**Background and Objectives**

Efavirenz (EFV) is the backbone of first-line antiretroviral therapy (ART) for HIV infection in most low- and middle-income countries (LMIC). WHO guidelines recommend ≥6 months of isoniazid (INH) preventive therapy for people living with HIV from LMIC where TB is endemic, including pregnant women. While mainly cleared by CYP2B6, a secondary metabolic pathway for EFV is CYP2A6, which is inhibited by INH, creating a potential drug-drug interaction. Objective: Evaluate the interaction of EFV and INH during pregnancy and postpartum.

**Methods**

HIV infected pregnant women at 14 to 34 weeks of gestation were recruited and ARM A immediately initiated INH 300-mg daily for 28 weeks then switched to placebo. ARM B started on placebo then switched to INH at 12 weeks postpartum.

Intensive PK sampling (pre-dose, 1, 2, 4, 6, and 12 hours after INH dosing), sparse PK samples (around 2 hours after INH dose) once at ≥ 2 weeks after recruitment and again at 12-21 weeks after delivery. EFV was frequently dosed at around 2 postpartum.

CYP2B6 and CYP2A6 genotype information was captured, categorizing patients into extensive, intermediate or slow metabolizer groups.[1]

Population PK modelling in NONMEM [2] was used to interpret the data:
1. 2-compartment model, transit compartment absorption, and hepatic clearance and first-pass metabolism due to hepatic extraction $E_D$
2. Allometric scaling [4] of all clearances based on fat-free mass (FFM) and volumes based on body weight (WT).
3. Model assumption: The free fraction of efavirenz ($f_{un}$) in plasma was assumed 0.5% [5].

**Results**

- **Parameter estimates**: Table 2, visual predictive check: Figure 2.
  
  As expected, the effect of CYP2B6 genotype on EFV clearance was significant. Each phenotype had a specified estimated clearance.
  
  After adjusting body size (with allometry) and CYP2B6 genotype effect, pregnancy increased isoniazid clearance by 16%.

  INH decreased the clearance of EFV by 7% in the fast metabolizers and 14% in the intermediate and slow metabolizers.

  No significant effect of CYP2A6 on the clearance. This might be due to the small sample size of slow metabolizers (1%) as shown in Table 1.

**Conclusions**

Similar to previous reports [7 & 8] efavirenz exposure was decreased during pregnancy, due to increased clearance.

Isoniazid increased plasma efavirenz exposure, especially in intermediate and slow metabolizers. The effect of CYP2B6 genotype on plasma exposure was much greater than the effect of pregnancy.

The intermediate CYP2B6 metabolizers were the most affected with much different influence between the slow and fast metabolizers. The consequences of reduced efavirenz exposure during pregnancy and the drug-drug interaction on the safety and effectiveness of efavirenz therapy needs further investigation.

**References**


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