Tenofovir Disoproxil Fumarate (TDF) Pharmacokinetics (PK) with Increased Doses in HIV-1 Infected Pregnant Women and their Newborns (HPTN 057)

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Background

- Need for an alternative to perinatal single dose NVP
- Tenofovir (TFV):
  - Is highly effective in protecting newborn macaques against SIV infection with no major toxicity and no development of resistance
  - Is available as a pro-drug (tenofovir disoproxil fumarate - TDF) in an oral tablet for maternal dosing and powder for oral suspension for infants
- Can we develop a simple TFV regimen for use in place of NVP for prevention of HIV PMTCT in pregnant women during labor and in the newborn?

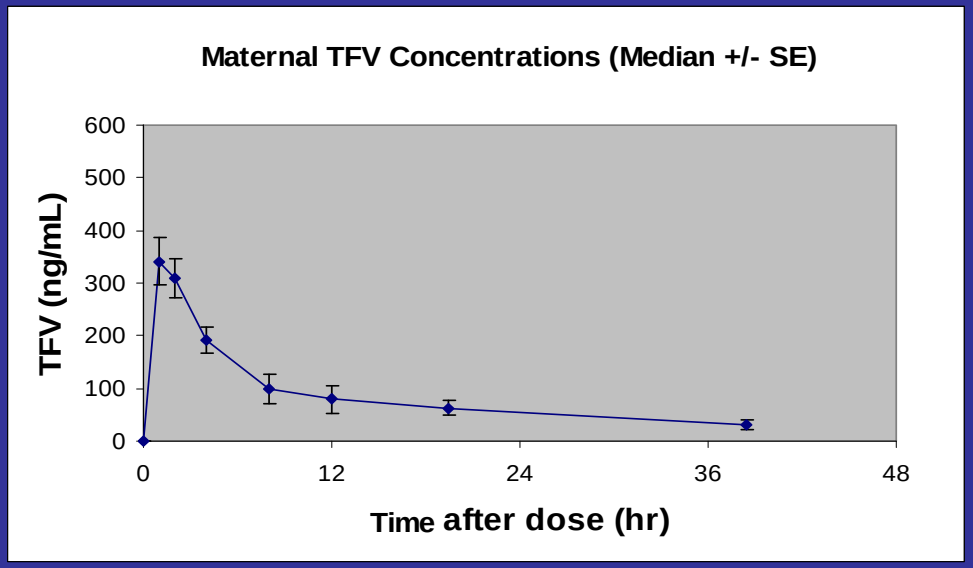
HPTN 057

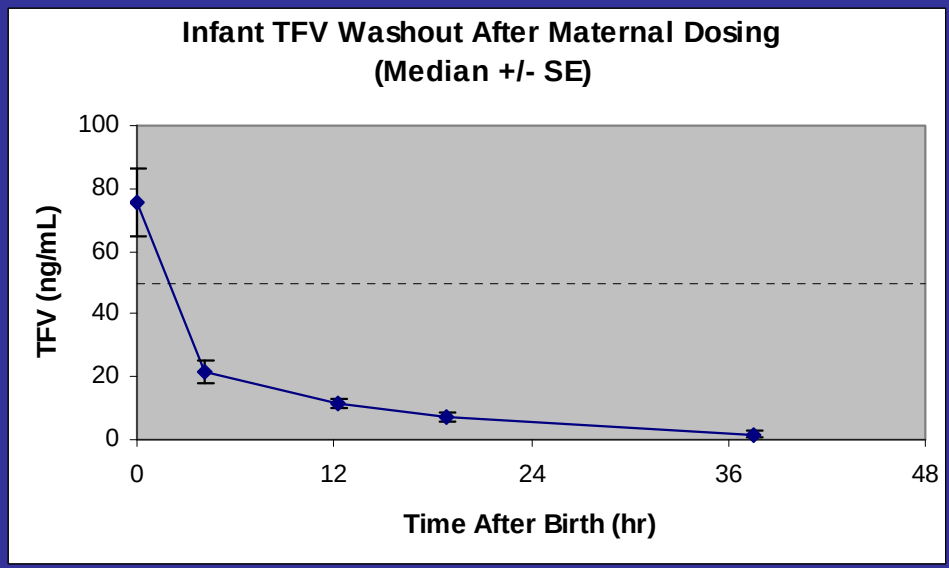
- Study of PK and safety of TDF administered to HIV infected pregnant women in labor and their infants
- PK Goal: To maintain infant TFV concentration throughout the first week of life above 50 ng/mL, the mean trough TFV concentration in adults receiving chronic dosing with TDF
- Sites: Blantyre, Malawi; 4 sites in Brazil
- Subjects received local PMTCT standard of care plus TDF dosing as below:

Cohort	n	Maternal TDF Dosing (in labor)	Infant TDF Dosing
1	30	600 mg x1	None
2	20	None	4 mg/kg within 12 hours of birth, day 3 and day 5
3	30	600/900 mg x1	4/6 mg/kg within 12 hours of birth, day 3 and day 5

Results from Cohort 1

600 mg maternal dosing, no infant dosing





Median (range)

	057 Cohort 1 (n=30)	Nonpregnant adults 600 mg single dose
Tmax (hr)	1.1 (1.0 - 8.0)	1.5
Cmax (ng/ml)	448 (110 - 928)	573
AUC (ng*hr/ml)	4221 (2767 - 24459)	4389
$t_{1/2}$ (hrs)	19.5 (11.1 - 32.8)	11.9

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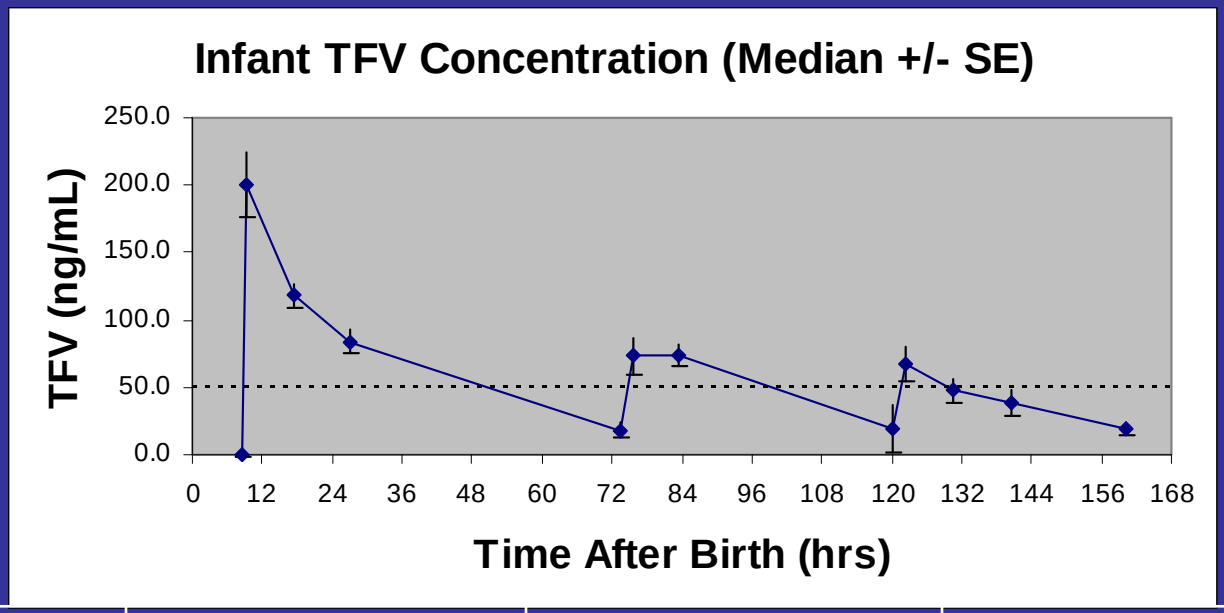
Results from Cohort 2:
no maternal dosing, 4 mg/kg infant dosing



Median (range)

Day of Dose	0 n=23	3 n=21	5 n=21	Adults 300 mg qd
Tmax (hr)	2.0 (1.6 - 10.0)	2.1 (1.9 - 43.9)	2.0 (1.8 - 18.0)	2.0
Cmax (ng/ml)	200 (66 – 428)	78 (27 – 363)	87 (22 - 252)	375
AUC (ng*hr/ml)	4013 (2003-8874)	2365 (728-8000)	1631 (884-4317)	3179
$t_{1/2}$ (hrs)	21.6 (16.0 - 124.5)	19.5 (6.8 - 44.0)	18.1 (5.2 - 61.3)	11.7
Cl/F (mL/kg/hr)	691(134 – 1808)	1375 (566 – 3425)	1713 (451 – 3562)	584

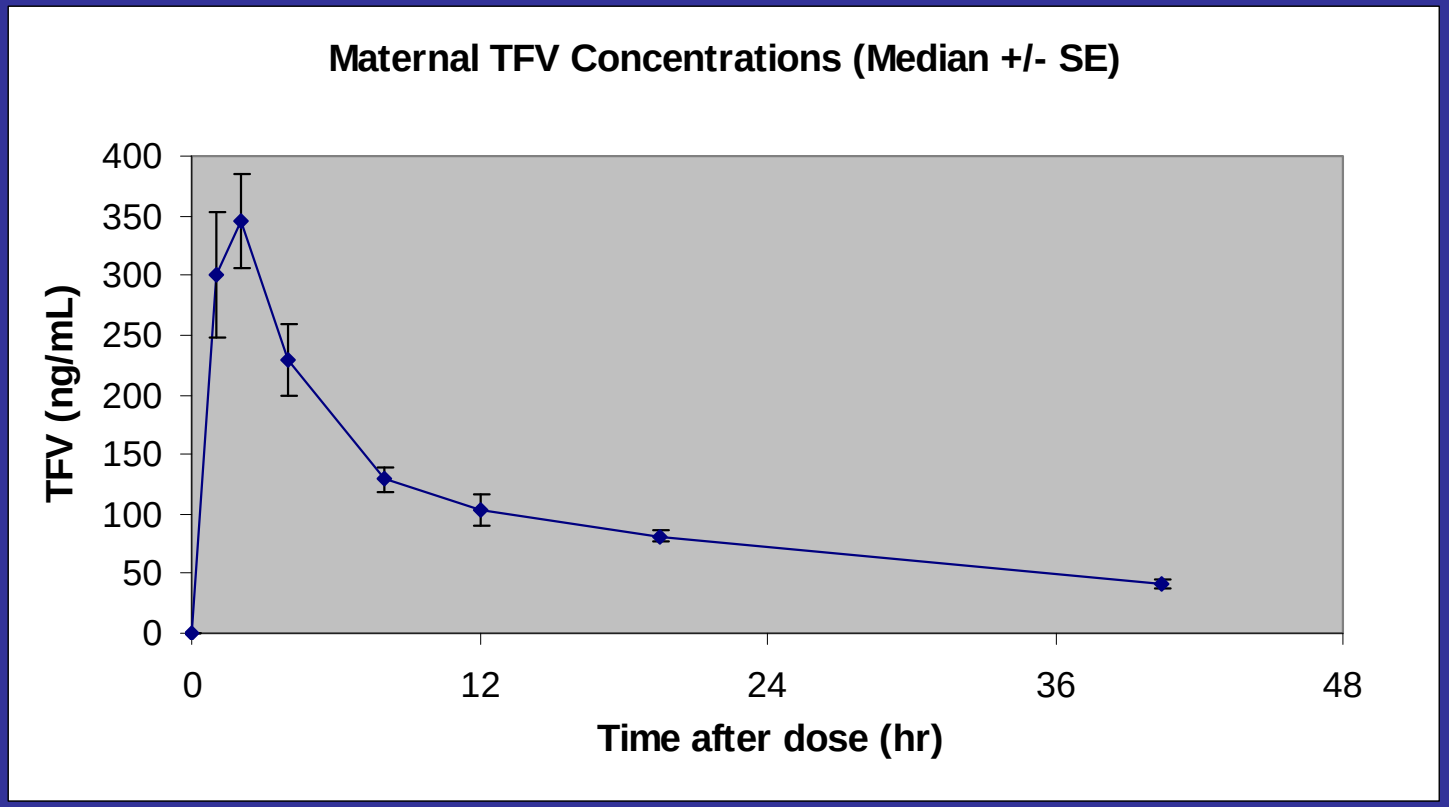
HPTN 057 – Cohort 3

- Mothers: 900 mg in labor or 4 hrs before C/S
- Infants: 6 mg/kg as soon as possible after birth and on days 3, 5
- Sampling:
  - Mother: Pre-dose & 1, 2, 4, 8, 12, 18-24, and 36-48 hrs after dose
  - Infant:
    - After birth - cord blood, pre 1st dose & 2, 10, 18-24 hrs after dose
    - Days 3 and 5 - Pre-dose & 2, 10, 18-24, 36-48 hrs after dose
- Assayed by HPLC-MS/MS with LOQ of 5 ng/mL

Results

- Enrolled 36 mother-infant pairs
  - 23 vaginal deliveries
  - 13 Cesarean sections
- Data presented as median (range)
- Maternal delivery weight: 67 (49 - 116) kg
- Delivered at 3.3 (0.4 - 39.3) hrs after dose
- Infant birth weight: 3010 (2300 - 3800) gm
- Infant dose administered at 4.5 (1.5-18.3) hrs after birth

Mothers: 900 mg TDF in labor



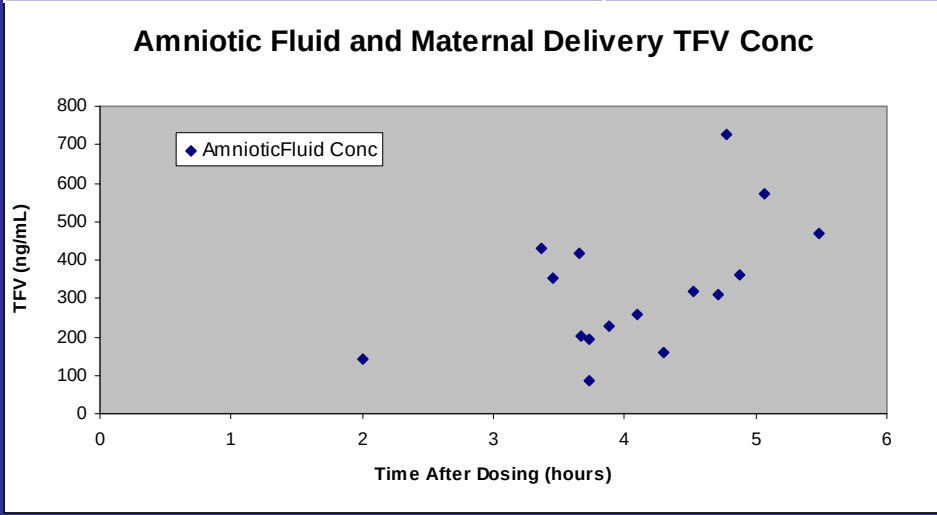
Median (range)

Tmax (hrs)	Cmax (ng/mL)	AUC (ng*hr/mL)	t½ (hr)
2 (1-12)	458 (134-1149)	5283 (3513-10670)	16.4 (11.6-28.5)

Amniotic Fluid TFV Concentrations

- Amniotic fluid collected from 16 mothers [5 in cohort 1 (600 mg doses) and 11 in cohort 3 (900 mg doses)] at 4.0 (2.0 - 5.5) hrs after dosing

Amniotic Fluid Conc (ng/mL	Maternal Delivery Conc (ng/mL)	Ratio
318 (84-75)	184 (39-556)	1.79 (0.37-4.90)



Amniotic Fluid TFV Concentrations

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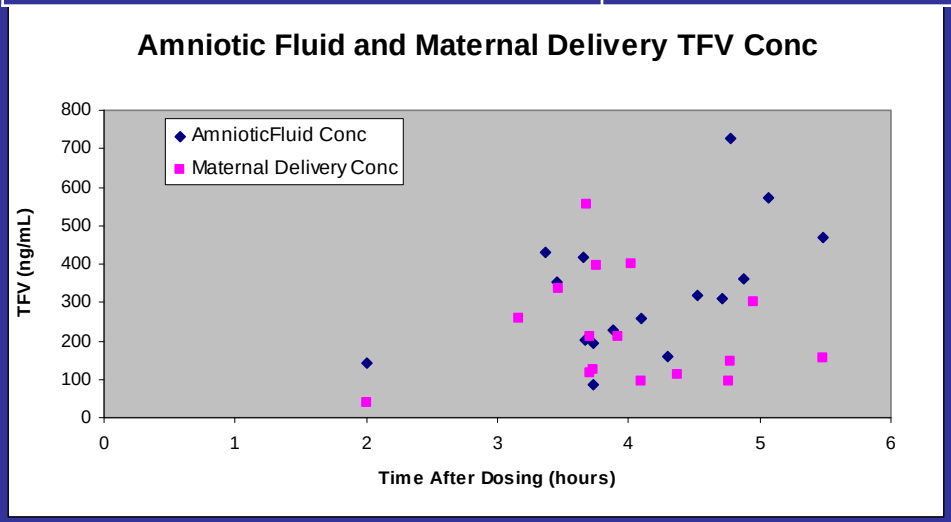

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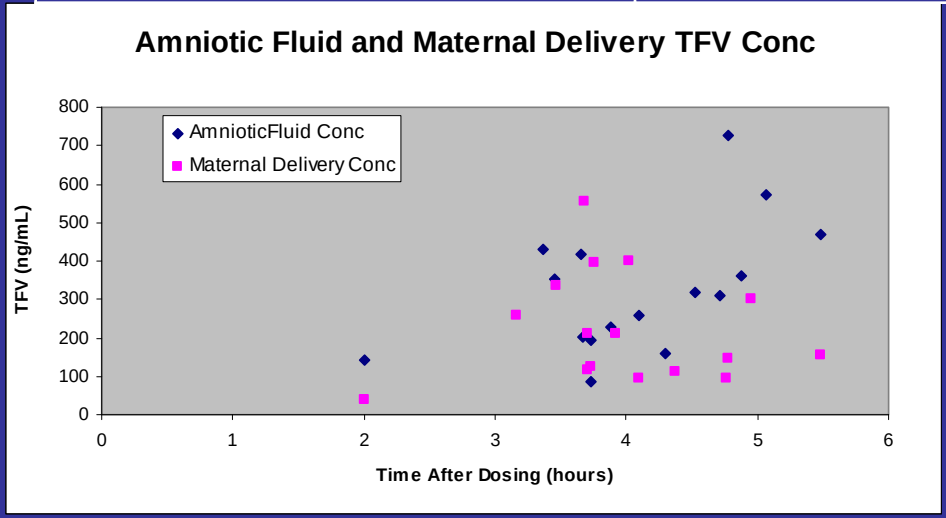
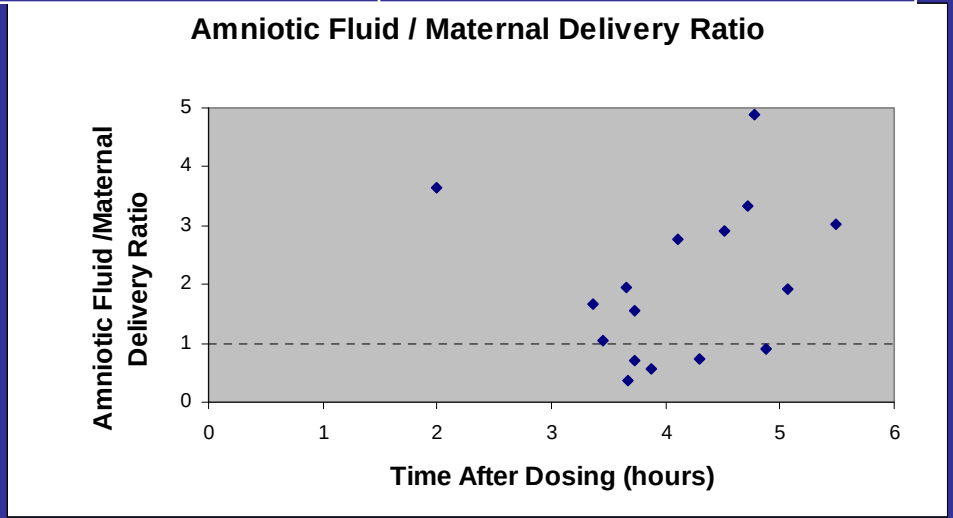
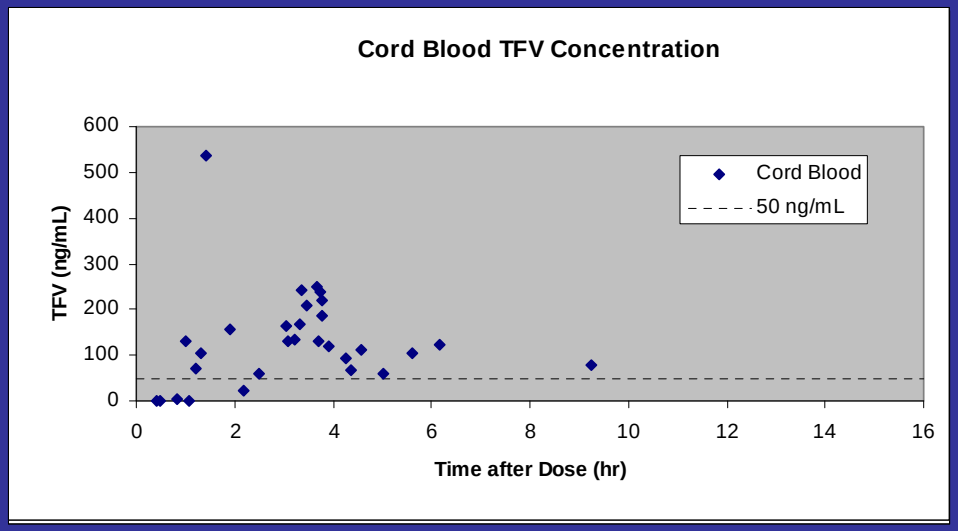




Cord Blood TFV Concentrations

- Cord blood TFV conc: 123 (blq-538) ng/mL
- Cord blood TFV > 50 ng/mL: 26/31
- Maternal TFV conc at delivery: 123 (blq-538) ng/mL
- Cord blood/maternal delivery ratio: 0.59 (0-3.06)



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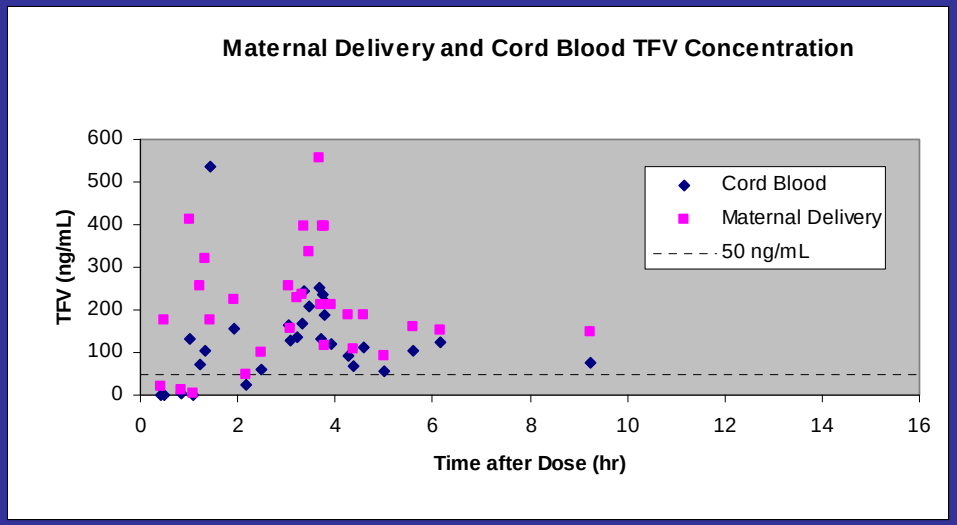

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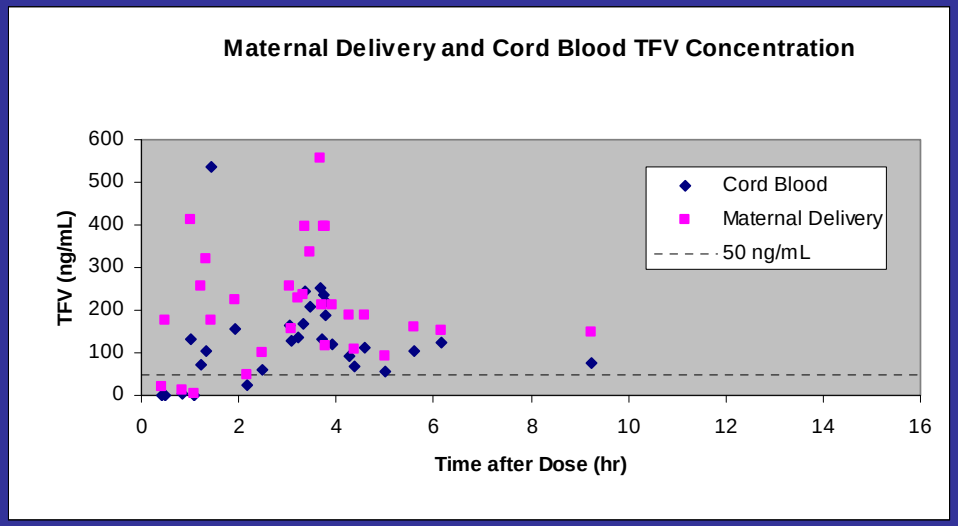
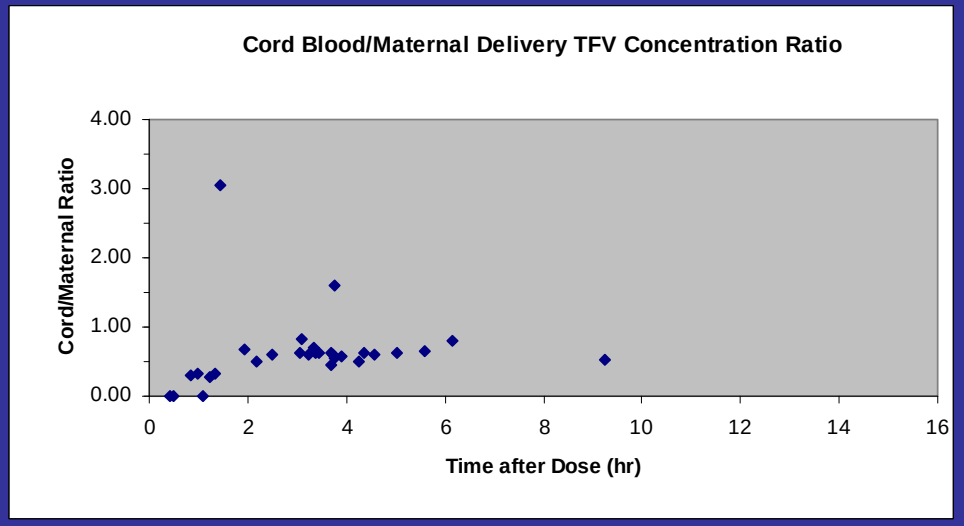
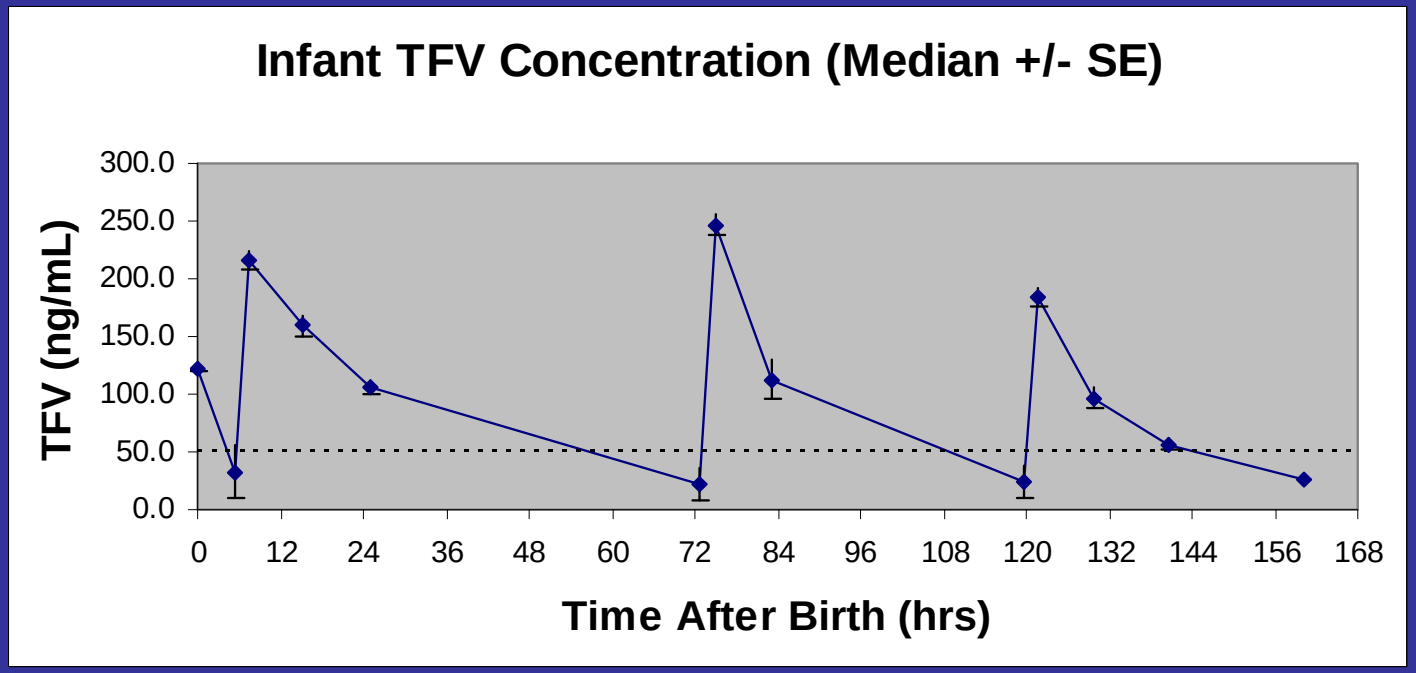




Infant: 6 mg/kg x 3 doses



Median (range)

	Predose (ng/mL)	Predose >50 ng/mL	Tmax (hr)	Cmax (ng/mL)	AUC (ng*hr/mL)	t½ (hr)
Initial Dose	33 (blq-86)	7/32	2.9 (2.1-16)	242 (43-700)	5801 (1471-9664)	22.2 (17.5-36.7)
Dose 2 (72 hrs)	22 (9-69)	2/34	2.3 (2.1-10.8)	236 (21-577)	3821 (653-7256)	16.2 (9.3-28.7)
Dose 3 (120 hours)	24 (6-71)	2/32	2.3 (2.0-10.7)	188 (21-518)	3139 (349-5345)	17.0 (12.2-31.2)

Safety

- All mothers and infants tolerated TDF well
- Mild/moderate abnormal laboratory results according to the DAIDS Toxicity Tables were common but appeared representative of local site background values in HIV infected women and their newborns.
- No severe or life-threatening adverse events or deaths were assessed by the Protocol Safety Review Team as possibly, probably, or definitely related to TDF
- An HPTN Study Monitoring Committee reviewed safety and toxicity data from this study and noted no safety concerns.

Conclusions

This regimen of maternal 900 mg doses in labor and 3 infant 6 mg/kg doses during the 1st week of life:

- Achieved cord blood tenofovir above 50 ng/mL target in most infants
- Failed to keep infant TFV conc above 50 ng/mL during the first week of life due to more rapid than expected infant TFV elimination

- Fourth cohort with 600 mg maternal doses and daily 6 mg/kg infant dosing is underway