

A Randomized, Placebo-controlled Trial of Amdoxovir vs Placebo with Enfuvirtide plus Optimized Background Therapy for HIV-infected Subjects Failing Current Therapy (AACTG 5118)

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Abstract

Background. Cross resistance limits the ability to construct effective antiretroviral regimens for persons failing current therapies. AACTG 5118 compared the use of amdoxovir (DAPD), a novel nucleoside analog to placebo in combination with enfuvirtide (ENF) plus optimized background therapy (OBT) in ENF-naïve subjects who had failed ≥ antiretroviral (ARV) regimens including at least 2 NRTIs, 2 PIs and 1 NNRTI.

Methods. This randomized, prospective, double-blind, placebo-controlled study assessed the antiretroviral activity and safety of DAPD (300mg PO bid) vs. placebo with ENF (90mg SQ bid) plus OBT (3-5 agents selected based on genotypic and phenotypic testing at screening) in subjects described above. The primary endpoints were comparison between arms of time-averaged area under the curve minus baseline (AAUCMB) in plasma HIV-1 RNA copy/mL at 24 wk and time to first serious (DAIDS ≥2 Grade 3 or 4) adverse event (AE). Planned sample size was 50 subjects; however an unplanned interim review was convened when the long term development plans for DAPD became uncertain and accrual was slow. The review panel found no safety concerns, but determined the study was unlikely to be able to show a difference between study arms and recommended closing enrollment. Subjects on study were unblinded and allowed to continue through 48 wk; 24 wk data on the 18 subjects (9 per arm) enrolled are reported here.

Results. Median baseline CD4+ cell count was 36 cells/mm³ (range, 11-537); HIV-1 RNA was 4.8 log₁₀ copies/mL (range, 3.5-6.3). Baseline samples showed a median of 6 NRTI mutations and 8 PI mutations; NNRTI resistance was present in samples from 13/18 subjects. 4 subjects discontinued therapy prior to wk 24, 3 for poor virologic response (2 on DAPD, 1 on placebo), 1 subject on placebo discontinued for ENF injection site reactions. Two subjects (one per arm) briefly interrupted therapy for decreased creatinine clearance. By intention-to-treat analysis, the AAUCMB was -1.1 log₁₀ copies/mL (95%CI -0.19 -2.01) in the DAPD arm and -0.8 log₁₀ copies/mL (95%CI -0.151, 4.5) in the placebo arm (p=0.69). Mean CD4+ increase was 70 cells/mm³ (95%CI=35, 105) in the DAPD arm and 54 (95%CI=14, 94) in the placebo arm (p=0.45). Time to first serious AE did not differ between arms. ENF injection site reactions were the most common AE (6 subjects). Mild decreases in creatinine clearance were observed with a similar frequency between arms, and no subject developed an increase in lens opacity score. HIV associated morbidities were frequent (8/18 subjects, and 2 AIDS-related deaths). **Conclusions.** In this pilot study, the addition of DAPD to ENF with optimized background therapy in advanced and highly resistant subjects appeared safe, but did not add statistically significant antiretroviral activity. HIV-associated morbidity is frequent in this resistant population. Further studies of DAPD in this setting are warranted.

Introduction

Cross resistance limits the ability to construct effective antiretroviral regimens in persons failing current therapies.
•Amdoxovir (DAPD) is a nucleoside reverse transcriptase inhibitor (NRTI) active in vitro on AZT and 3TC resistant viruses, as well as viruses containing the 69 insertion. In vitro resistance to DAPD is associated with the K65R and L74V mutations, as well as the Q151M complex.
•AACTG 5118 was a randomized, placebo-controlled trial of DAPD (300mg orally twice a day) with enfuvirtide (ENF) (90mg SQ twice a day) plus optimized background (OBT) therapy in subjects who have failed at least 2 drug regimens containing at least 2 NRTIs, 2 protease inhibitors (PI), and 1 n-NNRTI (NNRTI).

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Study Design

Objectives:
•Compare the antiviral activity of DAPD in combination with ENF plus OBT to that of ENF plus OBT alone
•Explore the safety and tolerability of DAPD versus placebo arms

Endpoints:
•The time-averaged area under the curve minus baseline (AAUCMB) in plasma HIV-1 RNA copy/mL from baseline to week 24
•Time to first DAIDS Grade ≥3 or 4 sign, symptom, or laboratory abnormality

Drug Regimens:
•DAPD arm: DAPD (300mg by mouth twice a day) plus ENF (90mg SQ twice a day) plus OBT (3-5 approved antiretroviral agents, selected based on the genotype at screening).
•Placebo arm: DAPD placebo (twice a day) plus ENF (90mg SQ twice a day) plus OBT
OB was to remain stable for the first 24 weeks of study.
•Study drugs were discontinued after week 24 for a confirmed loss of response (HIV RNA less than 0.5 log₁₀ copies/mL from baseline AND a CD4+ cell count less than 30 cells above baseline).

Eligible Subjects:
•HIV RNA >5000 copies/mL on stable ART for 8 weeks
•Failed at least two regimens containing 3 or more drugs, including 2 NRTIs, 1 NNRTI and 2 PIs, and on ART for a total of at least 24 months
•No prior DAPD or ENF therapy

Sample Size and Follow-up:
•Initially planned to be 50 subjects, 25 per arm
•Interim review precipitated by slow accrual and uncertain plans for DAPD development halted enrollment at 18 subjects (9 per arm) when panel found study unlikely to be able to determine a difference between study arms
•Of the 18 subjects enrolled, 4 did not complete 24 weeks of therapy (3 stopped for poor response, 2 in DAPD arm and 1 in placebo, and 1 stopped for ENF injection site reactions).
•Median study follow-up was 48 weeks in DAPD arm and 49 weeks in placebo arm.

Statistical Methods:
•AAUCMB to week 24 and change in CD4+ cells from baseline were compared (intent-to-treat) across arms using a Wilcoxon rank test
•Time to first Grade ≥3 or 4 sign or symptom was compared using a log rank test
•All tests performed are non-parametric and P-values are two-sided.

Table 1: Baseline demographics (including a summary of baseline resistance)

		Treatment Arm		P-value	
		All subjects	DAPD (n=9)		Placebo (n=9)
Sex	Male	15 (83%)	7 (78%)	1 (89%)	1.00
	Female	3 (17%)	2 (22%)	1 (11%)	
Age	Mean (SD)	43.8 (8.9)	41.7 (10.5)	45.9 (6.8)	0.31
	Race/ethnicity	White Non-Hispanic	11 (61%)	4 (44%)	7 (78%)
	Black Non-Hispanic	2 (11%)	1 (11%)	1 (11%)	
	Hispanic (Regardless of Race)	5 (28%)	4 (44%)	1 (11%)	
IV drug use	Never	18 (100%)	9 (100%)	9 (100%)	
	Mean (SD)	5.0 (0.7)	4.7 (0.7)	5.2 (0.7)	0.17
HIV-1 RNA (log ₁₀ copies/mL)	Median (Q1, Q3)	4.8 (4.5, 5.5)	4.7 (4.3, 5.4)	5.3 (4.7, 5.7)	
	Min, Max	3.5, 6.3	3.5, 5.8	4.3, 6.3	
CD4+ (cells/mm ³)	Median (Q1, Q3)	36 (18, 123)	72 (15, 163)	25 (18, 79)	
	Min, Max	11, 537	13, 537	11, 199	
# of ARTI mutations*	Median (Q1, Q3)	6 (4, 7)	6 (1, 8)	7 (5, 7)	0.59
	Min, Max	1, 9	1, 9	3, 8	
# of nnRTI mutations	Median (Q1, Q3)	1 (0, 2)	1 (0, 2)	1 (1, 2)	0.75
	Min, Max	0, 3	0, 2	0, 3	
# of PI mutations	Median (Q1, Q3)	8 (7, 10)	7 (5, 10)	9 (8, 10)	0.35
	Min, Max	1, 12	1, 12	7, 11	
Optimized background (OB) GSS**	0.0	7 (39%)	3 (33%)	4 (44%)	0.55
	0.5	4 (22%)	2 (22%)	2 (22%)	
	1.0	2 (11%)	1 (11%)	1 (11%)	
	1.5	2 (11%)	0 (0%)	2 (22%)	
	2.0	1 (6%)	1 (11%)	0 (0%)	
	3.0	2 (11%)	2 (22%)	0 (0%)	
OB GSS (<=1)	<1	11 (61%)	5 (56%)	6 (67%)	1.00
	1+	7 (39%)	4 (44%)	3 (33%)	

* No subject had a K65R or Q151M at baseline (exclusionary); 6 subjects had a L74V, 4 in the DAPD arm and 2 in the placebo arm
** A genotypic sensitivity score (GSS) was calculated for the OB regimen using the baseline TruGene genotype (no resistance =1, possible resistance =0.5, resistant=0)

Table 5. Virologic response by Genotypic Sensitivity Score of Optimized Background (all subjects)

	Mean (SD)	Optimized background regimen Genotypic sensitivity score		P-value
		<1 (n=11)	1+ (n=7)	
Week 24 AU/CMB (log ₁₀ copies/mL)	-0.6 (0.5)	-0.5 (-0.9, -0.1)	-2.1 (-3.1, -0.1)	0.11
		Median (Q1, Q3)		
		Min, Max		

Subjects with a GSS of OB ≥1 tended to have a better virologic response

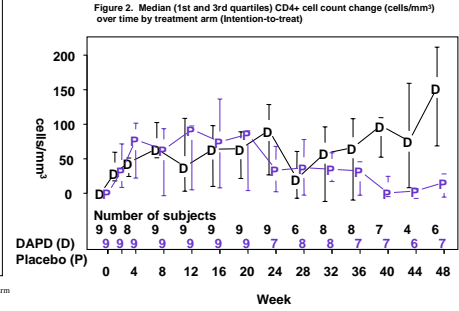
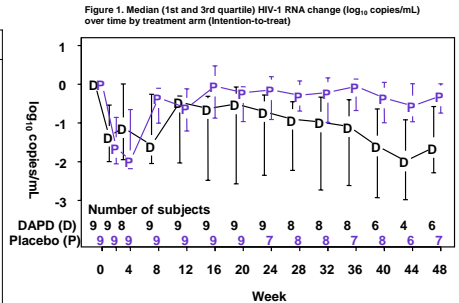


Table 2. Virologic and Immunologic Responses at Week 24

	DAPD n=9	Placebo n=9	p value
HIV-1 RNA AAUCMB (log ₁₀ copies/mL)	-1.1	-0.8	p=0.69
HIV-1 RNA change from baseline (log ₁₀ copies/mL)	-1.1	-0.8	p=0.35
HIV-1 RNA < 200 copies/mL	3 subjects	1 subject	p=0.58
Change in median CD4+ cells (cells/mm ³)	+70	+54	p=0.45

There was no significant difference in HIV RNA decline or CD4+ cell increase at 24 weeks between arms

Table 3. Adverse events*

DAIDS Grade 3 or 4 Event	DAPD N=9	Placebo N=9
ENF injection site reaction	3	2
Fever	0	3
Bilirubin	1	3
Fasting triglycerides	1	1
Lipase	1	0
Other adverse events		
Creatinine clearance 50-80 mL/min	3	4
Increase in lens opacity score (LOCS III)	0	0

* There was no difference in time to first Grade 3 or 4 adverse event between arms (p=0.9)

Table 4. Clinical Events

Number of subjects with a serious clinical event	DAPD N=9	Placebo N=9
Pneumocystis pneumonia	2	1
CMV retinitis	1*	1 (later died with CMV encephalitis)
Mycobacterium avium complex	1*	
Squamous cell carcinoma	1 (anus)*	1 (skin)
Bacterial pneumonia	1 (died)**	1
HSV encephalitis	1	

* These three events occurred in one subject ** This subject also had PCP earlier in study

Conclusion

The addition of DAPD to ENF plus OBT did not confer a statistically significantly greater antiviral activity at 24 weeks compared to placebo plus ENF plus OBT in this small study of subjects with highly resistant virus. Both arms had an approximately one log₁₀ drop in HIV RNA and a doubling of CD4+ cells/mm³ at 24 weeks.

The addition of DAPD to ENF plus OBT appears to be safe, with no difference in time to Grade 3 or 4 adverse event between treatment arms. Local ENF injection site reactions (induration, erythema) were the most common adverse event in this study. No subject developed ocular lens opacities.

HIV-associated morbidities occurred in 44% of subjects in this treatment experienced population followed for 48 weeks. Six AIDS-defining illnesses and 2 AIDS-related deaths occurred.

Given the morbidity that may be associated with drug-resistant virus in the setting of advanced HIV disease, further studies of new agents with potential activity against resistant strains, such as DAPD, are needed.