Poster H-523-344

45th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Washington DC, December 16–19, 2005

Barbara DaSilva, MD
200 Abbott Park Rd.
Dept. R48U, Bldg. AP30-3
Abbott Park, IL 60064-6146
email: barbara.dasilva@abbott.com

Comparative Safety and Anti-HIV Activity of a Dual Protease Inhibitor Regimen (Lopinavir/ritonavir + Saquinavir) versus a Nucleoside-Containing Regimen

D.W. Cameron[1], J. Eron[2], C. Farthing[3], C. Hicks[4], E. Daar[5], T. Marsh[6], D. Calhoun[6], B. Bernstein[6], M. King[6], B. da Silva[6], G. Hanna[6]
[1]University of Ottawa at The Ottawa Hospital, Ottawa, ON, Canada; [2]University of North Carolina, Chapel Hill, NC; [3]AIDS Healthcare Foundation Research Center, Los Angeles, CA; [4]Duke University Medical Center, Durham, NC; [5]Harbor-UCLA Medical Center, Torrance, CA; [6]Abbott, Abbott Park, IL

BACKGROUND

Lopinavir (LPV) is an HIV protease inhibitor (PI) that is co-formulated with ritonavir (r), which functions as a pharmacokinetic enhancer. LPV/r is marketed as Kaletra®. The approved adult dose of LPV/r is 400/100 mg twice-daily (BID). In the U.S., a dose of LPV/r 800/200 mg once-daily (QD) is also approved for antiretroviral-naïve adults.

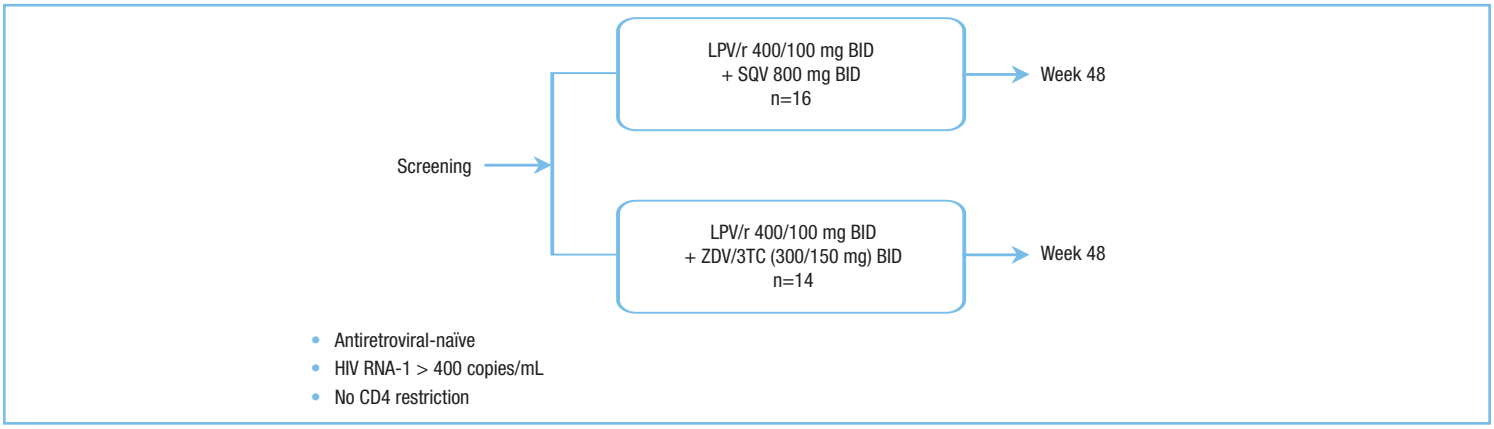
Treatment with combination antiretroviral therapy has had a profound impact in the management of HIV. However, antiretroviral therapy is sometimes associated with metabolic adverse effects including hypertriglyceridemia, lipoatrophy and insulin resistance.[1,2] Recent data have shown that hypertriglyceridemia and lipoatrophy may be related at least in part to nucleoside reverse transcriptase inhibitor (NRTI) use, most notably stavudine.[3] Since NRTIs may be associated with metabolic toxicities, it was hypothesized that use of an NRTI-sparing regimen may alleviate some metabolic toxicities. Previously, a pilot single-arm study of LPV/r and saquinavir (SQV) twice daily in 20 PI-naïve adults showed potent virologic suppression and immunologic improvements with this dual-boosted PI regimen.[4]

Study 384 is a pilot study designed to evaluate efficacy, safety and metabolic toxicities associated with two LPV/r-based regimens in antiretroviral-naïve subjects: dual PI, NRTI-sparing regimen of LPV/r plus SQV versus a nucleoside-containing regimen of LPV/r plus co-formulated zidovudine and lamivudine (ZDV/3TC). 48-week efficacy and safety results are reported.

METHODS

- Study 384 is a randomized, open-label study conducted at 6 sites in the U.S. and Canada.
- Subjects were antiretroviral-naïve with plasma HIV-1 RNA >400 copies/mL. There was no CD4 count restriction for enrollment.
- 30 subjects were randomized 1:1 to receive SQV 800 mg BID (n=16) or ZDV/3TC (300/150 mg) BID (n=14). All subjects received LPV/r soft gel capsules 400/100 mg BID (Figure 1).

Figure 1. Study 384 Design



- Plasma HIV-1 RNA levels were measured every 4 weeks through Week 16, then every 8 weeks through Week 48 using Roche Amplicor HIV-1 Monitor Ultrasensitive Quantitative PCR Assay, Version 1.5 (limit of quantitation, 50 copies/mL).
- Fasting lipids and glucose were determined at Baseline, Week 24, and Week 48.
- Complete blood counts were performed every 4 weeks through Week 16, then every 8 weeks through Week 48.
- The proportion of subjects with HIV-1 RNA below 50 copies/mL was assessed using an intent-to-treat, noncompleter=failure (ITT NC=F) method, in which missing values were considered failure unless the immediately preceding and following values were below 50 copies/mL. An observed data (OD) method was also used, in which missing values were excluded from the analysis.
- Cumulative incidence of adverse events through 48 weeks was summarized.

RESULTS

Demographics

- Demographics and other baseline characteristics are summarized in Table 1. Notably, baseline CD4 cell count was statistically significantly lower in the LPV/r+ZDV/3TC group (p=0.045).

Table 1. Study 384: Baseline Characteristics

Variable	LPV/r+SQV (n=16)	LPV/r+ZDV/3TC (n=14)
Male	16 (100%)	14 (100%)
White	10 (63%)	4 (29%)
Black	2 (13%)	7 (50%)
Hispanic	2 (13%)	0
Other	2 (13%)	3 (21%)
Age (years)		
Mean (range)	42 (25–64)	40 (21–59)
Hepatitis B/C positive*	4 (25%)	5 (39%)
Baseline HIV-1 RNA (log_{10} copies/mL)		
Median (range)	5.0 (3.7–5.9)	5.3 (4.1–6.2)
Baseline CD4+ T-cell Count (cells/mm^3)**		
Median (range)	269 (3–687)	120 (9–428)
CD4 <200 cells/mm^3	6 (38%)	10 (71%)

* Hepatitis B surface antigen positive and/or hepatitis C virus antibody positive.
** Statistically significant difference between treatment groups, p=0.045.

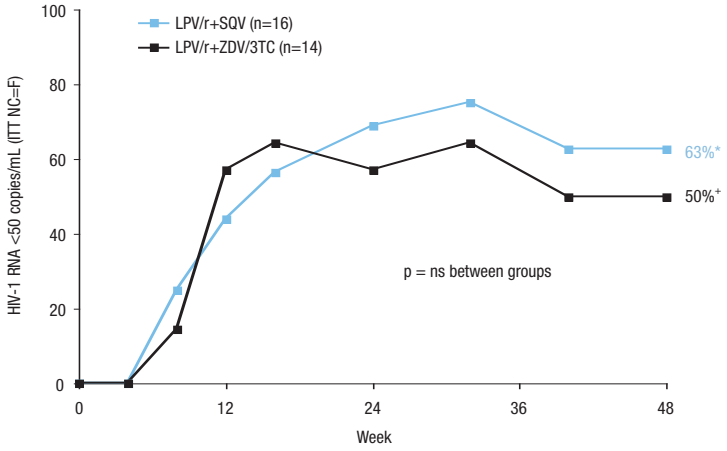
Subject Disposition

- 3 subjects in the LPV/r+SQV group discontinued prematurely prior to Week 48
  - 1 discontinued due to an adverse event (gastrointestinal symptoms)
  - 1 lost to follow-up
  - 1 due to virologic failure
- 5 subjects in the LPV/r+ZDV/3TC group discontinued prematurely prior to Week 48
  - 1 subject died (progressive multifocal leukoencephalopathy)
  - 3 discontinued due to adverse events (gastrointestinal symptoms [2], elevated liver function tests [1])
  - 1 withdrawn by investigator due to non-adherence

Efficacy

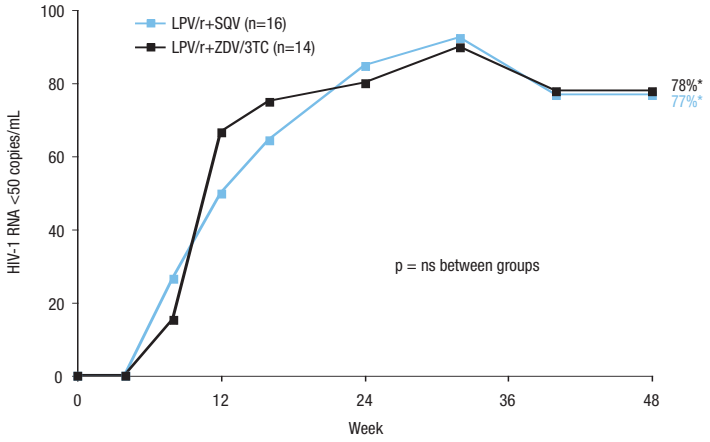
- In the intent-to-treat (noncompleter=failure) and observed data analyses, a similar proportion of subjects achieved plasma HIV-1 RNA <50 copies/mL through 48 weeks of treatment (Figures 2–3).
- 3 subjects in the LPV/r+SQV group and 2 subjects in the LPV/r+ZDV/3TC group had HIV-1 RNA above 50 copies/mL at Week 48; however, HIV-1 RNA was <80 copies/mL for all 5 subjects.

Figure 2. Study 384: HIV-1 RNA <50 copies/mL (ITT NC=F)



* In the LPV/r+SQV arm, 81% of subjects had HIV-1 RNA levels <80 copies/mL at Week 48.
+ In the LPV/r+ZDV/3TC arm, 64% of subjects had HIV-1 RNA levels <80 copies/mL at Week 48.
ns = not significant

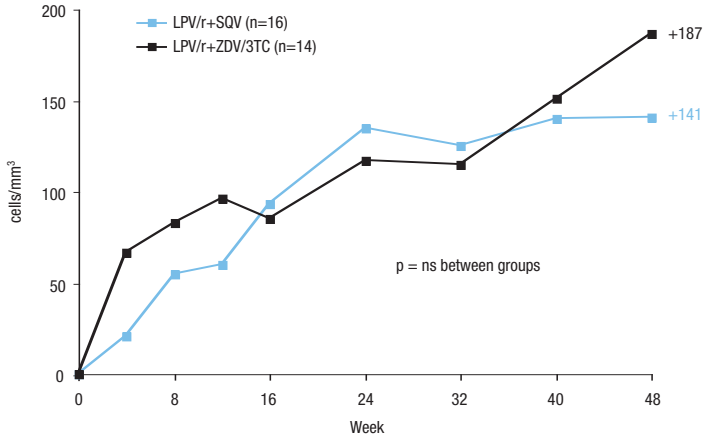
Figure 3. Study 384: HIV-1 RNA <50 copies/mL (observed data)



* In both the LPV/r+SQV and LPV/r+ZDV/3TC arms, 100% of subjects had HIV-1 RNA levels <80 copies/mL at Week 48.
ns = not significant

- Statistically significant mean increases in CD4+ T-cell count from baseline to each study visit were observed in both the LPV/r+SQV and the LPV/r+ZDV/3TC groups (Figure 4).

Figure 4. Study 384: Mean Change from Baseline in CD4+ T-cell Count



ns = not significant

Safety

- Moderate or severe adverse events of probable or possible relationship to study drug and occurring in >2 subjects in either treatment group are summarized in Table 2.

Table 2. Study 384: Most Common Adverse Events of Moderate or Greater Severity

Moderate or Severe Study Drug-Related Adverse Events	LPV/r+SQV (n=16)	LPV/r+ZDV/3TC (n=14)	P-value
Diarrhea	3 (19%)	3 (21%)	ns
Nausea	3 (19%)	4 (29%)	ns
Vomiting	3 (19%)	3 (21%)	ns

- Grade 3/4 SGOT/AST and SGPT/ALT elevations (>5xULN) occurred in 1 subject in the LPV/r+SQV group and 2 subjects in the LPV/r+ZDV/3TC group (including 1 subject with a single transient grade 3 SGOT/AST and SGPT/ALT elevation). All 3 subjects were HIV/HCV co-infected. 1 additional subject in the LPV/r+ZDV/3TC group (HIV/HBV-co-infected) demonstrated a single transient grade 3 SGPT/ALT elevation at Week 32.
- No other grade 3/4 laboratory abnormalities occurred in >1 subject in either treatment group.
- After 4 weeks of treatment, significantly different mean changes from baseline were observed for fasting glucose (LPV/r+SQV: –5 mg/dL; LPV/r+ZDV/3TC: +13 mg/dL, p=0.025) and hematocrit (LPV/r+SQV: –0.6%; LPV/r+ZDV/3TC: –4.2%, p=0.003). However, these early differences were no longer apparent after 48 weeks of treatment (glucose: –3 mg/dL in each group, p=0.94; hematocrit: LPV/r+SQV: –0.1%; LPV/r+ZDV/3TC: –0.6%, p=0.65).

- Mean increases from baseline to Week 48 in total cholesterol (+60 mg/dL in each group) and triglycerides (+85 mg/dL in the LPV/r+SQV group and +64 mg/dL in the LPV/r+ZDV/3TC group) were similar between groups. Most subjects remained at Grade 0–1 total cholesterol or triglyceride levels in both treatment groups through 48 weeks.
- Cholesterol increases included increases in both HDL cholesterol and LDL cholesterol. In the LPV/r+SQV group, the LDL:HDL cholesterol ratio was similar at baseline (3.5) and Week 48 (3.6); in the LPV/r+ZDV/3TC group, the ratio increased from 2.9 to 3.6. However, neither change was statistically significantly different from baseline, and the difference between groups was not significant.
- No subjects were initiated on lipid lowering agents during the 48-week study period.

SUMMARY

- In this pilot study, a regimen of LPV/r+SQV demonstrated similar efficacy based on the proportion of subjects with HIV-1 RNA <50 copies/mL and change from baseline in CD4+ T-cell counts through 48 weeks, compared to those receiving a standard triple regimen of LPV/r+ZDV/3TC.
- Similar frequencies and types of moderate or severe adverse events were noted between the 2 treatment groups.
- The only grade 3+ lab abnormalities noted in >1 subject were AST and ALT elevations, which occurred at similar rates in hepatitis coinfected subjects in both treatment groups.
- A similar degree of total cholesterol and triglyceride elevation was noted in both treatment groups through 48 weeks.
- No change in fasting glucose was noted in either treatment group in subjects treated for 48 weeks.

CONCLUSIONS

- The dual PI (NRTI-sparing) regimen of LPV/r plus saquinavir had similar efficacy and safety compared to a LPV/r-based standard combination antiretroviral regimen, with no more frequent lipid abnormalities and no elevation of fasting blood glucose over time.
- Although the small sample size limits the ability to discern differences between treatment groups, additional controlled studies of dual PI regimens may be considered to further assess possible metabolic benefits over the long term in treatment-naïve patients and the ability to treat NRTI-resistant HIV-1 in treatment-experienced patients. It may also be of greater interest to assess the potency, tolerability, and safety of dual PI combinations as new dosage forms become available.

REFERENCES

1. Nolan D, Mallal S. Complications associated with NRTI therapy: update on clinical features and possible pathogenic mechanisms. *Antiviral Therapy* 2004;9(6):849–863.
2. Currier JS, Havlir DV. Complications of HIV disease and antiretroviral therapy. *Topics in HIV Medicine* 2005;13(1):16–23.
3. Stazsewski S, Gallant JE, Pozniak AL et al. Efficacy and safety of tenofovir DF (TDF) versus stavudine (d4T) when used in combination with lamivudine and efavirenz in antiretroviral naïve patients: 96-week preliminary interim results. 10th CROI, Boston, MA, 2003; Poster 564b.
4. Hellinger J, Cohen CJ, Morris AB et al. A pilot study of saquinavir and LPV/r twice daily in protease inhibitor-naïve HIV-positive individuals: protease inhibitor concentrations and week 48 results. 2nd IAS. Paris, France, 2003; Poster 571.

ACKNOWLEDGMENTS

Study 384 Subjects

Study 384 Clinical Site Coordinators:

Man Ming Tse – Pacific Horizon Medical Group, San Francisco, CA
Richard Guenette – University of Ottawa at The Ottawa Hospital, Ottawa, ON, Canada
Nancy Lamoureux – University of Ottawa at The Ottawa Hospital, Ottawa, ON, Canada
Anne-Marie Dugal – University of Ottawa at The Ottawa Hospital, Ottawa, ON, Canada
David Ragan – University of North Carolina, Chapel Hill, NC
Laurie Frarey – University of North Carolina, Chapel Hill, NC
Linda Manor – University of North Carolina, Chapel Hill, NC
Julieta Giner – Duke University Medical Center, Durham, NC
Ken Shipp – Duke University Medical Center, Durham, NC
Robert Cordova – AIDS Healthcare Foundation Research Center, Los Angeles, CA
Zenaida Vasquez – AIDS Healthcare Foundation Research Center, Los Angeles, CA
Jacqui Pitt – Harbor-UCLA Medical Center, Torrance, CA

Abbott Laboratories:

Kathy Sheehan
Travis Yanke
Cheryl Foit