

Background

- Tenofovir DF (TDF), a NtRTI is approved for once daily use in HAART regimens in treatment-naive and treatment-experienced patients
 - Serum half-life ~17 hours, intracellular half-life ~10-50 hours
- Abacavir (ABC) is a purine nucleoside analogue RTI that is approved for twice daily dosing in HAART regimens
 - Plasma half-life ~1.5 hours, intracellular half-life (carbovir-TP) ranging from 2.5-12 hr¹⁻³
- Recently, data with once or twice daily ABC-containing HAART regimens, including those containing TDF, have yielded suboptimal virologic results
 - AZT + 3TC + ABC BID (ACTG 5095)⁴
 - TDF + 3TC + ABC QD (ESS 30009, Farthing C, et al. 2nd IAS, 2003.)^{5,6}
- In vitro* assays indicate lack of intracellular antagonism with ABC and tenofovir
- Four drug-drug interaction studies with TDF and didanosine (ddI), also a purine nucleoside RTI, have shown that TDF increases ddI exposure⁷⁻¹²
 - A putative mechanism for this interaction is inhibition of ddI metabolism by purine nucleoside phosphorylase (PNP) by tenofovir monophosphate¹³
 - Abacavir is not a substrate for PNP²

Objective

- To evaluate the drug interaction potential of TDF with ABC
 - Evaluation of an ABC - TDF drug interaction in subjects exhibiting a ddI interaction⁹ provides an opportunity to test the proposed mechanism of TDF on PNP vs. a more general effect on purine analogues
- To assess the safety of co-administration of ABC with TDF
- To evaluate if a single dose of ABC has substantial effects on tenofovir PK

Methods

- A single dose of ABC 300 mg was dosed alone and with TDF 300 mg to a subset of patients participating in a ddI drug interaction study
 - Due to the risk of ABC hypersensitivity and safety reasons, only the PK of single doses were evaluated
 - ABC was administered alone and following multiple dosing of TDF with food at tenofovir steady state to maximize the interaction potential on ABC
- Study drugs were administered within 5 minutes of completion of a standardized light meal (~373 kcal, 20% fat)
- Blood sampling was performed over 24 hours in EDTA containing collection tubes
- Tenofovir and ABC concentrations in plasma were determined by validated LC/MS/MS assays
- PK parameters estimated by noncompartmental methods using WinNonlinTM
- ABC AUC_{0-∞} and C_{max} results reported as 90% confidence intervals about the ratio of geometric means [GMR (90% CI)] for ABC + TDF vs. ABC alone
 - No change in PK concluded if 90% CI of GMR lies within 80-125% range
- Tenofovir PK compared to historical data when dosed with the same light meal

Results

- 8 subjects studied
 - 5 males; 3 females
 - mean age: 26 yr (range: 21-31 yr)
 - mean weight: 80 kg (range: 66-91 kg)
 - race: 7 Caucasian, 1 African American
- ABC concentration-time profiles ± TDF are presented in Figure 1
 - ABC concentrations were not measurable in plasma for greater than 6 to 8 hours post dosing
- ABC PK parameters are presented in Table 1
 - ABC PK when dosed alone were similar to historical data
- Tenofovir PK parameters for TDF alone (historical data) and with ABC are presented in Table 2

Results (cont'd)

Figure 1. Single Dose Abacavir Concentration - Time Profiles

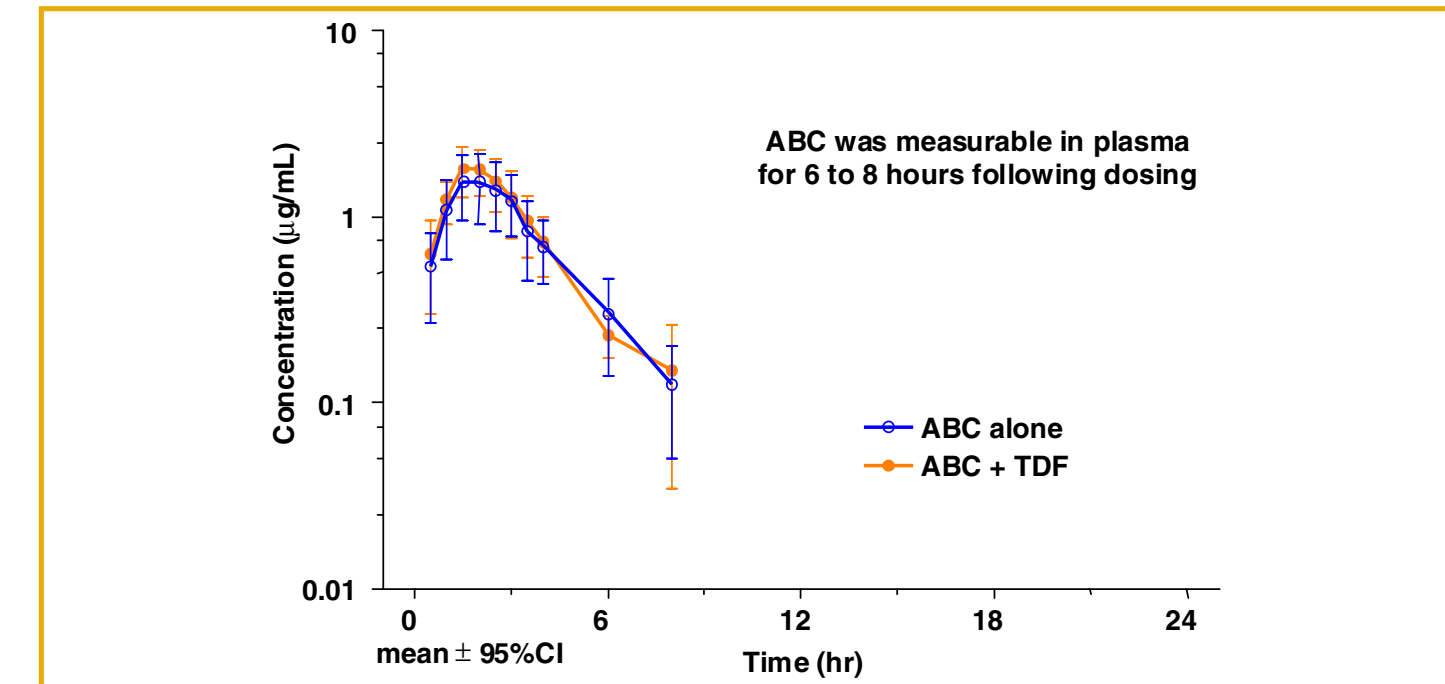


Table 1. Single Dose ABC Pharmacokinetics

Abacavir Pharmacokinetic Parameter	ABC Alone	ABC + TDF	% Mean Ratio (90% CI)
AUC _{0-∞} (ng•hr/mL)	5.67 (35.5)	6.01 (32.9)	110 (102, 118)
C _{max} (ng/mL)	1.77 (39.2)	1.95 (35.0)	112 (98.7, 126)
T _{1/2} (hr)	1.21 (1.00 – 1.36)	1.26 (1.15 – 1.38)	NA
T _{max} (hr)	1.50 (1.5 – 2.0)	1.50 (1.49 – 2.00)	NA

AUC_{0-∞} = area under the curve to infinite time; C_{max} = maximum plasma concentration; T_{1/2} = terminal elimination half-life; 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 ABC + TDF vs. ABC alone (90% confidence interval of the ratio)

Table 2. Steady State Tenofovir Pharmacokinetics with ABC

Tenofovir Pharmacokinetic Parameter	TDF Alone ^a (N = 24)	TDF + ABC (N = 8)	% Mean Ratio (90% CI)
AUC _{ss} (ng•hr/mL)	2620 (30.5)	2690 (26.0)	104 (85.7, 126)
C _{max} (ng/mL)	296 (26.7)	276 (33.3)	92.2 (76.0, 112)
C _t (ng/mL)	58.2 (34.0)	55.3 (29.2)	NA
T _{max} (hr)	1.50 (1.00 – 2.00)	1.75 (1.25 – 2.00)	NA

^a Historical data for TDF administered with the same light meal (~373 kcal, 20% fat). AUC_{ss} = steady state area under the curve over the dosing interval; C_{max} = maximum plasma concentration; C_t = minimum (trough) plasma concentration; 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)

Safety

- No serious adverse events were reported in this study
- 4 subjects experienced at least 1 treatment-emergent AE
 - Headache was the most common event experienced by 2 patients
 - One subject experienced heart palpitations and fatigue
 - One subject reported nausea

Conclusions

- ABC plasma PK were not significantly affected by TDF
- Tenofovir PK with a single dose of ABC was similar to historical data for TDF
- As TDF and ABC have been shown to have additive antiviral effects *in vitro*, additional data on intracellular concentrations and PK of carbovir-TP are needed to assess the appropriate use of QD ABC
- These PK results do not explain the suboptimal clinical outcome of studies using TDF with 3TC and ABC QD

References

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