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In Vivo Viral Dynamics and Pharmacokinetics of Tenofovir Disoproxil Fumarate (TDF) and Abacavir (ABC): Evidence of a Non-Additive Antiviral Effect

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Introduction

- High rates of early virologic failure were observed when TDF+ABC+3TC regimens were used in treatment-naïve patients. Considering the good virologic responses obtained with TDF/3TC- and ABC/3TC-based regimens, the likely negative interaction is between TDF and ABC.
- Individually both TDF & ABC have high antiviral potency.
  - Median decline in HIV-1 RNA during monotherapy in treatment-naïve patients (ABC: 1.5 $\log_{10}$ copies/mL over 4 weeks[1] and TDF: 1.6 $\log_{10}$ copies/mL over 3 weeks[2])
  - Inhibition constant (Ki) for inhibition of incorporation by ddNTP of the corresponding dNTP in proviral DNA by HIV RT is 21 nmol/L for carbovir triphosphate (CBV-TP)[3] and 180 nmol/L for tenofovir diphosphate (TFV-DP)[4]
  - No intracellular interaction with TDF+ABC was observed in previous clinical study[5] and in vitro work has shown TFV+ABC to have additive antiviral activity[6]
- We hypothesized that co-administration of TDF would decrease the intracellular exposure of CBV-TP, the active metabolite of ABC, and reduce phase I viral decay.

Methods

Study Design: This is a prospective, open-label study of 21 treatment-naïve subjects that were randomized to 7 days of TDF 300mg QD (n=10) or ABC 600mg QD(n=11) mono-therapy, followed by a 35 day washout period, with an additional 7 days of TDF+ABC (n=21). After the mono- and dual-therapy courses all subjects received combination therapy with EFV+ABC+3TC and were monitored for an additional 46 weeks. Resistance testing was done at baseline and after dual-therapy (day 49). Study medications were administered as a witnessed-dose for all visits during the 7-day mono-and dual-therapy sequences (**Figure 1**).

Viral decay (VD) rates: The relative potencies of mono-therapy regimens with either TDF or ABC were compared to a dual-therapy with TDF+ABC as assessed by the slope of the phase I viral decay. Plasma for HIV-1 RNA loads was collected during mono-therapy (screen and days 1, 2, 3, 5 and 8) and dual-therapy visits (days 37, 42, 43, 44, 46 and 49). Pre-mono/dual therapy baseline HIV RNA was calculated as the average of Screening + Day 1 and Day 37 + Day 42, respectively. All HIV-1 RNA loads for VD were done at UCSD using the Amplicor HIV-1 Monitor Assay (by Roche Molecular Systems).

Pharmacokinetics: Intracellular concentrations (ICs) of CBV-TP and TFV-DP were measured in PBMCs using two validated LC/MS/MS techniques. Samples were collected after mono- (days 7 & 8) and dual-therapy (days 48 & 49) at the following times: pre-dose, 3-hr, 6-hr and 24-hr post-dose. All assays for IC CBV-TP were performed at Taylor Laboratories and Gilead Sciences Inc. performed all IC TFV-DP. The area under the curve (AUCt) was approximated using the linear trapizoidal method (Winnonlin).

Statistics: With a sample size of 10 subjects per arm, this study had 80% power to detect a 30% difference in Phase I VD rates and a 30% difference in ICs between mono- and dual-therapy. Linear mixed effects models and Wilcoxon rank-sum tests were used to assess differences in VD rates and ICs, respectively, between mono- and dual-therapy.

References

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Figure 1. Study Design for Phase 1 Viral Dynamics & IC dNTP sampling

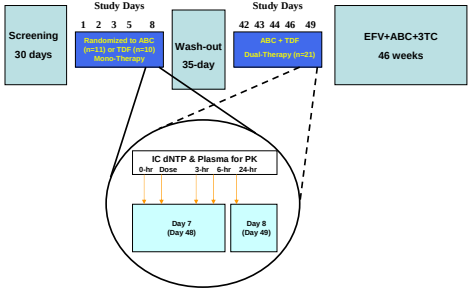


Table 1. Baseline Characteristics

Characteristics	Abacavir (n=11)	Tenofovir (n=10)
Male (%)	82%	60%
Age (yrs)	33	46*
BMI	25.7	28.2
HIV RNA ($\log_{10}$ copies/ml)	4.7	4.8
CD4 (cells/mm^3)	353	350
35 day wash-out		
HIV RNA ($\log_{10}$ copies/ml)	4.94	4.90

* $p<0.05$

Table 2. Subject Disposition Post Mono- & Dual-Therapy (# subjects)

Characteristics	Abacavir (n=11)	Tenofovir (n=10)
HIV RNA ≤ 75 c/mL at end of study	9*	10
Virologic Failure	2**	0
New HIV Drug Resistance Mutations[†]	0	0

* 1 subject had viral blip at week 48 (HIV RNA=98 c/mL); subsequently confirmed viral suppressed

** Virologic failure defined as failure to achieve a < 2.0 log drop in plasma HIV RNA by week 8 from day 49 and/or a ≥ 0.5 log increase from nadir. Both instances of viral failure occurred at study week 24

† Evidence of primary resistance mutations from resistance testing at screening after dual therapy (day 49). All subjects had wild-type virus at entry

Figure 2. Phase 1 Viral Decay Dynamics during Mono & Dual-Therapy

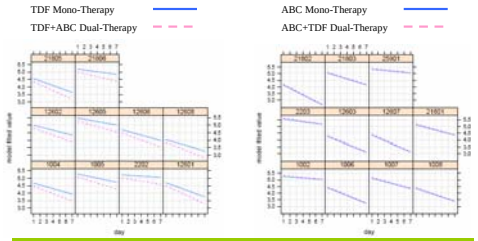


Table 3a. Mixed Effects Models (w/o day 0): Mono vs. Dual-Therapy

Intercept	Δ viral decay slope (log10 copies/ml per day)	SE	DF	p-value
TDF : TDF+ABC (n=10)	-0.043482	0.01484438	67	0.0046
ABC : ABC+TDF (n=11)	-0.008085	0.01978585	72	0.6840

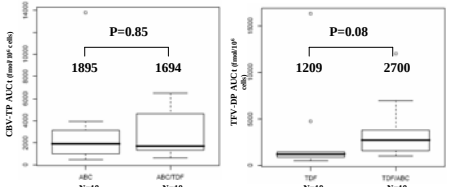
Mean values; Mixed effects model used for all comparisons

Table 3b. Linear-Model Viral Dynamics (w/o day 0): ABC vs. TDF

	ABC (n=11)	TDF (n=10)	p-value
Mono-Therapy ($\log_{10}$/day)	-0.16	-0.11	0.13
Dual-Therapy ($\log_{10}$/day)	-0.15	-0.15	0.92

Median values; Wilcoxon-rank sum tests used for all comparisons

Figure 3. IC ddNTP Mono & Dual-Therapy [median AUCt (fmol/10^6 cells)]



Results

Study Population & Treatment Outcome

21 subjects (71% male) were randomized to initial mono-therapy with ABC (n=11) or TDF (n=10). Baseline characteristics were similar (median: CD4 324 cells/mm^3, HIV RNA 4.99 $\log_{10}$ copies/mL), except ABC subjects were younger (median: 32 yrs vs. 48 yrs; P=0.014) (**Table 1**). No new HIV drug resistance mutations were observed in resistance testing obtained at baseline and after dual-therapy and 9 of 11 subjects randomized to initial ABC mono-therapy and 10 of 10 subjects randomized to initial TDF mono-therapy had viral suppression at time of study discontinuation (**Table 2**).

Phase 1 Viral Decay Dynamics during Mono & Dual-Therapy

VD during TDF+ABC dual-therapy was an average of 0.04 $\log_{10}$/day faster than TDF mono-therapy (P=0.005) (**Figure 2, Table 3a**), but was similar to VD during ABC mono-therapy (median: -0.16 $\log_{10}$/day vs. -0.15 $\log_{10}$/day). VD was faster for ABC (median: -0.16 $\log_{10}$/day) vs. TDF (median: -0.11 $\log_{10}$/day) mono-therapy, but this difference was not statistically significant (P=0.13) (**Table 3b**).

Intracellular dNTP Pharmacokinetics during Mono & Dual-Therapy

Median IC CBV-TP and TFV-DP exposures were similar to previously studies:

- CBV-TP (fmol/10^6 cells) C-3hr, C-24hr Mono-therapy (dual-therapy): 76.77 (100.92), 78.36 (76.89)
- TFV-DP (fmol/10^6 cells) C-3hr, C-24hr Mono-therapy (dual-therapy): 49.70 (104.07), 46.64 (96.01)

None of the PK metrics for ICs of CBV-TP nor TFV-DP was correlated with VD during mono- or dual-therapy (data not shown).

The addition of second NRTI did not affect the IC of CBV-TP or TFV-DP. IC CBV-TP was similar during both mono- and dual-therapy (median AUCt [fmol/10^6 cells]: 1895 vs. 1694), however, IC TFV-DP was two-fold higher after re-exposure in the TDF arm (median AUCt [fmol/10^6 cells]: 2700 vs. 1209; P=0.08) (**Figure 3**).

Discussion/Conclusions

1. The combination of TDF+ABC did not demonstrate additive antiviral activity compared to ABC alone, suggesting a pharmacodynamic interaction.
2. However, we observed no negative pharmacokinetic interaction resulting in a decrease of either IC CBV-TP or TFV-DP concentrations between mono and dual-therapy.
3. Further, no new primary mutations were observed between pre-therapy and post dual-therapy resistance testing.