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Pharmacokinetic (PK) Evaluation of the Combination of Atazanavir (ATV), Enteric Coated Didanosine (ddI-EC), and Tenofovir Disoproxil Fumarate (TDF) for a Once-Daily Antiretroviral Regimen

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Abstract

Background: The triple combination of ATV, ddI-EC, and TDF is a promising once-daily HAART regimen. This study investigated the PK interaction of this triple combination.

Methods: In this study, 36 healthy subjects participated in the following protocol. Day 1: 400 mg ddI-EC in the fasted state; Days 2-7: 400 mg ATV once-daily with food; Day 8: 500 mg ddI-EC + 400 mg ATV with food; Days 9-15: 400 mg ATV + 300 mg TDF once daily with food; Day 16: 250 mg ddI-EC + 400 mg ATV + 300 mg TDF with food; Days 17-23: washout period; and Days 24-30: 300 mg TDF with food. Serial blood samples were collected over a 24-hour period on Days 1, 7, 8, 15, 16, and 30 and ddI, ATV, or TDF were analyzed by LC/MS/MS. PK parameters were calculated by non-compartmental analysis.

Results:

PK Parameter	Geometric Mean Ratio (90% Confidence Interval)			
	Day8:Day1	Day8:Day7	Day15:Day7or30	Day16:Day1,7,or30
C_{max}, ddI-EC	1.08(0.95-1.22)			0.95(0.84-1.07)
AUC, ddI-EC	1.26(1.15-1.37)			1.15(1.06-1.25)
C_{max}, ATV		0.88(0.81-0.95)	0.79(0.73-0.86)	0.76(0.70-0.82)
AUC, ATV		0.89(0.83-0.96)	0.75(0.70-0.81)	0.74(0.69-0.79)
C_{max}, TDF			1.14(1.08-1.20)	1.12(1.06-1.19)
AUC, TDF			1.24(1.21-1.28)	1.25(1.22-1.28)

Conclusions: **(1)** Coadministration of 250 mg ddI-EC, 400 mg ATV, and 300 mg TDF with food results in equivalent ddI exposure (AUC). **(2)** A 26% reduction in ATV AUC and a 25% increase in TDF AUC were observed when ATV was administered with TDF with or without ddI-EC. **(3)** C_{min} for ddI-EC and TDF were increased by 89% and 25%, respectively, and ATV C_{min} was decreased by 39%. **(4)** PK data from CROI 03 suggest that approaches to increase the C_{min} and AUC of ATV may be possible to compensate the effect seen in this study. **(5)** The mechanism for the two-way interaction between ATV and TDF is unknown at the present time.

Introduction

- The combination of enteric-coated didanosine (ddI-EC)/atazanavir (ATV)/tenofovir disoproxil fumarate (TDF) is a promising once-daily (QD) highly active antiretroviral therapy (HAART) regimen.
- The recommended once-daily doses of ddI-EC (a nucleoside reverse transcriptase inhibitor), ATV (a protease inhibitor), and TDF (a nucleotide reverse transcriptase inhibitor) in HIV-infected subjects is 400 mg for subjects ≥60 kg (250 mg for subjects <60 kg) under fasted conditions,[1] 400 mg with food[2], and 300 mg with food[3], respectively.
- The bioavailability of 400 mg ddI-EC is reduced by ~ 20-25% with food.[4]
- Coadministration of 400 mg ddI-EC and 300 mg TDF results in ~ 60% increase in ddI exposure, but the exposure of TDF is unaltered.[5,6]
- However, exposure of reduced dose of 250 mg ddI-EC with 300 mg TDF and food is comparable to exposure of 400 mg ddI-EC given alone in the fasted state.[7,8]
- Administration of 200 mg ddI chewable/dispersible buffered tablet and 400 mg ATV in the fasted state reduced ATV exposure by almost 90%, but the exposure of ddI was unchanged.[2]
- Data from CROI 2003 (PUZZLE 2 [ANSR 107]) suggest that when a ritonavir (R) (100 mg)-boosted ATV (300 mg) regimen was combined with 300 mg TDF, ATV C_{max}, AUC, and C_{min} values were decreased by approximately 28%, 25%, and 23%, respectively, compared to the 300 mg/100 mg ATV/R reference treatment.[9] Despite these effects, the ATV C_{max}, AUC, and C_{min} values were still 1.4-, 2.3-, and 4.1-fold higher, respectively, for the ATV/R + TDF regimen, relative to historical data for 400 mg ATV/R alone.[10]
- It is unknown if PK interactions between ddI-EC and ATV, ATV and TDF, and between the triple combination of ddI-EC, ATV, and TDF exist.

Objectives

Primary Objective:

- To evaluate whether the PK of ddI-EC (250 mg), TDF (300 mg QD), or ATV (400 mg QD) when coadministered with food are comparable to single-agent administration of ddI-EC (400 mg under fasted conditions), TDF (300 mg QD with food), or ATV (400 mg QD with food).

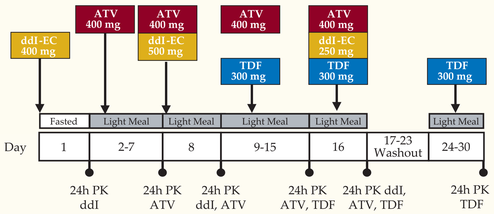
Secondary Objectives:

- To evaluate whether the PK of ddI-EC (500 mg) or ATV (400 mg QD) when coadministered with food are comparable to single-agent administration of ddI-EC (400 mg under fasted conditions) or ATV (400 mg QD with food).
- To evaluate whether the PK of TDF (300 mg QD) or ATV (400 mg QD) are affected by their coadministration.
- To assess the safety of ddI-EC, TDF, and ATV when administered alone or in combination.

Methods

- Phase I, open-label study in 36 healthy subjects weighing ≥60 kg.
- The design of this study (Figure 1) incorporated the sequential introduction of specified drug or drug combinations.
- Serial blood samples were collected on Days 1, 7, 8, 15, 16, and 30 at pre-dose and up to 24 hours post-dose.
- Plasma or serum samples were assayed for ddI, ATV, and/or TDF by validated LC/MS/MS assay methods.
- PK parameters for ddI, ATV, and TDF were derived using a non-compartmental analysis.
- Absence of drug interaction was concluded if the 90% confidence interval (CI) for the ratio of test to reference geometric means fell within 0.80-1.25 interval for AUC; similar assessments were conducted for C_{max} and C_{min}.
- Clinical safety evaluations were performed at screening, during the study, and at the time of discharge from the study.

Figure 1: Study Design



Light Meal: 373 kcal; 68% carbohydrate, 20% fat (8.2g), 12% protein

Results

SAFETY AND TOLERABILITY

- This study enrolled 36 subjects, of which 33 completed the study.
  - All 3 discontinuations were for personal reasons.
- There were no deaths or other serious adverse events (SAEs).
- The most frequently reported AEs were:
  - ATV alone: diarrhea and pruritis (8.3% each)
  - ddI-EC+ATV and ATV+TDF: diarrhea (5.9%)
  - TDF alone: pharyngitis (12.1%)
- Most laboratory abnormalities were Grade 1 (73.8%) or Grade 2 (19.4%).
- There were two Grade 3 elevations in total bilirubin (ATV alone) with normal hepatic transaminases, and one Grade 3 elevation in amylase (TDF alone) with normal lipase. These abnormalities were transient and did not require any intervention.

Table 1: Baseline Demographic Characteristics

Mean Age, years (Range)	30 (20-44)
Gender, N (%)	
Male	34 (94.4)
Female	2 (5.6)
Race, N (%)	
Black	29 (80.6)
White	6 (16.7)
Asian/Pacific Islander	1 (2.8)
Mean Weight, kg (Range)	78.9 (63.5-95.0)
Mean Height, cm (Range)	177.1 (157.0-196.0)
Mean Body Mass Index, kg/m^2 (Range)	25.2 (20.1-29.8)

PHARMACOKINETICS OF ATAZANAVIR

Figure 2: Mean (SD) Plasma Concentration-Time Profiles for ATV Following 400 mg ATV Alone in the Fed State (Day 7), 500 mg ddI-EC + 400 mg ATV in the Fed State (Day 8), 400 mg ATV + 300 mg TDF in the Fed State (Day 15), and 250 mg ddI-EC + 400 mg ATV + 300 mg TDF in the Fed State (Day 16)

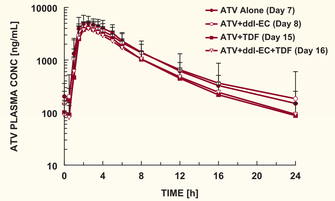


Table 2: Geometric Means and Point Estimates (90% CI) for AUC, C_{max}, and C_{min} for ATV (N=34)

Parameter (units)	Treatment	Adjusted Geometric Mean	Ratio of Adjusted Geometric Means Point Estimate (90% CI)
AUC (ng.h/mL)	400 mg ATV + Meal (Reference)	29195.5	-
	500 mg ddI-EC + 400 mg ATV + Meal	26037.4	0.89 (0.83, 0.96)
	400 mg ATV + 300 mg TDF + Meal	21865.5	0.75 (0.70, 0.81)
	250 mg ddI-EC + 400 mg ATV + 300 mg TDF + Meal	21555.4	0.74 (0.69, 0.79)
C_{max} (ng/mL)	400 mg ATV + Meal (Reference)	5784.7	-
	500 mg ddI-EC + 400 mg ATV + Meal	5061.4	0.88 (0.81, 0.95)
	400 mg ATV + 300 mg TDF + Meal	4578.8	0.79 (0.73, 0.86)
	250 mg ddI-EC + 400 mg ATV + 300 mg TDF + Meal	4391.2	0.76 (0.70, 0.82)
C_{min} (ng/mL)	400 mg ATV + Meal (Reference)	117.6	-
	500 mg ddI-EC + 400 mg ATV + Meal	96.6	0.82 (0.72, 0.94)
	400 mg ATV + 300 mg TDF + Meal	69.9	0.60 (0.52, 0.68)
	250 mg ddI-EC + 400 mg ATV + 300 mg TDF + Meal	71.9	0.61 (0.53, 0.70)

PHARMACOKINETICS OF DIDANOSINE

Figure 3: Mean (SD) Plasma Concentration-Time Profiles for ddI Following 400 mg ddI-EC Alone in the Fasted State (Day 1), 500 mg ddI-EC + 400 mg ATV in the Fed State (Day 8), and 250 mg ddI-EC + 400 mg ATV + 300 mg TDF in the Fed State (Day 16)

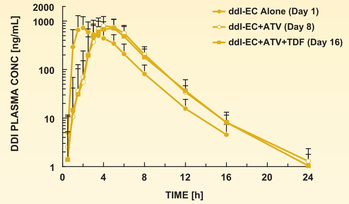


Table 3: Geometric Means and Point Estimates (90% CI) for AUC, C_{max}, and C_{min} for ddI (N=34).

Parameter (units)	Treatment	Adjusted Geometric Mean	Ratio of Adjusted Geometric Means Point Estimate (90% CI)
AUC (ng.h/mL)	400 mg ddI-EC Fasted (Reference)	2758.2	-
	500 mg ddI-EC + 400 mg ATV + Meal	3463.2	1.26 (1.15, 1.37)
	250 mg ddI-EC + 400 mg ATV + 300 mg TDF + Meal	3170.2	1.15 (1.06, 1.25)
C_{max} (ng/mL)	400 mg ddI-EC Fasted (Reference)	922.9	-
	500 mg ddI-EC + 400 mg ATV + Meal	992.0	1.08 (0.95, 1.22)
	250 mg ddI-EC + 400 mg ATV + 300 mg TDF + Meal	874.6	0.95 (0.84, 1.07)
C_{min} (ng/mL)	400 mg ddI-EC Fasted (Reference)	0.461	-
	500 mg ddI-EC + 400 mg ATV + Meal	1.004	2.18 (1.74, 2.73)
	250 mg ddI-EC + 400 mg ATV + 300 mg TDF + Meal	0.872	1.89 (1.51, 2.37)

PHARMACOKINETICS OF TENOFOVIR

Figure 4: Mean (SD) Plasma Concentration-Time Profiles for TDF Following 300 mg TDF Alone in the Fed State (Day 30), 400 mg ATV + 300 mg TDF in the Fed State (Day 15), and 250 mg ddI-EC + 400 mg ATV + 300 mg TDF in the Fed State (Day 16)

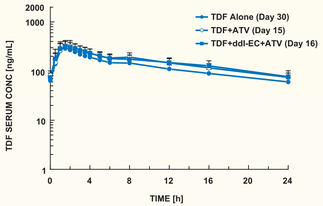


Table 4: Geometric Means and Point Estimates (90% CI) for AUC, C_{max}, and C_{min} for TDF (N=33)

Parameter (units)	Treatment	Adjusted Geometric Mean	Ratio of Adjusted Geometric Means Point Estimate (90% CI)
AUC (ng.h/mL)	300 mg TDF + Meal (Reference)	2950.8	-
	400 mg ATV + 300 mg TDF + Meal	3664.6	1.24 (1.21, 1.28)
	250 mg ddI-EC + 400 mg ATV + 300 mg TDF + Meal	3680.7	1.25 (1.22, 1.28)
C_{max} (ng/mL)	300 mg TDF + Meal (Reference)	313.8	-
	400 mg ATV + 300 mg TDF + Meal	358.0	1.14 (1.08, 1.20)
	250 mg ddI-EC + 400 mg ATV + 300 mg TDF + Meal	352.2	1.12 (1.06, 1.19)
C_{min} (ng/mL)	300 mg TDF + Meal (Reference)	58.8	-
	400 mg ATV + 300 mg TDF + Meal	71.9	1.22 (1.15, 1.30)
	250 mg ddI-EC + 400 mg ATV + 300 mg TDF + Meal	73.4	1.25 (1.18, 1.33)

Discussion/Conclusions

PHARMACOKINETICS OF ATAZANAVIR

- Atazanavir exposures are decreased compared to 400 mg ATV given alone in the fed state, when 400 mg ATV is coadministered with 300 mg TDF and food or with 250 mg ddI-EC, 300 mg TDF, and food. PK data from CROI 2003 (PUZZLE 2 [ANSR 107]) suggest that increasing ATV exposure may compensate the effect seen in this study. Furthermore, interim data from IAS 2003 (AI424045) suggest that ATV 300 mg/R 100 mg was successful clinically with a backbone that included TDF and the safety profile for ATV 300 mg/R 100 mg in treatment-experienced patients was comparable to ATV 400 mg-treated patients in other clinical trials.
- Atazanavir exposures (AUC and C_{max}) are equivalent to 400 mg ATV given alone in the fed state, when 400 mg ATV is coadministered with 500 mg ddI-EC and food.

PHARMACOKINETICS OF DIDANOSINE

- Didanosine exposures (AUC and C_{max}) are equivalent to 400 mg ddI-EC given alone in the fasted state, when 250 mg ddI-EC is coadministered with 400 mg ATV and 300 mg TDF in the fed state.
- Didanosine AUC was increased and C_{max} was equivalent to 400 mg ddI-EC given alone in the fasted state, when 500 mg ddI-EC was coadministered with 400 mg ATV and food. The differences in AUC were probably related to the use of non-equimolar doses of ddI-EC. These results suggest that the PK of 400 mg ddI-EC with ATV and food needs to be explored.

PHARMACOKINETICS OF TENOFOVIR

- Tenofovir exposures are increased compared to 300 mg TDF given alone in the fed state, when 300 mg TDF is coadministered with 400 mg ATV and food or with 250 mg ddI-EC, 400 mg ATV, and food. The increase in tenofovir exposure is not considered to be clinically important. The mechanism for the two-way interaction between ATV and TDF is unknown at the present time.

SAFETY AND TOLERABILITY

- Didanosine-EC, ATV, and TDF were generally safe and well-tolerated when administered alone or in combination in normal healthy subjects.

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