

A Phase I/II Randomized, Double-Blind, Placebo-Controlled Pilot Study of β -D-2,6-Diaminopurine Dioxolane (DAPD) Versus DAPD Plus Mycophenolate Mofetil (MMF) in Treatment-Experienced Subjects (ACTG 5165)

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Abstract

Background: DAPD is a guanosine nucleoside analog RT inhibitor (NRTI) with *in vitro* activity against wild type and most NRTI-resistant HIV-1. MMF, an inhibitor of *de novo* guanosine nucleotide synthesis, increases DAPD potency against NRTI-resistant HIV-1 *in vitro*. ACTG 5165 evaluated the safety, tolerability and antiviral activity of DAPD +/- MMF in heavily pre-treated subjects.

Methods: At entry, subjects added DAPD 500 mg BID & MMF placebo BID (n=20), or DAPD 500 mg BID & MMF 500 mg BID (n=20) to their failing regimens, which excluded abacavir. Primary endpoints at week 2 were analyzed by intent-to-treat, using rank-based tests. The geometric mean of the pre-entry + entry HIV-1 RNA (VL) was compared with week 2 VL. Subjects responding to DAPD +/- MMF (VL decline from baseline >0.5 log₁₀) at week 2 optimized antiretrovirals and continued study therapy for up to 96 weeks.

Results: 40 adults (male, 90%; white, 55%; 40-49 yrs, 70%) with VL \geq 2000 copies/mL (median 4.5 log₁₀ copies/mL) and CD4+ cell count \geq 250 cells/mm³ (median 184 cells/mm³) enrolled. At entry, subjects had a median of 6 (range 1-8) NRTI mutations (IAS-USA). These and other characteristics between the arms were balanced. A significant decline in VL (median -0.29 log₁₀; p < 0.0001) was seen in the pooled treatment arms at week 2. There was no significant difference between the DAPD alone (median -0.37 log₁₀) and DAPD & MMF (median -0.23 log₁₀) arms. 10 of 40 subjects had a virologic response at week 2; 4 of 10 responses persisted after week 2. As expected, 4 subjects with K65R and/or Q151M complex did not respond. Among the remaining subjects, virologic response was associated with the baseline genotype having \leq 5 NRTI mutations (p = 0.12) and < 4 TAMs without E44D or V118I (p = 0.08). There were two Grade 3 events by week 2 not clearly related to study treatment. 31 subjects continued on study after week 2; 5 beyond week 24. Potential drug-related toxicities such as CD4+ cell decline < 50% of baseline, significant lens changes, or \geq Grade 2 renal or glucose toxicities were not observed.

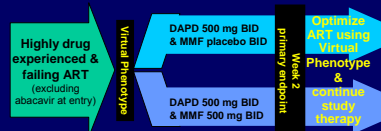
Background

- The use of fully active antiretrovirals is advised after failure of therapy, but few agents with full activity are available to heavily experienced patients
- DAPD is a guanosine nucleoside analog RT inhibitor (NRTI) with *in vitro* activity against wild type and most NRTI-resistant HIV-1
- Mycophenolate mofetil (MMF), an inhibitor of *de novo* guanosine nucleotide synthesis, can selectively decrease dGTP pools in lymphocytes
- MMF increases the potency of NRTIs, including DAPD, against NRTI-resistant HIV-1 *in vitro*

Objectives

- Determine the antiviral activity of DAPD in heavily pre-treated subjects
- Assess the ability of MMF to increase DAPD activity
- Primary study endpoint at **week 2**
 - Change in HIV-1 RNA from baseline
 - Safety and tolerability

Study design and analysis



- Primary endpoints at week 2 were analyzed by intent-to-treat, using rank-based tests
- The geometric mean of the pre-entry + entry HIV-1 RNA (VL) was compared with week 2 VL
- Subjects responding to DAPD +/- MMF with HIV-1 RNA decline from baseline \geq 0.5 log₁₀ at week 2 could optimize background antiretrovirals and continue study therapy for up to 96 weeks
- Follow-up and analysis of secondary endpoints beyond week 2 has yet to be completed

Study Cohort

- 20 adults enrolled in each arm:
 - Enrolled 2003-2005
 - closed prior to target of 28/arm
 - male, 90%; white, 55%; age 40-49 yrs, 70%
- HIV-1 RNA \geq 2000 copies/mL
 - median 4.5 log₁₀ copies/mL
- CD4+ cell count \geq 50 cells/mm³
 - median 184 cells/mm³
 - 53% of subjects enrolled with \leq 200 cells/mm³
- These and other baseline characteristics between the arms were well balanced

•NRTI Mutations at entry (IAS-USA): Median of 6

No. of mutations	Frequency
1	2 (5%)
3	4 (10%)
4	5 (12.5%)
5	6 (15%)
6	10 (25%)
7	7 (17.5%)
8	6 (15%)

Virologic Response

Significant decline from baseline in VL in the pooled treatment arms at week 2

	Pooled arms	DAPD	DAPD & MMF
Mean VL change	-0.29 log ₁₀	-0.35 log ₁₀	-0.24 log ₁₀
Median VL change	-0.26 log ₁₀	-0.37 log ₁₀	-0.23 log ₁₀
p value from baseline	<0.0001	0.012	0.001

No significant difference between the DAPD alone and DAPD & MMF arms (p = 0.59)

Virologic Response

correlation with baseline genotype

- 4 subjects with K65R and/or Q151M complex did not respond to DAPD or DAPD & MMF
- Among remaining subjects, trends toward better response were associated with
 - \leq 5 NRTI mutations (p = 0.12)
 - < 4 TAMs without E44D or V118I (p = 0.08)

Toxicities: few observed

- Two Grade 3 events (elevated lipase, flatus) were reported by week 2, but not clearly related to study treatment.
- 31 subjects continued on study after week 2; five subjects beyond week 24.
- 3 subjects discontinued study therapy after Grade 3 events at weeks 4, 16, and after week 16. Two of these Grade 3 events appear unlikely to be related to study treatment.
- Potential drug-related toxicities such as CD4+ decline < 50% of baseline, or \geq Grade 2 renal toxicities were not observed
- Careful, validated eye exams (LOCS III) were performed every 3 months; no ophthalmologic toxicities were observed
- One Grade 2 elevation of glucose reported as possibly/probably related to study treatment was observed
- At week 2, CD4+ increased in 19 subjects, decreased in 21. Median change in CD4+ at week 2 was -4 cells/mm³

Responses beyond week 2

- 10 of 40 subjects had a decline of VL >0.5 log₁₀ or more at week 2
 - 7 of 20 in the DAPD alone arm
 - 3 of 20 in the DAPD&MMF arm
- After optimization of background therapy, 4 of 10 responses persisted beyond week 2, and 3 of 10 persisted beyond week 24
- At time of primary analysis:
 - 7 subjects on study treatment
 - Of these 5 are beyond week 48
- 9 subjects on follow-up but off DAPD +/- MMF
- 24 subjects off study (only 2 prematurely)

Conclusions

- DAPD alone and in combination with MMF was safe and well tolerated
- DAPD monotherapy had modest antiretroviral activity (-0.35 log₁₀) in heavily pre-treated subjects with extensive NRTI resistance
- In contrast to synergy observed *in vitro*, DAPD activity over two weeks was not increased by MMF 500 mg BID in this study
- Assays of DAPD and mycophenolate exposure based on pharmacokinetic studies are underway to investigate this discrepancy.

Participating Sites

University of Hawaii at Manoa; University of Texas Southwestern Medical Center at Dallas; University of Pennsylvania; Washington University; University of Washington; University of California, Davis; University of Colorado Health Sciences Center, Denver; Case Western Reserve University; University of Minnesota; Stanford University; University of Pittsburgh; Beth Israel Medical Center; University of Miami; Columbia University; Johns Hopkins University; University of Texas, Galveston

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