

Background

- The prevalence of HIV infection in women is increasing, reinforcing the need for safe and effective HAART regimens for women of child bearing potential
- Tenofovir DF (TDF), is one of three pregnancy category B RTIs that is approved for once daily use in HAART regimens in treatment-naive and treatment-experienced patients
- Hormonal contraception is an important concomitant medication in women with HIV infection
- While tenofovir would not be expected to interact with hormonal contraceptive medications, a PK study was conducted to confirm the lack of a drug-drug interaction

Objective

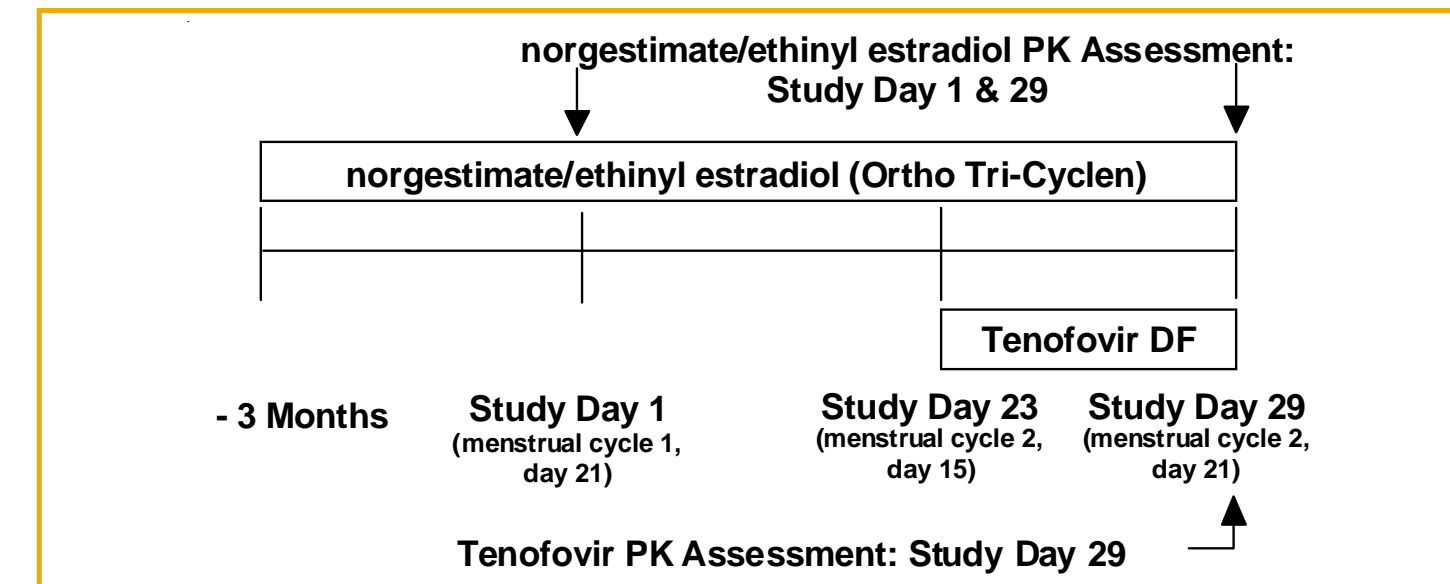
- To evaluate the effect of TDF co-administration on the PK and safety of hormonal contraceptive medications
- To evaluate the steady-state PK of tenofovir during administration of TDF in women receiving hormonal contraceptive medications

Methods

- HIV-negative female subjects receiving elective oral contraception regimens with a frequently used and representative oral contraceptive medicine containing both estrogenic and progestational components (Ortho tri-cyclen®, OTC)
- 29-day, open-label, drug-drug interaction study (see Figure 1)
- To ensure a stable dose/regimen and PK profile of contraceptive medications, all subjects were required to use OTC for 3 consecutive contraceptive cycles and have PK evaluations on the same day of 2 sequential cycles

Methods (cont'd)

Figure 1. Study Design



- Ethinyl estradiol and 17-deacetyl norgestimate (pharmacologically active metabolite of norgestimate) concentrations determined in plasma by validated LC/MS/MS assays
- Tenofovir concentrations determined in serum by validated LC/MS/MS assay
- PK parameters estimated by noncompartmental methods using WinNonlin™
- AUC_{0-∞}, C_{max} and C_t results for each analyte reported as 90% confidence intervals about the ratio of geometric means [GMR (90% CI)] for OTC + TDF vs. OTC alone:
 - No change in PK concluded if 90% CI of GMR lies within 80-125% range

Results

- 24 subjects enrolled
 - mean age: 25 yr (range: 19 - 36 yr)
 - mean weight: 64.1 kg (range: 47.7 - 82.7 kg)
 - race: 24 Caucasian
- 20 subjects evaluable for PK
 - 2 subjects discontinued for non-compliance (Day 2)
 - 2 subjects released when enrollment requirement was satisfied

Results (cont'd)

Figure 2. Oral Contraceptive Concentration - Time Profiles

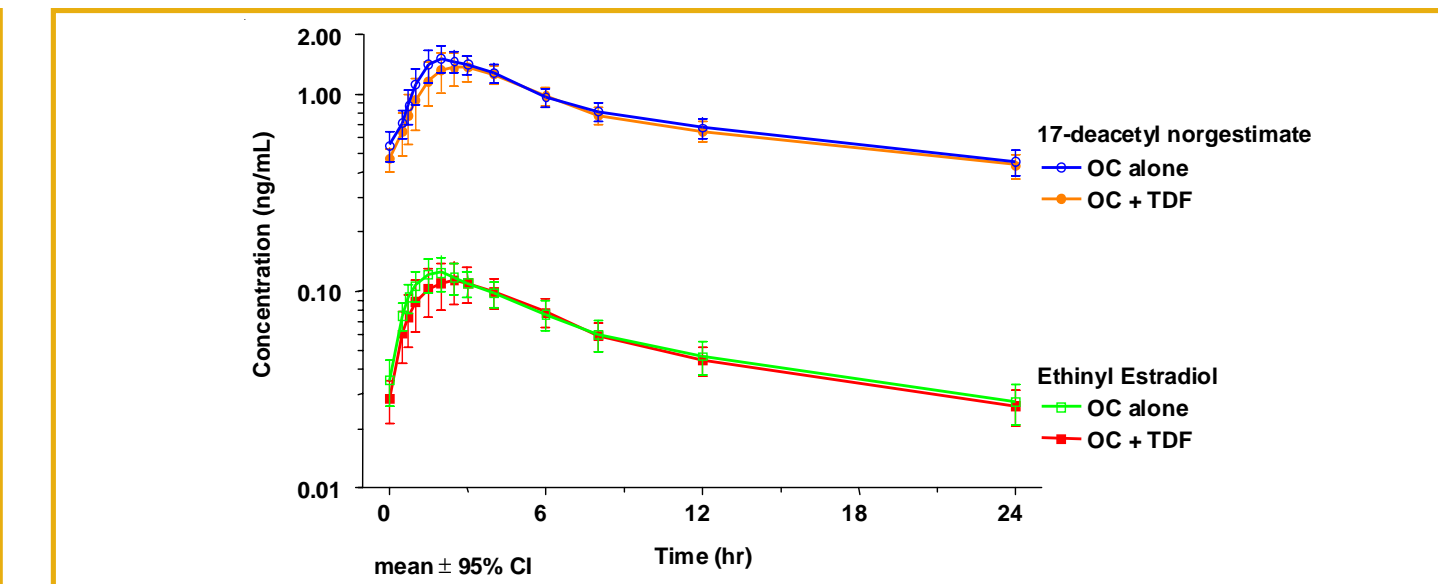


Table 1. Ethinyl Estradiol Pharmacokinetics

Ethinyl Estradiol Pharmacokinetic Parameter	OTC Alone	OTC + TDF	% Mean Ratio (90% CI)
AUC _{0-∞} (ng•hr/mL)	1.38 (35.8)	1.32 (37.5)	95.6 (90.7, 101)
C _{max} (ng/mL)	0.137 (36.2)	0.131 (40.7)	93.7 (87.5, 100)
C _t (ng/mL)	0.027 (48.2)	0.026 (43.9)	98.1 (90.8, 106)
T _{max} (hr)	2.02 (1.53 – 2.52)	2.75 (1.75 – 3.51)	NA

AUC_{0-∞} = area under the curve over the dosing interval; C_{max} = maximum plasma concentration; C_t = trough concentration at the end of the dosing interval; T_{max} = time to C_{max}
Data expressed as arithmetic mean (%CV) or median (IQR)
% Geometric mean ratio is the model-based anti-log of the difference of the treatment of OTC + TDF vs. OTC alone (90% confidence interval of the ratio)

Table 2. 17-Deacetyl Norgestimate Pharmacokinetics

17-Deacetyl Norgestimate Pharmacokinetic Parameter	OTC Alone	OTC + TDF	% Mean Ratio (90% CI)
AUC _{0-∞} (ng•hr/mL)	18.7 (23.0)	17.8 (23.2)	95.1 (91.0, 99.4)
C _{max} (ng/mL)	1.77 (20.5)	1.68 (26.5)	94.0 (87.2, 101)
C _t (ng/mL)	0.451 (32.5)	0.434 (29.7)	96.4 (92.4, 101)
T _{max} (hr)	2.02 (1.57 – 2.78)	2.75 (2.00 – 3.50)	NA

AUC_{0-∞} = area under the curve over the dosing interval; C_{max} = maximum plasma concentration; C_t = trough concentration at the end of the dosing interval; T_{max} = time to C_{max}
Data expressed as arithmetic mean (%CV) or median (IQR)
% Geometric mean ratio is the model-based anti-log of the difference of the treatment of OTC + TDF vs. OTC alone (90% confidence interval of the ratio)

Table 3. Steady State Tenofovir Pharmacokinetics

Tenofovir Pharmacokinetic Parameter	TDF Alone
AUC _{ss} (ng•hr/mL)	2970 (25.1)
C _{max} (ng/mL)	340 (25.0)
C _t (ng/mL)	53.3 (27.2)
T _{max} (hr)	2.00 (1.25 – 3.00)

AUC_{ss} = steady state area under the curve over the dosing interval; C_{max} = maximum plasma concentration; C_t = trough concentration at the end of the dosing interval; T_{max} = time to C_{max}
Data expressed as arithmetic mean (CV%) or median (IQR)
% Geometric mean ratio is the model-based anti-log of the difference of the treatment of TDF + ABC vs. historical data for TDF alone (90% confidence interval of the ratio)

- Tenofovir PK results were similar to those observed in previous studies in healthy subjects and HIV+ individuals

Safety Assessments

- No serious adverse events were reported in this study
- 10 of the 20 (50%) subjects experienced at least 1 treatment-emergent AE
- Most common AEs: headache, mild rash, dysmenorrhea, and nausea
- No clinically significant changes in laboratory parameters observed

Conclusions

- Co-administration of oral contraceptives with TDF did not affect the PK of either the estrogenic or progestational components
- Tenofovir PK results when given with oral contraceptives were consistent with previously observed values
- Co-administration of oral contraceptives with TDF was generally safe and well tolerated