Abstract # 433

Pharmacokinetics of Efavirenz 600 mg QD during Pregnancy and Postpartum

Stein Schalkwijk[1], Angela Colbers[1], Brookie Best[2], Alice Stek[3], David Hawkins[4], Jiajia Wang[5], Mark Mirochnick[6], David Burger[1],
on behalf of the IMPAACT P1026s Protocol Team and the PANNA Network

1 Radboud University Medical Centre, Nijmegen, The Netherlands; 2 University of California San Diego, San Diego, CA, USA; 3 University of Southern California, Los Angeles, CA, USA;
4 Chelsea & Westminster Hospital, London, UK; 5 Harvard School of Public Health, Boston, MA, USA; 6 Boston University, Boston, MA, USA

Stein Schalkwijk
Department of Pharmacy
Radboud university medical center
PO Box 9101
6500 HB Nijmegen
The Netherlands
Tel: +31-24-3616405
Stein.j.schalkwijk@radboudumc.nl

1. BACKGROUND

- Efavirenz (EFV) 600mg is currently recommended by WHO as a first-line antiretroviral agent in HIV infected adults. A dose reduction to 400mg EFV has been proposed because of concerns regarding toxicity and costs. EFV is widely used during pregnancy in those countries where HIV infection is most common. Pregnancy can reduce exposure to antiretroviral agents with a corresponding risk of poor maternal virological control and MTCT. Pharmacokinetics (PK) of EFV 600 mg have been previously studied in pregnancy with contradictory results.
- Both the IMPAACT P1026 protocol and the PANNA network have been established to describe the pharmacokinetics of anitretroviral agents in HIV-infected pregnant women in comparison to post-partum pharmacokinetics (www.impaactgroup.org and www.pannastudy.com).

Objectives:

1. To further investigate the PK of EFV 600 mg in pregnant women.
2. To describe the safety of the antiretroviral agents during pregnancy and monitor viral load response and pregnancy outcomes.

2. METHODS

- Data presented were collected in two studies: PANNA “Pharmacokinetics of Antiretroviral Agents in HIV-infected Pregnant Women” (Europe) and IMPAACT study P1026 “PK Properties of ARV Drugs During Pregnancy” (US, Argentina) (ClinicalTrials.gov identifiers NCT00825929 and NCT00042289).
- Both studies are non-randomized, open-label, parallel-group, multi-center phase-IV studies in HIV-infected pregnant women. PANNA recruits patients from HIV treatment centers in Europe; IMPAACT recruits patients from sites in the US, South America, Thailand and Africa.
- Here, we report on pregnant HIV-infected patients treated with EFV 600mg as part of their cART.
- Blood was collected for 24h pharmacokinetic curve (t = 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 24h) after observed intake of the medication in the second and third trimester. After at least 2 weeks continuation of therapy post-partum, intensive PK sampling was repeated. Where possible a cord blood sample and matching maternal blood sample were taken at delivery to estimate placental transfer.
- Safety and antiviral parameters were evaluated.
- EFV plasma concentrations were determined by validated methods of bioanalysis. Pharmacokinetic parameters were calculated using Phoenix (Certera®) version 6.3. Bioequivalence analysis was conducted using Phoenix. Subjects with concomitant rifampicin were not included in this analysis, but presented separately.

3. RESULTS

- Thirty-four HIV-infected pregnant women were included in this study. Thirteen in the PANNA network and 21 in the IMPAACT P1026 network.
- Subject characteristics per trimester and pregnancy outcomes are shown in Table 1.

Pharmacokinetics

- Geometric mean (GM) concentration-time profiles of EFV 600 mg QD during second trimester, third trimester and postpartum are shown in Figure 1.
- GM pharmacokinetic parameters of EFV 600 mg QD during second trimester, third trimester and postpartum are shown in Table 2.
- GM ratios and 90% confidence intervals (90%CI) of pharmacokinetic parameters of EFV 600 mg QD in second and third trimester compared to postpartum are shown in Table 3.
- Individual pharmacokinetic parameters after EFV 600 mg QD administration during second trimester, third trimester and postpartum are shown in Figure 2.
- One, two, and two subjects had C_{24h} below the suggested threshold of 1.0 mg/L in second trimester, third trimester and postpartum, respectively (Figure 2).
- The median (range) ratio of cord to maternal concentrations (n=4) was 0.81 (0.65-0.95).

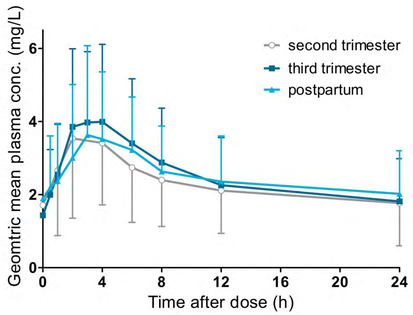
Table 1: Subject characteristics and pregnancy outcomes

General (n=34)	
Age (years)	30 (20-41)
White; black [n (%)]	5 (15%); 29 (85%)
Treatment naive at conception [n (%)]	11 (32%)
Conception on EFV [n (%)]	21 (62%)
Concomitant ARVs [n (%)]: NRTI	34 (100%); TNF 33 (97%), FTC 25 (74%), 3TC 9 (26%), ZDV 1 (3%)
Protease inhibitor	0 (0%)
Other	0 (0%)
Second trimester (n=13)	
Gestational age (weeks)	25 (21-26)
Weight (kg)	71 (48-132)
HIV RNA undetectable <50 cps/mL [n (%)]	7 (54%); < 400 cps/mL 11 (85%); 1 unknown
CD4 count (cells/uL)	402 (46-1012)
Concomitant rifampicin [n (%)]	3 (9%)
Third trimester (n=32)	
Gestational age (weeks)	34 (28-37)
Weight (kg)	78 (49-128)
HIV RNA undetectable <50 cps/mL [n (%)]	25 (78%); < 400 cps/mL 28 (88%); 4 unknown
CD4 count (cells/uL)	594 (60-1197)
Concomitant rifampicin [n (%)]	3 (9%)
Postpartum (n=25)	
Time after delivery (weeks)	5 (2-9)
Weight (kg)	67 (45-124)
HIV RNA undetectable <50 cps/mL [n (%)]	21 (84%); < 400 cps/mL 23 (92%); 1 unknown
CD4 count (cells/uL)	742 (64-1225)
Concomitant rifampicin [n (%)]	1 (3%)
Pregnancy outcomes (n=30)	
Gestational age (weeks)	39 (33-42)
Caesarian section [n(%)]	18 (60%); 3 unknown
Infant birth weight (grams)	3250 (1875-4150)
Infant HIV DNA PCR negative [n(%)]	15 (50%); 15 unknown

ARVs: antiretrovirals, NRTI: nucleoside/nucleotide reverse transcriptase inhibitors

3. RESULTS (continued)

Figure 1: Geometric mean (±%CV) concentration-time profile after administration of EFV 600mg QD during second trimester, third trimester and postpartum



Safety

- Three pregnancy-related serious adverse events were reported including preeclampsia, vaginal bleeding, and pregnancy-induced hypertension.
- In four newborns congenital abnormalities were reported, including mongolian spots, peyronie disease, syphilis and polydactily bilateral.
- Five preterm births were observed with a median (range) gestational age of 34 (33-36) weeks.

Table 2: EFV 600 mg QD geometric mean (%CV) pharmacokinetic parameters in second trimester, third trimester and postpartum

Pharmacokinetic parameters	Second Trimester (n=10)	Third Trimester (n=29)	Postpartum (n=23)
$AUC_{0\text{-}24h}$ (h*mg/L)	56 (55)	62 (52)	60 (51)
C_{24h} (mg/L)	1.8 (66)	1.8 (65)	1.7 (118)
CL_{ss}/F (L/h)	11 (55)	9.6 (52)	9.9 (51)
C_{max} (mg/L)	3.8 (52)	4.9 (42)	4.1 (49)
T_{half} (h)	34 (67)*	29 (51)*	41 (87)*

**For calculation of T_{half} n was 9, 28 and 22 respectively*

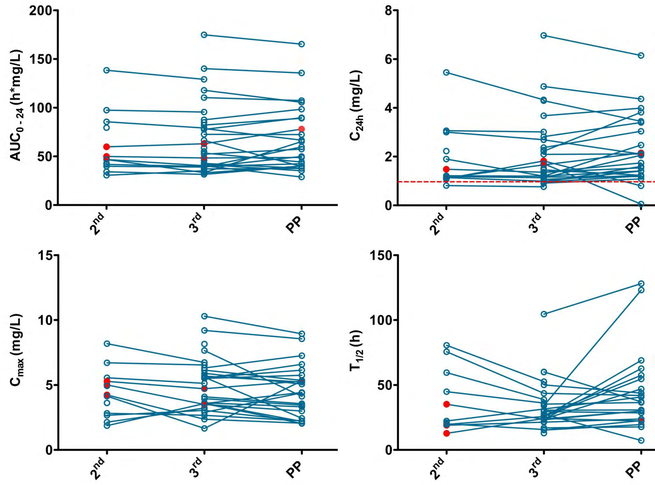
Table 3: Geometric mean ratios [90%CI] of pharmacokinetic parameters of EFV 600 mg QD in second and third trimester compared to postpartum

Pharmacokinetic parameters	GM Ratio (%) [90% CI] Second trimester / postpartum	GM Ratio (%) [90% CI] Third trimester / postpartum
$AUC_{0\text{-}24h}$ (h*mg/L)	96 [84 - 109]*	96 [89 - 104]*
C_{24h} (mg/L)	102 [70 - 150]	102 [80 - 131]
CL_{ss}/F (L/h)	104 [92 - 119]*	104 [96 - 112]*
C_{max} (mg/L)	104 [84 - 127]	112 [98 - 128]
t_{half} (h)	82 [57 – 118]	71 [56 - 89]

** Within the constraints for bioequivalence (80 - 125%)*

3. RESULTS (continued)

Figure 2: EFV 600 mg QD individual pharmacokinetic parameters during second trimester (2nd), third trimester (3rd) and postpartum (PP).



Parameters of individual subjects on concomitant rifampifcin are depicted in red.

Discussion

- Based on this analysis the C_{24}, C_{max}, and $T_{1/2}$ were not bioequivalent, possibly due to a high coefficient of variation related to CYP2B6 genotypes. A population pharmacokinetic analysis could give more insights into the effects of pregnancy on the EFV pharmacokinetics during pregnancy. Nevertheless, the amount of subjects with C_{24} below the suggested threshold of 1.0 mg/L was limited across pregnancy status.

4. CONCLUSIONS

- Overall EFV exposure was similar during pregnancy compared to postpartum. Although the C_{24} was not bioequivalent during pregnancy compared to postpartum, EFV 600mg led to adequate exposure during pregnancy.
- Prospective evaluation of the proposed EFV dose reduction to 400mg is warranted in pregnant women.

Acknowledgements

The authors wish to thank the women that participated in the protocol and the staff of the participating centres. The PANNA network is funded by: NEAT/PENTA; BMS, Merck, ViiV Healthcare, Janssen Pharmaceutica. P1026s is a protocol of the IMPAACT network, which is funded by NICHD, NIAID and NIMH.

Presented at 2016 Conference on Retroviruses and Opportunistic Infections, February 22 to 25, 2016, in Boston, Massachusetts.