

## Abstract: 3

*Pharmacokinetics for Pediatrics, Pregnancy, and Other Special Populations*



## Tenofovir disoproxil fumarate (TDF) pharmaco-kinetics (PK) with increased doses in HIV-1 infected pregnant women and their newborns (HPTN 057)

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**Background:** Tenofovir (TFV) has proven animal model efficacy in prevention of mother to child HIV transmission but there are few data describing its PK when administered to pregnant women during labor or to newborns. In previous dosing cohorts of this study, administration of a maternal 600 mg dose during labor and administration of three infant 4 mg/kg doses during the 1<sup>st</sup> week of life did not maintain target infant plasma TFV concentrations (>50 ng/mL) throughout the first week of life.

**Materials & Methods:** HPTN 057 is a phase I trial of tenofovir disoproxil fumarate (TDF) administered to HIV infected pregnant women and their neonates in Malawi and Brazil. In the current study cohort, women received a single 900 mg TDF dose at the onset of labor or 4 hours prior to C section (C/S) and newborns received 6 mg/kg TDF x 3 doses given as soon as possible after birth and 72 hours and 120 hours after birth. TFV concentration (conc) was determined by HPLC/MS/MS; lower limit of quantitation was 5 ng/mL. The pharmacokinetic target was to keep infant TFV conc >50 ng/ml (mean trough conc in nonpregnant adults) for the first week of life. Amniotic fluid samples were collected from C/S mothers. Data are presented as median (range).

**Results:** 36 mother-infant pairs were studied (23 vaginal deliveries, 13 C/S). Delivery occurred at a median of 3.33 (0.4 - 39.25) hours after dosing. Median maternal TFV conc at delivery was 200 (blq - 556) ng/mL. Median cord blood TFV conc was 123 (blq - 538) ng/mL. Cord blood TFV conc was > 50 ng/mL in 26/31 (84%) and median ratio of cord blood to maternal delivery TFV conc was 0.59 (0 - 3.06). Infant predose TFV conc was >50 ng/mL in 7/32 (22%) of infants before the initial TDF dose, 2/34 (6%) before the 72 hr dose and 2/32 (6%) before the 120 hr dose. Median TFV conc in amniotic fluid (n=11) was 319 (84-574) ng/ml and the median ratio of amniotic fluid to maternal delivery TFV conc was 1.05 (0.37 - 3.32). Median maternal PK parameters: AUC=5283 (3513 - 10670) ng\*hr/mL, Cmax=458 (134 - 1149) ng/mL, t<sub>1/2</sub>=16.4 (11.6 - 28.5) hrs. Median infant PK parameters following the initial dose were: predose conc=33 (blq - 86) ng/mL, Cmax=242 (43 - 700) ng/mL, AUC=5801 (1471 - 9664) ng\*hr/mL, t<sub>1/2</sub>=22.2 (17.5 - 36.7) hrs; following the 72 hrs after birth dose: predose conc= 22 (9 - 69) ng/mL, Cmax=236 (21 - 577) ng/mL, AUC=3821 (653 - 7256) ng\*hr/mL, t<sub>1/2</sub>=16.2 (9.3 - 28.7) hrs; following the 120 hrs after birth dose: predose conc=24 (6 - 71) ng/mL, Cmax=188 (21 - 518) ng/mL, AUC=3139 (349 - 5345) ng/mL, t<sub>1/2</sub>=17.0 (12.2 - 31.2) hrs. All mothers and infants tolerated TDF well.

**Conclusions:** Although this dosing regimen resulted in cord blood TFV above the 50 ng/mL target in most infants, TFV elimination was as rapid in the infants as in the mothers and the current dosing regimen failed to keep infant TFV conc above 50 ng/mL during the first week of life. A fourth cohort with daily infant dosing is underway.

No conflict of interest