

Absence of Pharmacokinetic (PK) Drug Interaction Between Amlaviroc[†] (APL, 873140) and Tenofovir Disoproxil Fumarate (TDF)

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Abstract

Background: Amlaviroc (APL; 873140), an entry inhibitor targeting CCR5, is in clinical development as an HIV entry inhibitor. As previous clinical studies with tenofovir disoproxil fumarate (TDF) have demonstrated unpredictable PK interactions with other antiretroviral agents, this study assessed the potential PK drug interaction between APL and TDF in healthy subjects.

Methods: 28 subjects were enrolled into this single center, 3-period, open label study. Successive treatments were: APL x 7 days, followed by a 5-7 day washout; then TDF x 7 days; and then APL + TDF x 7 days. Doses were APL 600mg BID and TDF 300mg QD; all taken with food. Serial plasma PK samples were obtained on Day 7 of each Period and assayed for APL and tenofovir by LC/MS/MS. PK parameters were estimated by non-compartmental methods and treatments were compared by ANOVA. Safety was assessed throughout the study.

Results: Co-administration of TDF had no effect on APL AUC or C_{max}, but moderately increased C_t. APL had no effect on TDF PK.

APL PK Parameter	Geometric Mean [95% CI], n=25		Ratio of GLS Mean [90% CI]
	APL Alone	APL +TDF	
AUC(0-τ), h.ng/mL	2227 [1826, 2715]	2595 [2085, 3229]	1.2 [1.1, 1.3]
C _{max} , ng/mL	1069 [851, 1342]	1045 [807, 1353]	1.0 [0.8, 1.2]
C _t , ng/mL	8.9 [7.2, 11.1]	15.7 [12.5, 19.6]	1.8 [1.5, 2.0]

The most common drug-related adverse events were gastrointestinal; most were mild to moderate in severity. 1 subject experienced a serious event, diverticulitis, at study follow-up. No grade 3/4 laboratory abnormalities were reported. 3 subjects withdrew prior to study completion for reasons unrelated to safety.

Conclusion: No clinically relevant changes in AUC, C_{max} or C_t were observed between APL and TDF, suggesting that no dosage adjustments of APL or TDF are necessary when they are co-administered.

Introduction

Amlaviroc (APL; 873140), a novel chemokine receptor 5 (CCR5) antagonist with a distinct binding profile, is in Phase 2b/3 clinical development as an entry inhibitor for the treatment of HIV infection. APL is metabolized by cytochrome P450 (CYP450) 3A4 and 2C19 in vitro. Clinical drug-drug interaction studies have shown that co-administration of APL with the CYP450 enzyme inducer, efavirenz, resulted in a 60% reduction in APL AUC and C_{max} values¹. In contrast, co-administration of APL with the CYP450 inhibitors, lopinavir/ritonavir and atazanavir/ritonavir, was shown to increase the APL daily AUC by approximately 7.5-fold^{2,3}.

Tenofovir disoproxil fumarate (TDF) is an ester prodrug of tenofovir, a nucleotide analog that inhibits HIV reverse transcriptase. Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion. Although neither TDF nor tenofovir are substrates/inhibitors of CYP450 enzymes, tenofovir has been shown to alter the PK of several antiretroviral drugs including atazanavir, atazanavir/ritonavir⁴. The mechanisms for the interactions are unknown. This study explored the potential for a drug-drug interaction between APL and TDF.

Objectives

Primary

- To compare steady-state APL PK with and without TDF
- To assess the safety and tolerability of repeat dose co-administration of APL with and without TDF

Secondary

- To compare steady-state tenofovir PK with and without APL

Methods

This was a Phase 1, single center, open label, non-randomized study in 28 healthy male and female adult subjects (≥18 and ≤55 years of age). The study was divided into the following 3 treatment periods:

Period 1 Treatment A	Period 2 Treatment B	Period 3 Treatment C
APL 600mg q12h x 7 days	TDF 300mg q24h x 7 days	APL 600mg q12h + TDF 300mg q24h x 7 days

Note: There was a 5-7 days washout between Period 1 and Period 2.

All APL and TDF doses were administered immediately after a moderate fat meal.

Pharmacokinetic Assessments

Serial blood samples were obtained at the following times (post-dose): Treatment A (Day 7): 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12h. Treatments B & C (Day 7): 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24h.

Plasma samples were analyzed for APL and tenofovir by validated LC/MS/MS methods. Plasma PK parameters for APL and tenofovir were estimated by standard non-compartmental methods using WinNonlin Professional v4.1 (Pharsight; Mountain View, CA).

Safety Assessments

Vital sign measurements, clinical laboratory tests and ECGs were conducted at various times and adverse events (AE) and serious adverse events (SAE) were monitored throughout the study.

Statistical Comparisons

Comparisons of interest were assessed by ANOVA using SAS (Cary, NC) PROC MIXED to construct the ratio of treatments of test versus reference.

Results

Table 1. Summary of Demographic Data

N (Started/Completed)	28/25
Age (yrs)*	40.5 (21-55)
Sex (M/F)	18/10
Race/Ethnicity	All Hispanic
Weight (kg)*	75.5 (55-95)
BMI (kg/m ²)*	27.3 (22.6-29.9)

*Data reported as median (range)

Pharmacokinetics

A total of 25 subjects provided PK parameter estimates for all 3 treatment periods and were included in the PK population.

Repeated co-administration of TDF did not affect APL AUC(0-τ) and C_{max}, but moderately increased APL C_t by 75% (Table 2; Figures 1 and 2).

Repeated co-administration of APL did not affect tenofovir AUC(0-τ) and C_t, but slightly decreased tenofovir C_{max} by 26% (Table 3)

Table 2. Amlaviroc PK Parameters and Treatment Comparisons

APL PK Parameter	Geometric Mean [95% CI], n=25		C/A Ratio of GLS Means [90% CI]
	Treatment A	Treatment C	
AUC(0-τ), h.ng/mL	2227 [1826, 2715]	2595 [2085, 3229]	1.17 [1.07, 1.27]
C _{max} , ng/mL	1069 [851, 1342]	1045 [807, 1353]	0.98 [0.82, 1.17]
C _t , ng/mL	8.9 [7.2, 11.1]	15.7 [12.5, 19.6]	1.75 [1.53, 2.00]

Note: Treatment A = APL 600mg q12h for 7 days.
Treatment C = APL 600mg q12h + TDF 300mg q24h for 7 days.

Figure 1. Median Amlaviroc Concentration-Time Profiles

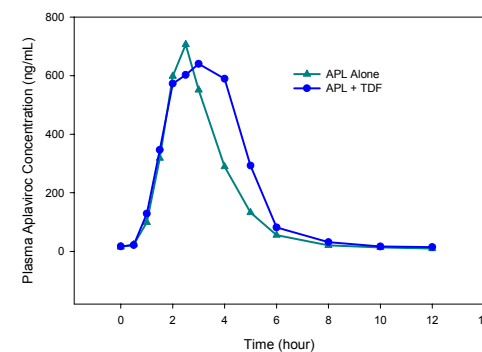


Figure 2. Amlaviroc Individual PK Parameter Comparison

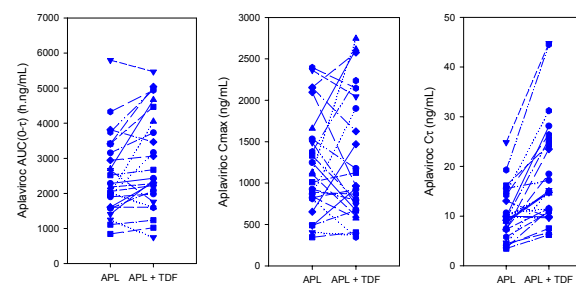


Table 3. Tenofovir PK Parameters and Treatment Comparisons

Tenofovir PK Parameter	Geometric Mean [95% CI], n=25		C/B Ratio of GLS Mean [90% CI]
	Treatment B	Treatment C	
AUC(0-τ), h.ng/mL	3062 [2693, 3482]	3102 [2754, 3494]	1.01 [0.95, 1.08]
C _{max} , ng/mL	373 [321, 433]	276 [244, 312]	0.74 [0.66, 0.83]
C _t , ng/mL	57.3 [50.9, 64.5]	54.9 [48.8, 61.7]	0.96 [0.90, 1.02]

Note: Treatment B = TDF 300mg q24h for 7 days.
Treatment C = APL 600mg q12h + TDF 300mg q24h for 7 days.

Safety & Adverse Events

Three subjects withdrew prior to study completion for reasons unrelated to safety.

Gastrointestinal (GI) related events were the most frequent AEs experienced by subjects during the study: 25 (25/28, 89%) subjects during Treatment A, 10 (10/27, 37%) subjects during Treatment B, and 19 (19/27, 70%) during Treatment C.

No subjects had abnormal ECG readings or vital sign measurements that the investigator considered an adverse event. No subject had a QTc >=500 msec or a change from baseline > 60 msec.

All AEs were mild to moderate in intensity and the majority were considered by the investigator to be drug-related.

There were no reports of deaths, and no subject prematurely discontinued from the study due to an AE. One subject experienced a SAE (diverticulitis), during the follow-up period, which required hospitalization. The diverticulitis stabilized with IV/oral antibiotics.

Table 4. Summary of Most Frequently Reported Drug-related Clinical Adverse Events (>10% subjects)

	Number (%) of Subjects		
	Treatment A N=28	Treatment B N=27	Treatment C N=27
Any AE	25 (89)	15 (56)	21 (78)
Gastrointestinal	25 (89)	10 (37)	19 (70)
Diarrhea	23 (82)	3 (11)	12 (44)
Nausea	1 (4)	3 (11)	11 (41)
Pruritis ani	8 (29)	0	0
Abdominal pain	0	4 (15)	5 (19)
Nervous system	5 (18)	6 (22)	13 (48)
Headache	4 (14)	4 (15)	6 (22)
Dizziness	1 (4)	3 (11)	6 (22)
Skin & subcutaneous tissue	0	5 (19)	0
Dry skin	0	4 (15)	0
Vascular disorders	0	0	4 (15)
Hot flush	0	0	4 (15)

Note:
Treatment A = APL 600mg q12h for 7 days.
Treatment B = TDF 300mg q24h for 7 days.
Treatment C = APL 600mg q12h + TDF 300mg q24h for 7 days.

Discussion

- No PK drug-drug interaction was expected or observed between APL and TDF since these 2 compounds do not share a common route of disposition.
- Co-administration of TDF 300mg q24h with APL 600mg q12h did not change APL AUC(0-τ) and C_{max}.
- Co-administration of TDF 300mg q24h with APL 600mg q12h increased APL C_t by about 75%, however, such an effect is unlikely to have any clinical significance for APL.
- Co-administration of APL 600mg q12h resulted in no change in tenofovir AUC(0-τ) and C_t and a slight decrease (approximately 26%) in tenofovir C_{max}. Such effect on tenofovir C_{max} is unlikely of any clinical significance.

Conclusion

- There is no clinically significant drug-drug interaction between amlaviroc and tenofovir, suggesting that no dosage adjustments of amlaviroc or tenofovir disoproxil fumarate are necessary when they are co-administered.
- The combination of amlaviroc and tenofovir disoproxil fumarate was generally well tolerated.

References

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- Viread Prescription Information

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[†]USAN approved only