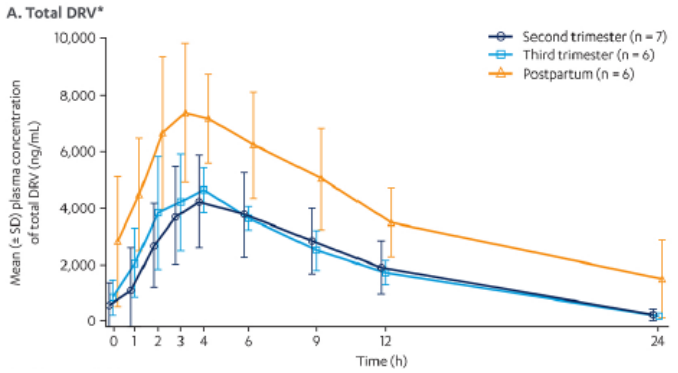
Darunavir/cobicistat 800/150mg QD

Figure 2. Mean (± SD) plasma concentration-time profiles of cobi during pregnancy and postpartum over the 24-hour dosing interval.



AUC COBI ↓ 49-63%

Figure 1. Mean (± SD) plasma concentration-time profiles of DRV during pregnancy and postpartum over the 24-hour dosing interval.



AUC DRV total ↓ 50-56%
AUC DRV unbound ↓ 40-55%

RTV boosted (DRV/RTV QD)
AUC total ↓ 34-35%
AUC unbound ↓ 20-34%

Crauwels et al, International Workshop HIV and women 2018

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Recommendations darunavir/cobi

FDA – 6 June 2018

PREZCOBIX is not recommended in pregnant women due to substantially lower exposures of darunavir and cobicistat during pregnancy.

One out of 6 women who completed the study experienced virologic failure with HIV-1 RNA >1,000 copies/mL from the third trimester visit through the postpartum period. Five women had sustained virologic response (HIV RNA <50 copies/mL) throughout the study period.

EMA – 25 June 2018 DHCP letter

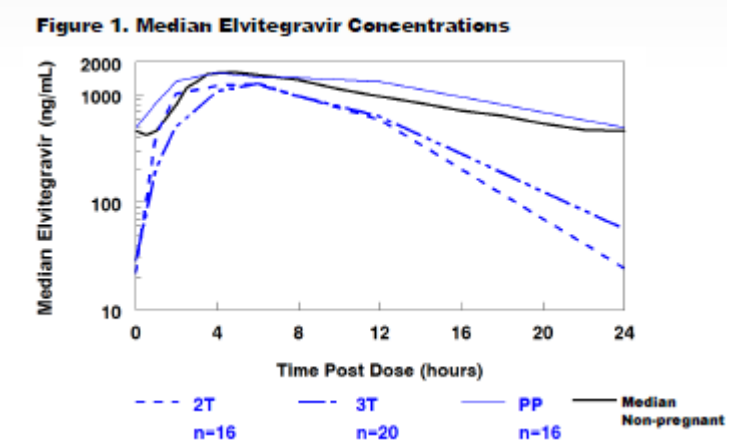
Same warning: replace COBI with RTV during pregnancy.

Case (2)

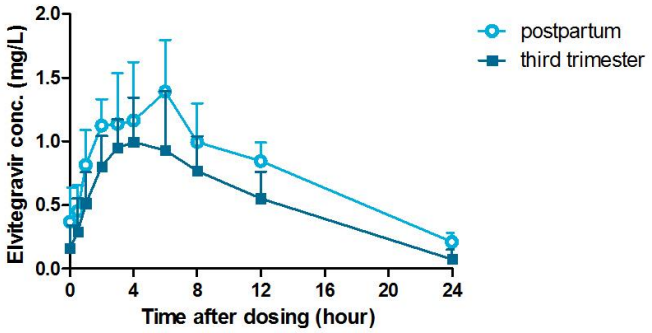
So DRV/c cannot be given, but changing to DRV/r + TDF/FTC means 3 separate pills. What about the FDCs Stribild® or Genvoya®?

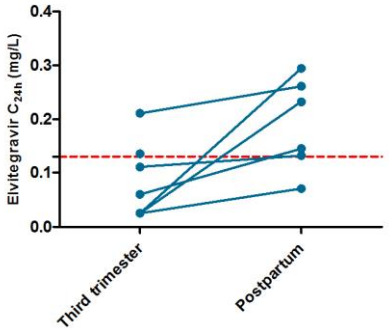
These also contain cobicistat as a booster, now with elvitegravir. Is there also a problem with cobicistat as a booster of EVG in pregnancy?

Elvitegravir/cobicistat (150/150mg QD)



AUC ↓ 42-49%





AUC ↓ 33%

C_{min} below target (0.13mg/L EC90) in pregnancy 71-85% versus 17-19% postpartum.
Case report reports decreased EVG fraction unbound in pregnancy.

Best et al, CROI 2017; Colbers et al ARV pharmacology workshop 2018; Marzolini et al, BJCP 2017; DeJesus et al, JAIDS 2006

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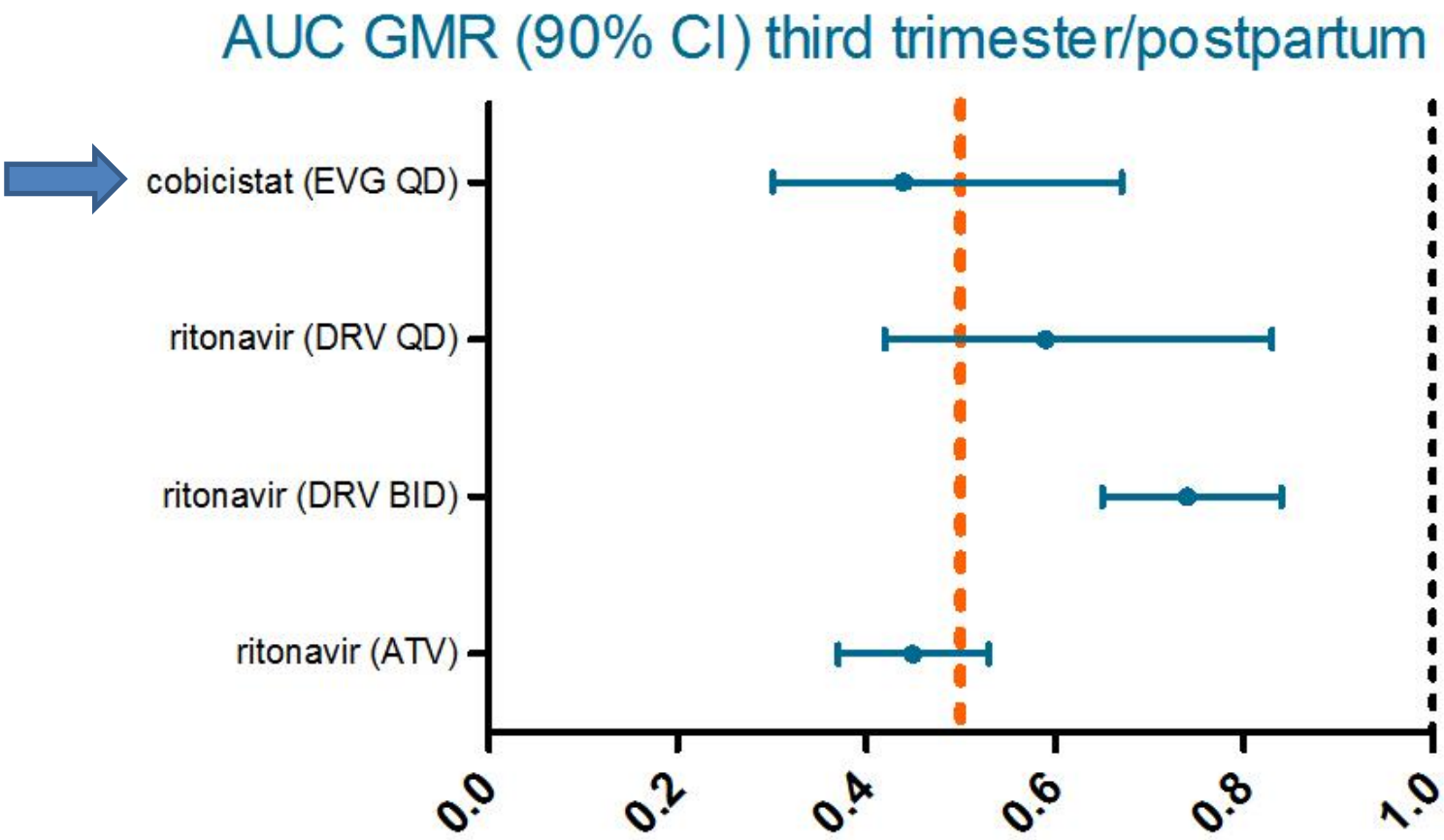
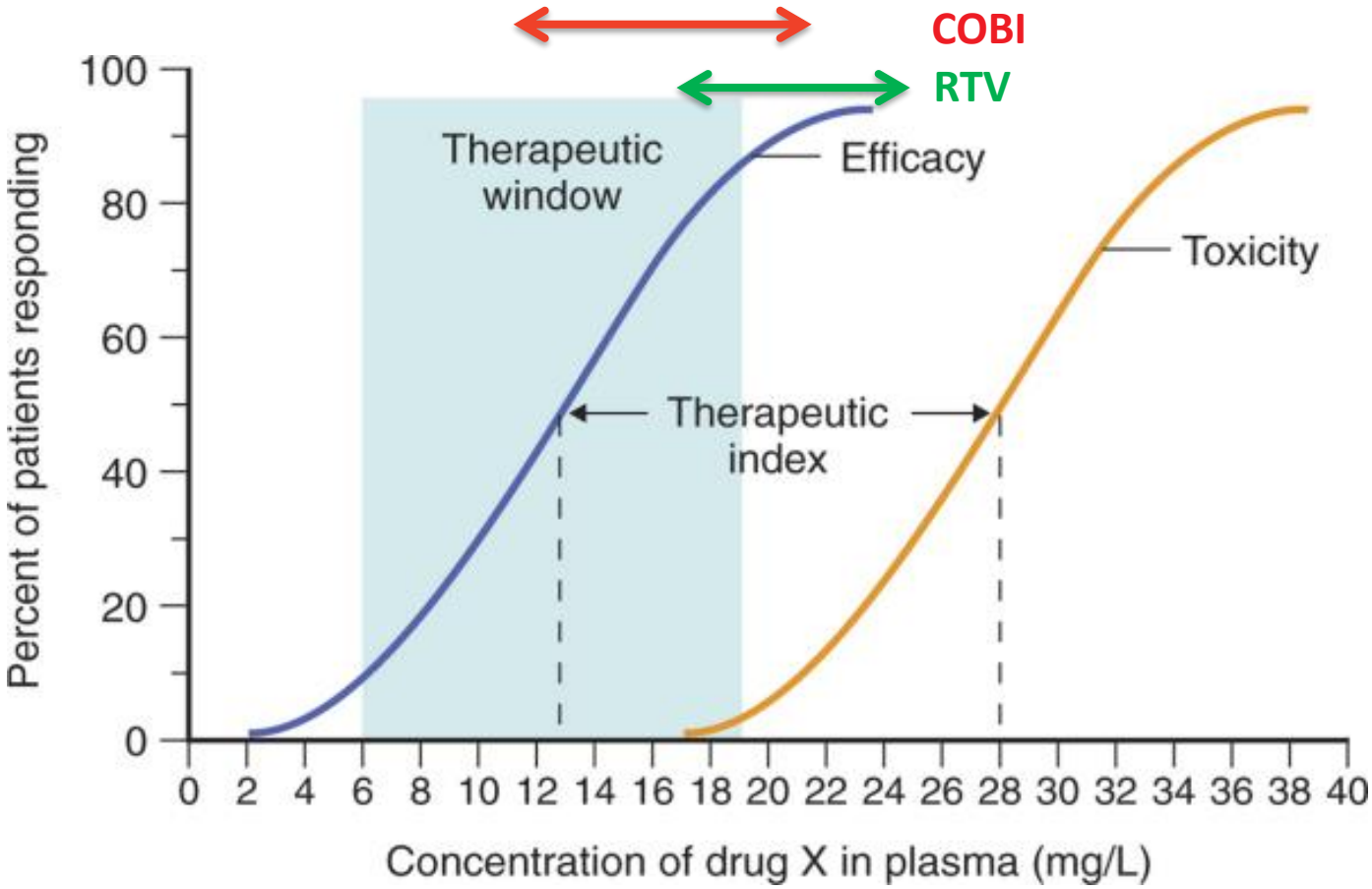
Elvitegravir/cobicistat (150/150mg QD)



PANNA study results summary

Cobi has a double problem in pregnancy



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Recommendations elvitegravir/cobi

DHHS – Dec 7, 2018

"If a woman is receiving a regimen that contains … elvitegravir/cobicistat when she presents to care, a provider should consider switching her to another regimen that is recommended for use in pregnancy. If the regimen is continued, absorption should be optimized and viral load should be monitored frequently."

FDA – (updated Oct 2018)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Not recommended for use during pregnancy because of substantially lower exposures of cobicistat and elvitegravir during pregnancy. GENVOYA should not be initiated in pregnant individuals. (2.5, 8.1)

EMA – (update Nov 2018)

Genvoya should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Case (3)

Despite these warnings, the physician and patient want to start with Genvoya® under the guidance of TDM. In case EVG trough levels are not OK extra cobicistat will be added. If that will not be successful the patient will change to another regimen before becoming pregnant.

But Genvoya® contains TAF (10mg): what do we know about TAF in pregnancy?

TAF and boosters ??

Table 1: Dose of Descovy according to third agent in the HIV treatment regimen

Dose of Descovy	**Third agent in HIV treatment regimen** (see section 4.5)
Descovy 200/10 mg once daily	Atazanavir with ritonavir or cobicistat Darunavir with ritonavir or cobicistat[1] Lopinavir with ritonavir
Descovy 200/25 mg once daily	Dolutegravir, efavirenz, maraviroc, nevirapine, rilpivirine, raltegravir

[1] Descovy 200/10 mg in combination with darunavir 800 mg and cobicistat 150 mg, administered as a fixed-dose combination tablet, was studied in treatment-naive subjects, see section 5.1.

EMA: Reduced TAF dose with boosted PIs
FDA: 25mg dose TAF with boosted PIs

Pregnancy effect on cobicistat and ritonavir: >50% reduction in exposure

Are adequate TAF/TFV drug levels reached in pregnancy when combined with boosted ARVs and 10mg TAF?

SmPC Descovy, EMA

TENOFOVIR ALAFENAMIDE PHARMACOKINETICS WITH AND WITHOUT COBICISTAT IN PREGNANCY

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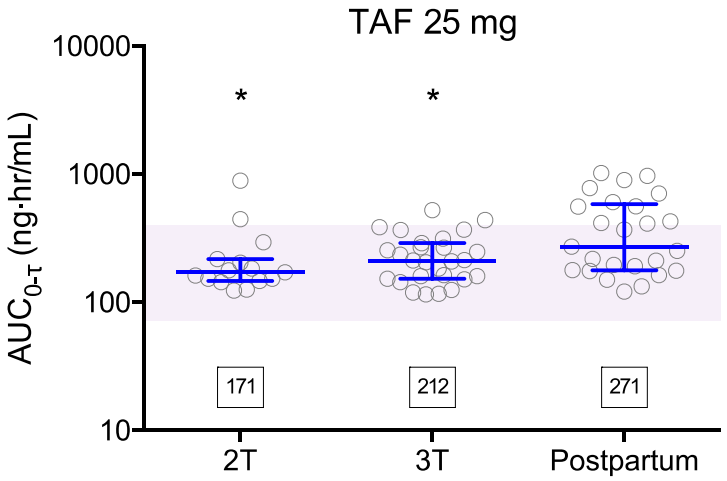
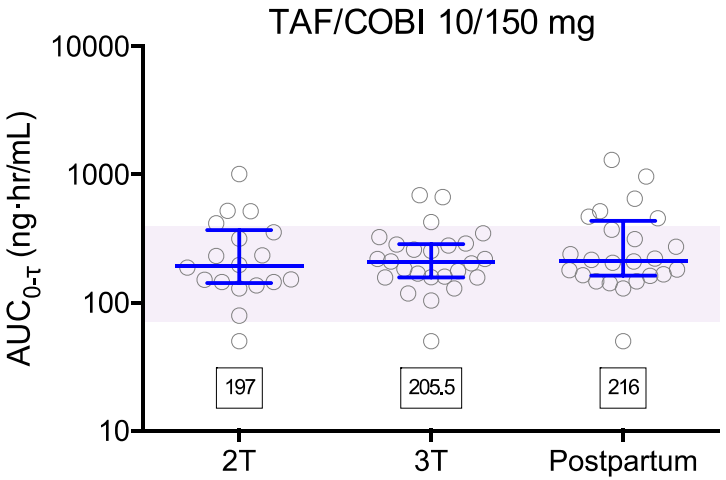
TAF Plasma AUC during pregnancy and postpartum





The shaded area displays the 5th to 95th percentile AUC in the E/C/F/TAF FDC (Genvoya®) reference population
Data presented as median with interquartile range. The median for each sampling period is denoted in the boxes

	GMR (90% CI): 2nd Trimester/ Postpartum	GMR (90% CI): 3rd Trimester/ Postpartum
TAF 25 mg	***n = 14***	***n = 25***
$AUC_{0-\tau}$ (ng·hr/mL)	0.57 (0.34 – 0.98)*	0.66 (0.54 – 0.82)*
TAF/COBI 10/150 mg	***n = 14***	***n = 22***
$AUC_{0-\tau}$ (ng·hr/mL)	0.79 (0.50 – 1.27)	0.86 (0.66 – 1.12)

- With TAF 25 mg, exposure was lower during pregnancy compared to postpartum, but this difference was driven by a higher than anticipated AUC postpartum
- Proportion of subjects exceeding the TAF target AUC (10th percentile non-pregnant adults) ranged from 84%-96% without differences during pregnancy and postpartum

Conclusions

- Plasma TAF exposures during pregnancy and postpartum were within the range of those typically observed in non-pregnant adults
- TAF was safe and well tolerated by mothers and babies in this small sample
- Analysis of all maternal delivery samples, cord blood samples and infant washout samples is not yet complete but no transplacental passage of TAF was observed in cord blood samples assayed to date
- Additional safety and outcome data from larger numbers of pregnant women receiving TAF and their infants are needed

Case (4)

8 months later, the patient has become pregnant. Because of low EVG levels, the regimen has been changed to raltegravir 400mg BID + TAF/FTC.

She develops anemia during pregnancy and Iron supplementation is started.

PK dolutegravir with cations (iron)

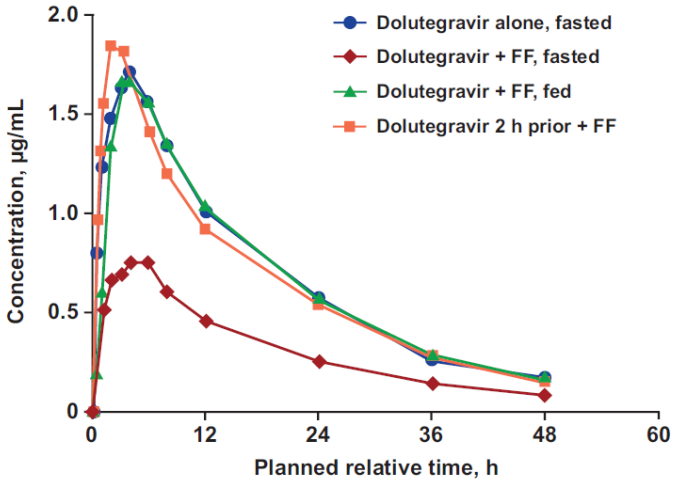


Figure 2. Mean plasma concentration-time profiles of dolutegravir (50 mg, single dose) administered with and without ferrous fumarate (FF) (324 mg, single dose).

AUC ↓ 56% FF and fasting

AUC ↓ 5-30% pregnancy

Iron + food and avoid simultaneous administration with InSTIs

AND in resource limited setting: possible interactions with soil/mumbwa

<u>Cave: slow-release Iron formulations! Always give InSTI first and wait 2 hours</u>

Song et al., JCP 2015

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Take home messages: DDIs in pregnancy

There is a potential combined effect of DDIs and pregnancy-induced changes in PK of ARVs

- **Physiological changes affect exposure to ARVs, in most cases lower exposure**

- **Altered interactions:**
  - **altered/reduced boosting**
  - **altered enzyme activities?**
  - **altered transporter interactions?**

- **TDM is indicated in case of complex clinical situations such as DDIs in pregnancy**

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- IMPAACT P1026 research team

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Thank you for your attention & and greetings from Nijmegen!