CLINICAL TRIAL SIMULATION TO IMPROVE HIV PREEXPOSURE PROPHYLAXIS DOSING IN PREGNANCY

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BACKGROUND

- Several studies of pregnant women on TDF/FTC report lower TFV exposures in the 2nd and 3rd trimesters due to pregnancy-related increased volume of distribution and renal clearance.
- The Partners Demonstration Project showed the largest decline during pregnancy compared to non-pregnant women – 45% to 58% in TFV and active TFV diphosphate concentrations, respectively. [1]
- We hypothesized that doubling the TDF/FTC PrEP dose in pregnancy would maintain plasma, PBMC, and tissue concentrations associated with high levels of TDF/FTC adherence, themselves associated with high levels of HIV protection.

METHODS

- We utilized population pharmacokinetic (POPPK) modeling and clinical trial simulation.
- We used plasma TFV concentration data along with electronic adherence measurements from pregnant women in the Partners Demonstration study to build the POPPK model.
- We updated our prior model (NONMEM with FOCEI method for parameter estimation) of TFV built from the Partners PrEP data.[2]
- We replaced creatinine clearance in the prior model[2] as a covariate, with pregnancy trimester as a time-dependent covariate on clearance.
- As the revised model fit the data well, we used it for further simulation.
- We performed a clinical trial simulation with 1,000 women starting with a “standard” oral 300 mg daily oral TDF dose prior to pregnancy.
- In pregnancy, the simulated patients were split into 2 study arms through the 3 trimesters of pregnancy: 1 arm continuing on a “standard” dose and the other arm receiving a pregnancy adjusted “double” dose.
- The estimated protective trough TFV concentration benchmark (35.5 ng/mL) was based on 90% sensitivity threshold for daily dosing in non-pregnant women in HPTN 066.[3]

- Our clinical trial simulation shows >50% of research participants on standard daily oral PrEP dosing will have 3rd trimester trough plasma TFV concentrations below levels associated with protection.

- Double-the standard daily dose arm median TFV concentration in pregnancy is very similar to non-pregnant standard daily dose median TFV.

RESULTS

- Observed plasma concentration versus time post dose is shown in Figure 1.
- Diagnostic plots indicate no major bias in the model fit (Figure 2).
- Prior POPPK model of TFV with trimester as covariate on clearance reasonably described concentrations in pregnant women (Figure 2).
- POPPK parameters from pregnant women are in agreement with prior model (Table 1).
- In the non-pregnant population, our simulation showed 3.7% of women on a standard regimen would have trough levels below the levels associated with daily adherence, secondarily associated with high levels of protection.
- In contrast, we found that 31.5%, 47.2%, and 62.6% of trough concentrations in the 1st, 2nd, and 3rd trimesters, respectively, were below the estimated protective threshold (Figure 3).
- By comparison, in the simulated double dose group, only 4.4%, 7.9%, and 14.4% of troughs fell below protective levels in the 1st, 2nd, and 3rd trimesters, respectively (Figure 3).

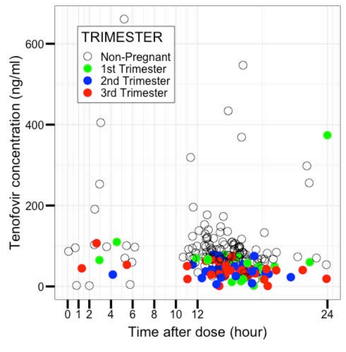

Figure 1. Plasma concentrations of TFV following daily 300 mg dose of TDF/FTC in women from the Partners Demonstration study

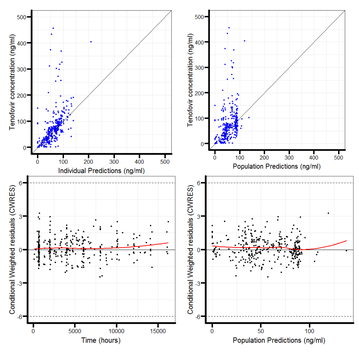

Figure 2. Goodness-of-fit plots of the optimized PPK model

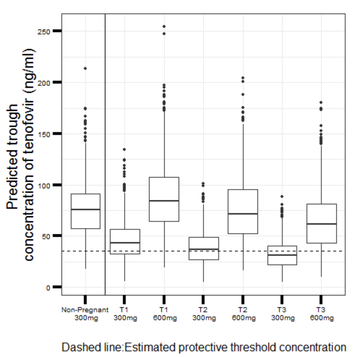

Figure 3. Simulated plasma trough concentrations of TFV during pregnancy at different dose levels (T1-1st trimester, T2-2nd trimester, T3-3rd trimester)

Table 1. Population pharmacokinetic parameters in Pregnant women compared to our prior model

Parameters	Present Study	Lu et al[1], 2016
	Estimates (%RSE)	Estimate (%RSE)
Clearance (Liters / h) –non-pregnant women	61.05 (5.4)	61.5 (2)
Effect of Trimester on Clearance (% increase) 1st Trimester 2nd Trimester 3rd Trimester	 55.9 (28.6) 72.2 (18.3) 98.6 (19.6)	
Central volume of distribution (Liters)	1800 (61.9)	345 (10)
Effect of creatinine clearance on clearance	NE	0.376 (13)
Absorption rate constant (1/h)	1.5 (fixed)	1.5 (fixed)
Inter-compartmental clearance (Liters / h)	447.3 (58.2)	231 (9)
Peripheral volume of distribution (Liters)	1547 (41.0)	830 (10)
Absorption lag time (h)	0.51 (97.5)	0.41 (18)
Residual Variability		
Additive error (ng/mL)	3.24 (56.6)	30.2 (8.48)
Proportional error (%CV)	38.7 (9.3)	20 (5)
Inter-individual variability on CL	26 (46.6)	16 (14)
Inter-individual variability on Vc	146 (89.7)	25 (119)
Inter-individual variability on Ka	NE	61 (69)
Inter-individual variability on Additive error	315 (60.4)	136 (11)

CONCLUSIONS

- Our clinical trial simulation shows that 47.2% and 62.6% of research participants on standard dosing will have 2nd and 3rd trimester trough plasma TFV concentrations, respectively, below levels associated with protection.
- The simulation indicates doubling the daily TDF dose results in <15% of pregnant women falling below protective levels compared to standard daily dosing, thus, providing the quantitative rationale to prospectively study a corrective dose.

REFERENCES

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