

Randomized Study of Twice-Daily Lopinavir/ritonavir (LPV/r) or Fosamprenavir (FPV) + Ritonavir (FPV + r) versus LPV/r + FPV (with Tenofovir DF [TDF] and Nucleosides [NRTIs]) as Rescue Therapy

AC Collier^{1*}, C Tierney², GF Downey², S Eshleman³, A Kashuba⁴, K Klingman⁵, E Vergis⁶, GE Pakes⁷, J Rooney⁸, A Rinehart⁹, J Mellors⁶ for the Adult AIDS Clinical Trials Group Protocol 5143 Team

¹Univ. of Washington, Seattle, WA; ²Harvard School of Public Health, Boston, MA; ³Johns Hopkins Univ, Baltimore, MD; ⁴Univ. of North Carolina, Chapel Hill, NC; ⁵National Institutes of Health, Bethesda, MD; ⁶Univ. of Pittsburgh, Pittsburgh, PA; ⁷GlaxoSmithKline, Research Triangle Park, NC; ⁸Gilead Sciences, Foster City, CA; ⁹Virco Lab, Inc., Durham, NC

Ann C. Collier, MD
acollier@u.washington.edu
Phone: 206-731-3293
Fax: 206-731-3483

ABSTRACT

Background: Better therapies are needed for patients failing antiretroviral treatment. This study tested whether LPV 400mg/r 100mg + FPV 700 mg BID (double PI) leads to superior HIV-1 RNA response compared with LPV/r or FPV + r (single PI) in persons with virologic failure to protease inhibitor (PI)-based therapy.

Methods: Open-label, multicenter, selectively randomized study. Subjects were randomized based on prior LPV/r, amprenavir (APV) or FPV experience; all received at least 1 new PI. The PIs were given with TDF and 1-2 NRTIs chosen using a Virtual Phenotype. Analyses compared the combined single PI arms to the double PI arm in intent-to-treat (ITT) and as-treated (AT) analyses stratified by prior LPV/r and APV or FPV experience. Virologic response was defined as $>1 \log_{10}$ copies/mL (c/mL) decline from baseline or having RNA <50 c/mL at week (wk) 24.

Results: Baseline characteristics and NRTI use were similar between groups. Median entry CD4+ cells and HIV-1 RNA were 188/mm³ and 4.5 \log_{10} c/mL. When a pharmacokinetic sub-study interim analysis showed that LPV and APV exposures were significantly lower in the double PI arm than in the single PI arms ($p \leq 0.0008$ and <0.0001 , respectively), enrollment was stopped early at 56 out of a planned 216 subjects, follow-up was shortened from 48 to 24 wks, and subjects on the double PI arm had to stop LPV/r or FPV. Wk 24 virologic responses were 75% with double (N=28) and 61% with single (N=23) PIs (ITT, $p=0.17$), and 100% with double (N=12) and 64% with single (N=25) PIs (AT, $p=0.02$). At wk 24, HIV-1 RNA was <50 c/mL in 54% and 46% of double and single PI subjects (ITT, $p=0.37$), and 75% and 48% (AT, $p=0.14$), respectively. In the 26 subjects with virologic failure, 5 subjects taking double PIs and 10 taking single PIs developed ≥ 1 new resistance mutation. CD4+ cells increased a median of 81 and 41/mm³ (ITT, $p=0.4$) and 114 and 43/mm³ (AT, $p=0.08$) in double and single PI groups, respectively. Clinical events and toxicity rates were similar among groups.

Conclusions: The comparison between double and single PI groups was limited by early termination of enrollment and the resulting small sample size. RNA and CD4+ cell responses did not differ significantly between groups in the ITT analyses and trends favored the double PI group in the AT analyses, although this should be interpreted cautiously. Reduction of drug exposure to LPV and FPV in the double PI arm did not adversely affect virologic responses.

BACKGROUND

Strategies for salvage (rescue) therapy include:
Simpler regimens
Fos-amprenavir (Lexiva, FPV), prodrug of APV
Fewer, smaller tablets
Greater potency
Ritonavir-enhancement
Two ritonavir-enhanced PIs
Resistance testing to choose Rx

STUDY HYPOTHESIS AND DESIGN

Combining LPV/r + FPV will have a superior HIV RNA response compared with LPV/r or FPV + r in persons with virological failure to PI-based regimens.

Design: Open-label, selectively randomized study in 216 patients with PI-regimen failure

Duration: 24 weeks with optional extension to 48 weeks

STUDY DESIGN

Arms:

- A: LPV/r (400/100mg) BID (single PI)
- B: FPV (700 mg) + r (100mg), BID (single PI)
- C: LPV/r (400/100mg) + FPV (700 mg), BID (double PI)

All with TDF (300 mg) + 1-2 NRTIs chosen based on study Virtual Phenotype
PK substudy at wk 2

Selective Randomization

If no prior LPV or APV or FPV: All arms, 1:1:2.
If prior LPV: Arms B or C, 1:1
If prior APV or FPV: Arms A or C, 1:1

STUDY ENDPOINTS AND ANALYSES

1^o Endpoints:

Antiviral Activity:

Double PI (Arm C) vs Combined Single PI Arms (Arms A + B)

Virologic Response Endpoint Definitions:

Change in RNA from baseline to week 24
If $>30\%$ had RNA <50 copies/mL, binary endpoint of $\geq 1 \log_{10}$ decrease or RNA <50 copies/mL at week 24 was to be used

Safety and Tolerability

Signs, Symptoms, Hematology and Chemistry tests (DAIDS grading scale)

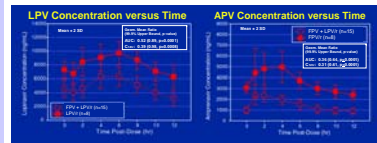
2^o Endpoints included virologic failure (VF):

- Definition of VF: $<0.5 \log_{10}$ decline at wk 8 or Confirmed $1 \log_{10}$ rise above nadir or 2 consecutive HIV RNAs ≥ 200 copies/mL after 2 consecutive < 200 copies/mL or HIV RNA ≥ 200 copies/mL at wk 24

Final Analysis:

Exploratory 2^o small sample size
Focus on week 24
Intent-to-treat (ITT)
As-treated (AT) (data cut-off when study PI d/ced)

PK SUBSTUDY RESULTS



PK substudy showed LPV and APV steady-state mean concentrations were significantly lower when LPV/r + FPV were given together than when given as a sole ritonavir-enhanced PI (Kashuba et al, AIDS 2005; 19:145-52)

STUDY HISTORY

When PK Data known:

Enrollment was stopped August, 2003

	N
Total	56
Arm A	14
Arm B	14
Arm C	28

Arm C: Pts. had to d/c LPV/r or FPV

All subjects to have f/u to wk 24

BASELINE CHARACTERISTICS

	ITT		AT	
	Single PI (N=28)	Double PI (N=28)	Single PI (N=25)	Double PI (N=12)
Sex, % male	93%	82%	92%	83%
Race/Ethnicity				
White	46%	46%	40%	58%
Black	32%	32%	38%	33%
Hispanic	14%	18%	18%	8%
Asian	4%	4%	4%	0%
American Indian	4%	0%	4%	0%
Age, yr, median	40	44	40	43
HIV RNA, log₁₀, median	4.8	4.5	4.8	4.5
CD4, median	185	253	182	319
Q1-Q3	85-299	117-427	89-288	150-473
Selective Randomization				
Prior LPV	18%	21%	18%	0%
Prior APV	18%	11%	20%	17%
Native to LPV+APV	64%	68%	64%	83%
NRTIs besides TDF				
1	57%	64%	60%	58%
2	43%	36%	40%	42%
Dec. susceptibility to				
LPV	18%	4%	20%	0%
APV	11%	4%	12%	0%

CLINICAL RESULTS

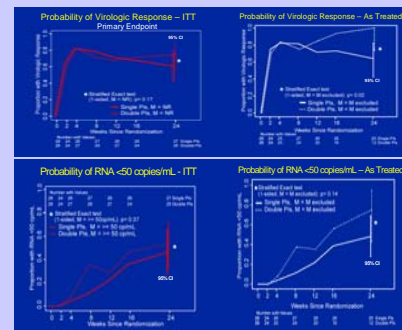
Follow-up
Median 20 wk (To 8/12/03)
Median 28 wk (To Pt. Data Cut-off)
12 of 28 subjects continued Double PI until week 24

Clinical Events

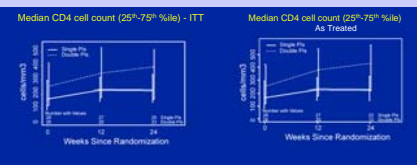
Single PI (8 events in 5 subjects):
Recurrent thrush and esop. candidiasis, MI, periph. neuropathy, fat accumulation, ABC hypersensitivity
Double PI (Arm C) 3 events in 3 subjects:
Fungal abscess; hyperlipidemia, fat accum.
2 deaths, not study related, 1 on each arm

VIROLOGIC RESULTS

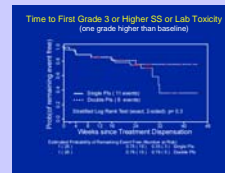
Virologic Response	Single PI	Double PI
	ITT	17/28 (61%)
ATT	16/25 (64%)	12/12 (100%)



CD4 RESULTS



SAFETY RESULTS



SS= Sign or Symptom

VIRAL RESISTANCE

	Single PI (N=28)	Double PI (N=28)	Total (N=56)	P
Virologic Failure	15 (54%)	11 (39%)	26 (46%)	0.27
> 1 newly obs. Mutation *	10 pts	5 pts		
> 1 newly obs. PI Mutation	8 pts	2 pts		

* No subject developed a K65R mutation

Double PI arm did not appear to be associated with inc. resistance at failure

NEWLY OBSERVED MUTATIONS IN SINGLE PI ARM

LPV/r
2 pts with multiple PI mutations
2 pts with I54V
1 pt with M184V

FPV+r
2 pts with I50V

CONCLUSIONS

Study had limited power 2^o early stop to enrollment and small sample size
No significant differences in RNA + CD4 responses in ITT analyses
Trends suggested better RNA and CD4 responses with double PIs as treated analyses (AT)
No difference in toxicity between Double vs Single PIs

DISCUSSION

AT analyses must be interpreted with caution 2^o :
Limited data
Fewer subjects with LPV/r or FPV experience.
AT results favoring double PI's are intriguing given the lower mean drug concentrations.
Main study question (Is LPV/r + FPV is better than single ritonavir-enhanced PIs?) is still not answered.
PK lead-in is a useful study design for future studies.

ACKNOWLEDGEMENTS

Study Subjects	Nicole Grosskopf
Participating Sites	Belinda Ha
Ed Acosta	Bernadette Jarocki
George Bishropic	Ana Martinez
Barbara Brizz	Jane Reid
Marlene Cooper	Trevor Scott
Linda Gedeon	Nancy Tustin