
Background
Physiological changes during pregnancy may alter drug pharmacokinetics. Trimester differences in isoniazid (INH) and rifampin (RMP) exposure in pregnant women treated for tuberculosis have not been described. We explored the effects of pregnancy on INH and RMP pharmacokinetics in women treated for tuberculosis with and without efavirenz (EFV)-based antiretroviral treatment (ART) co-treatment.

Methods
International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) P1026s is an ongoing, non-blinded, phase IV, prospective study of antiretroviral and antituberculosis pharmacokinetics in HIV-infected and uninfected pregnant women. Intensive steady-state 12-hour pharmacokinetic profiles of INH and RMP were performed during the 2nd trimester (2T), 3rd trimester (3T) and 2-8 weeks postpartum (PP). Daily antituberculosis fixed-dose combination tablets were given according to WHO-recommended weight-banded dosing guidelines. Additionally, HIV-infected women also received EFV-based ART. INH and RMP plasma concentrations were measured using High Performance Liquid Chromatography (HPLC); detection limits being 0.117 µg/ml and 0.098 µg/ml, respectively. The pharmacokinetic parameters were characterized using noncompartmental analysis and compared to published non-pregnant South African adult data. Exposure at each timepoint was compared between ART and non-ART groups using a Wilcoxon rank-sum test. Two-sided P-values <0.10 were considered statistically significant.

Results
Preliminary pharmacokinetic data are available for 25 participants; 14 African, 6 Thai and 5 of other descent. The median age at 3T was 29 (range 23-33) years and the median weight 58 (range 54-62) kg. Eleven women were HIV-infected on EFV-based ART, with 3T median CD4 count 534 (range 93-708) cells/mm3 and median viral load <40 copies/mL. The INH and RMP pharmacokinetic data in 2T, 3T and PP were available for 7, 10 and 7 women in the ART-group and 5, 11 and 8 women in the non-ART-group. All but 5 were sampled more than once. INH median AUC0–∞ was 7.9, 8.4 and 8.7 µg·h/ml and 6.2, 10.9 and 14.8 µg·h/ml in the 2T, 3T and PP groups with and without ART respectively. INH median Cmax was 2.8, 3.3, and 3.0 µg/ml and 3.0, 3.5 and 3.6 µg/ml respectively.
INH exposure was low across all stages of pregnancy compared to historical South African non-pregnant INH exposure: AUC0–∞ 32.5 µg·h/ml and Cmax 6.5 µg/ml (45% male, 10% HIV-infected not receiving antiretrovirals, McIlleron et al. 2006). RMP median AUC0–∞ was 36.8, 35.8 and 31.2 µg·h/ml and 30.6, 41.4 and 32.7 µg·h/ml respectively. RMP median Cmax was 8.4, 6.1, and 6.6 µg/ml and 4.5, 6.9 and 7.9 µg/ml respectively. RMP exposure was similar or higher in 2T, 3T and PP compared to historical data. The respective INH and RMP exposures in each trimester were not statistically different between the ART- and non-ART-groups, though small sample sizes limited the statistical power to detect differences. Pregnancy outcomes, tuberculosis treatment outcomes and safety outcomes are being analyzed.

Conclusions
In pregnant women treated for tuberculosis, INH concentrations were lower compared to non-pregnant concentrations, irrespective of EFV-based ART co-treatment. RMP concentrations in pregnancy were similar or higher. The clinical relevance of low INH exposure when treating pregnant woman with tuberculosis needs to be determined.