Prenatal Efavirenz Exposure Is Independently Associated With Foetal *CYP2B6* Genotype

Poster 00456

Adeniyi Olagunju[1,2], Damien Anweh[3], Ogechi Okafor[4], Alieu Amara[2], Oluseye Bolaji[1], Ebunoluwa Adejuyigbe[1,5], Saye Khoo[2], Andrew Owen[2]

[1]Obafemi Awolowo University, Ile-Ife, Nigeria; [2]University of Liverpool, Liverpool, UK; [3]Federal Medical Centre, Makurdi, Nigeria; [4]Bishop Murray Medical Centre, Makurdi, Nigeria; [5]Obafemi Awolowo University Teaching Hospital, Ile-Ife, Nigeria

INTRODUCTION

- The factors that affect prenatal exposure and their relative contribution are poorly understood for most drugs.
- Understanding the possible role of foetal and maternal genetics on prenatal drug exposure will help advance assessment of observed risk-benefit differentials during pregnancy.
- VADICT (NCT03284645) is a cohort study that started recruiting in June 2017 in four Nigerian hospitals.
- The aim of study is to investigate viral and drug dynamics in fluids important for mother-to-child transmission.

OBJECTIVES

- The objective of this sub-study was to investigate the influence of functional *CYP2B6* polymorphisms on prenatal exposure to efavirenz.

METHODS

- VADICT enrolled HIV-infected women who started efavirenz-based regimens before or during pregnancy, or in the early postpartum period. Patients were followed until breastfeeding ended.
- For this sub-study, dried blood spots (DBS) were collected from each mother-newborn pair immediately after delivery before breastfeeding started. Cord DBS were also collected.
- Genomic DNA was extracted from maternal and newborn DBS using commercially available kits.
- Genotyping was conducted by real-time PCR using TaqMan 5' nuclease assays for *CYP2B6* 516G>T (rs3745274) and 983T>C (rs28399499) single nucleotide polymorphisms (SNPs).
- Efavirenz concentrations in DBS (maternal, newborn and cord) were quantified using a validated LC-MS/MS method.
- Univariate and multivariate linear regression was used to explore relationships between maternal, newborn and cord concentrations, and associations of genetic and non-genetic factors with maternal and newborn efavirenz concentrations.

Foetal exposure to efavirenz (assessed at delivery) ranged from 15.9 to 9230 ng/mL and was **independently associated with foetal *CYP2B6* genotypes** (969 ng/mL in fast versus 1790 ng/mL in slow metabolisers).

RESULTS

- A total of 171 samples were available for this analysis from 86 women and 84 newborns, including 81 paired samples.

Participants characteristics at delivery	Value (mean, SD)
Maternal age	30 (5.2) years
Maternal body weight	73.7 (14.0) kg
Gestational age	40 (3.3) weeks
Baby birth weight	2.9 (0.5) kg
APGAR score	7.6 (1.4)
Time of sampling after maternal dose	18.5 (10.1) h

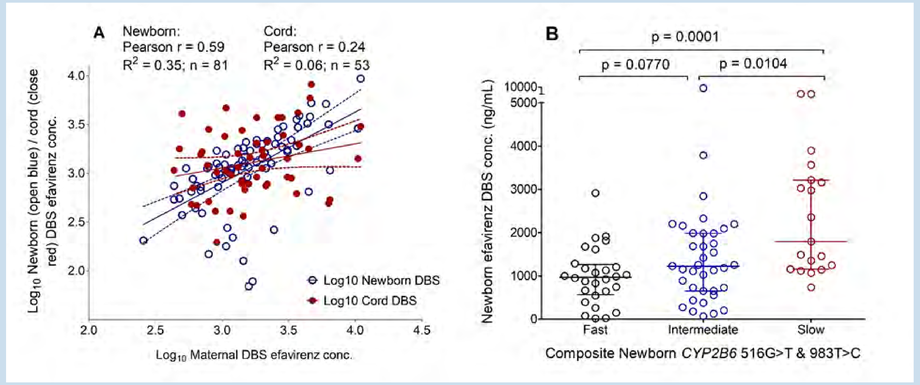

Figure 1 A correlation was observed between maternal & newborn efavirenz concentrations (A). Median (range) newborn concentration was 1180 (15.9-9230) ng/mL in pooled analysis; 969 (15.9-2910), 1230 (69.2-9230) and 1790 (735-5230) ng/mL in fast (n = 28), intermediate (n = 37) and slow (19) metabolisers, respectively (B).

- Linear regression analysis showed that the following factors were independently associated with prenatal exposure to efavirenz (assessed at delivery):

Factors[a]	Coef. (β, 95% CI)	P value
Newborn *CYP2B6* 516G>T	0.182 (0.059, 0.305)	0.004
Maternal *CYP2B6* 516G>T	0.207 (0.075, 0.339)	0.003
APGAR score	-0.097 (-0.17, -0.023)	0.003

[a]Dependent variable: Log_{10} DBS efavirenz concentration in newborn.

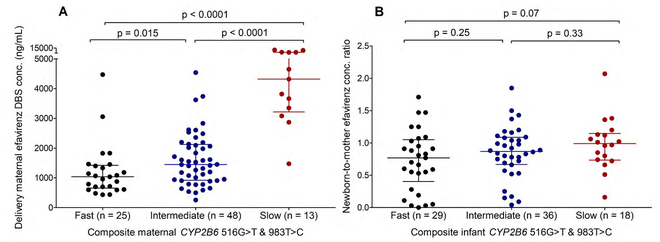

Figure 2 Pooled median maternal efavirenz DBS concentration at delivery was 1450 ng/mL (calculated plasma concentration = 2090 ng/mL) (A). Newborn-to-mother concentration ratio was 0.88 (range: 0.04-2.07), with a trend towards higher penetration in slow compared with fast metaboliser babies (B).

- In multivariate analysis, composite *CYP2B6* genotype was independently associated with newborn-to-maternal efavirenz concentration ratio (β = 0.12 (0.01, 0.251), p = 0.049).

CONCLUSION

- For the antiretroviral drug efavirenz, both maternal and foetal *CYP2B6* genotype influenced prenatal exposure to efavirenz.
- Prenatal pharmacogenetics may help rationalise drug selection by informing the risk-benefit during pregnancy.
- These data are being used to further qualify a mechanistic model of prenatal drug exposure.

OTHER KEY INFORMATION

- **Correspondence:** aeolagunju@oauife.edu.ng
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