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Safety of Kaletra as Initial Therapy: A Combined Analysis of Phase II and III Clinical Trials

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Background

Lopinavir (LPV) is an HIV protease inhibitor (PI) that is co-formulated with ritonavir (r), an inhibitor of cytochrome P450-3A. In adults, LPV/r is dosed at 400/100 mg BID or 800/200 mg QD.

LPV/r has demonstrated safety and efficacy in numerous clinical trials and patient categories.[1,2,3,4] In the developed world, LPV/r is a recommended option for initial therapy in antiretroviral-naïve patients.[5] In resource-constrained settings, LPV/r is recommended as a second-line agent for patients failing an initial regimen of a non-nucleoside reverse transcriptase inhibitor (NNRTI) plus nucleoside reverse transcriptase inhibitors (typically stavudine plus lamivudine).[6] The recently introduced LPV/r tablet does not require refrigeration, can be dosed with or without food, has less pharmacokinetic variability, and requires fewer pills (4 tablets per day) than the soft-gelatin capsule formulation (6 capsules per day), key properties which are expected to increase patient access to effective protease inhibitor-based antiretroviral therapy in developing countries.

Early pivotal trials of LPV/r used stavudine (d4T) in the nucleoside backbone,[1,3,7] consistent with then-current standards of care. Recent studies have used zidovudine (ZDV) or tenofovir (TDF) instead of d4T.[2,8,9] Since ZDV and TDF have demonstrated improved tolerability and less impact on lipids and body fat composition (BFC) than d4T,[10-14] we compared the safety and tolerability of LPV/r when used in combination with d4T vs. non-d4T-containing regimens in antiretroviral-naïve subjects.

Methods

- The safety and tolerability of LPV/r over 96 weeks were examined in combined analyses of results from Phase II and III clinical trials of antiretroviral-naïve subjects.
- Adverse event (AE) severity and relationship to study drug were derived from the original study reports.
- 788 subjects from six clinical trials of LPV/r were included in the analysis (Table 1). All studies used the soft-gelatin capsule formulation of LPV/r.
- Prevalence and incidence of adverse events through 96 weeks were assessed, as were changes from baseline in laboratory values and the time to events of BFC changes.
- Analyses compared results between subjects receiving d4T-based NRTI-regimens (d4T group, n=464) and those receiving other NRTIs (non-d4T group, n=324).
- Events of BFC changes were based on investigator-reported adverse events, as specific criteria for BFC changes were not pre-specified.

Table 1. Study Designs

Study	Subjects Receiving LPV/r-Based Regimens	Design	Duration
M97-720	100	3 blinded doses for 48 weeks, open-label LPV/r 400/100 mg BID thereafter, NRTIs: d4T+3TC BID	7 years (360 weeks)
M98-863	326	Double-blinded, active-controlled (vs. nelfinavir), LPV/r 400/100 mg BID, NRTIs: d4T+3TC BID	60 weeks
M99-056	38	Open-label, pilot comparison of QD (800/200 mg) vs. BID (400/100 mg) LPV/r, NRTIs: d4T+3TC BID	96 weeks
M01-384	30	Open-label, LPV/r 400/100 mg BID, plus SQV BID vs. 3TC/ZDV BID	96 weeks
M02-418	190	Open-label, QD (800/200 mg) vs. BID (400/100 mg) LPV/r, NRTIs: TDF+FTC QD	96 weeks
M03-613	104	Open-label, active-controlled (vs. efavirenz), LPV/r 400/100 mg BID + NRTIs for induction phase followed by LPV/r 400/100 mg BID monotherapy, NRTIs: 3TC/ZDV BID	96 weeks

Results

- Subjects were primarily male and white, and demographics and baseline characteristics were generally comparable between the d4T group and the non-d4T group (Table 2).

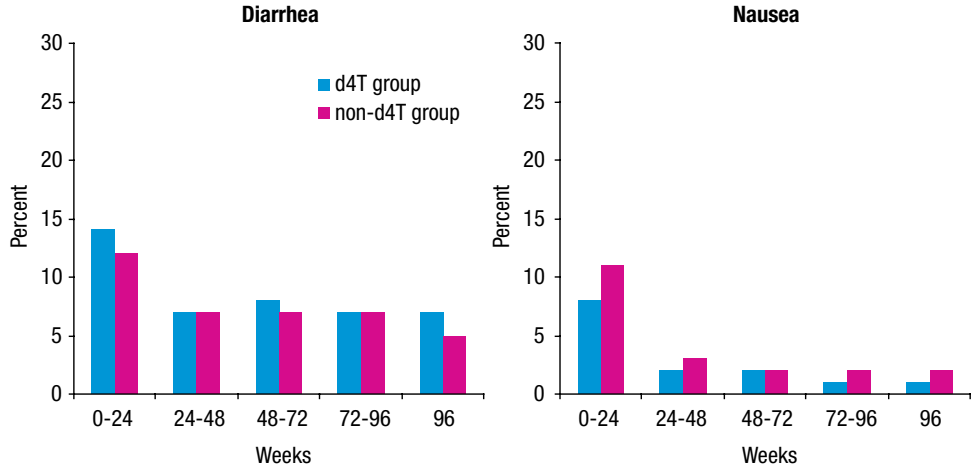
Table 2. Demographics and Baseline Characteristics

Variable	LPV/r + d4T-Based Regimens	LPV/r + non-d4T-Based Regimens	Combined
Age (yrs) *			
N	464	324	788
Mean ± SD	37.7 ± 9.6	39.4 ± 10.5	38.4 ± 10.0
Sex, n (%)			
N	464	324	788
Male	382 (82)	263 (81)	645 (82)
Female	82 (18)	61 (19)	143 (18)
Race, n (%) *			
N	464	324	788
Asian	11 (2)	15 (5)	26 (3)
Black	132 (28)	96 (30)	228 (29)
Mixed	3 (1)	3 (1)	6 (1)
Native American	3 (1)	3 (1)	6 (1)
White	315 (68)	196 (60)	511 (65)
Other	0	11 (3)	11 (1)
Ethnicity, n (%) **			
N	464	324	788
Hispanic	63 (14)	24 (7)	87 (11)
Hepatitis B/C, n (%)			
N	464	324	788
Positive	70 (15)	56 (17)	126 (16)
Negative	387 (83)	268 (83)	655 (83)
Unknown	7 (2)	0	7 (1)
Baseline HIV-1 RNA (log_{10} copies/mL)			
N	464	324	788
Mean ± SD	4.9 ± 0.73	4.9 ± 0.69	4.9 ± 0.72
Baseline CD4+ T-cell (cells/mm^3) *			
N	463	324	787
Mean ± SD	277 ± 222.0	246 ± 190.5	264 ± 210.0

*, ** Statistically significant difference between groups at the p=0.05 and 0.01 levels, respectively.
Note: Non-whites were combined for analysis of race, and unknown values were excluded prior to calculations of p-values.

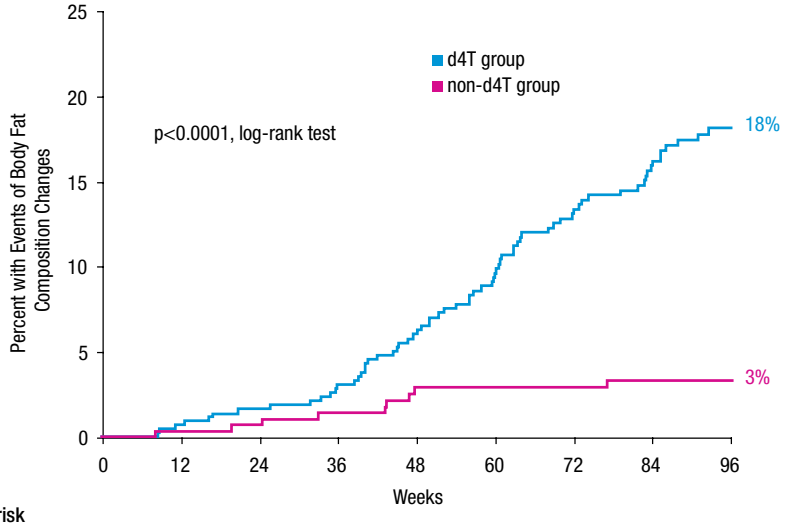
- Overall, 7% and 10% (p=0.188) of subjects in the d4T and non-d4T groups discontinued study drug due to AEs.
- Adverse events generally occurred early, were self-limiting and seldom led to discontinuation.
- Over 96 weeks, the most common moderate/severe AEs with a probable/possible/unknown relationship to study drugs were diarrhea (18% vs. 15% for d4T vs. non-d4T; p=0.242) and nausea (10% vs. 11%; p=0.477), respectively.
- At 96 weeks, the prevalence of diarrhea and nausea was 7% vs. 5% (p=0.455), and 1% vs. 2% (p=0.472), respectively, for d4T vs. non-d4T (see Figure 1).

Figure 1. Prevalence of Moderate or Severe Study Drug-Related AEs through 96 Weeks



- Hepatobiliary, cardiovascular, and pancreatic clinical events of any severity were uncommon and rarely resulted in discontinuation (<1% discontinuation rate for each).
- Through Week 96, BFC changes (by spontaneous investigator report) were significantly more common in the d4T group than the non-d4T group (18% vs. 3%, p<0.0001, Figure 2). In a subset of subjects taking d4T and followed for up to 7 years the risk for BFC continued to accumulate.

Figure 2. Subjects with Events of Body Fat Composition Change



No. at risk					
d4T group	464	414	376	319	193
non-d4T group	324	286	256	230	142

- Increases in total cholesterol (TC) and triglycerides (TG) occurred early (within 12 weeks) and generally remained stable over time. Changes from baseline at Week 96 in total cholesterol and triglycerides were significantly larger for the d4T group than the non-d4T group (p≤0.002 for each). Median TG and TC values over time are shown in Figures 3 and 4.
- Through Week 96, the rates of grade 3+ TC and TG elevations were significantly higher for d4T vs. non-d4T groups (14% vs. 7%, p=0.007 for TC; 13% vs. 7%, p=0.003 for TG; Figure 5).

Figure 3. Median Triglyceride Values at Each Visit

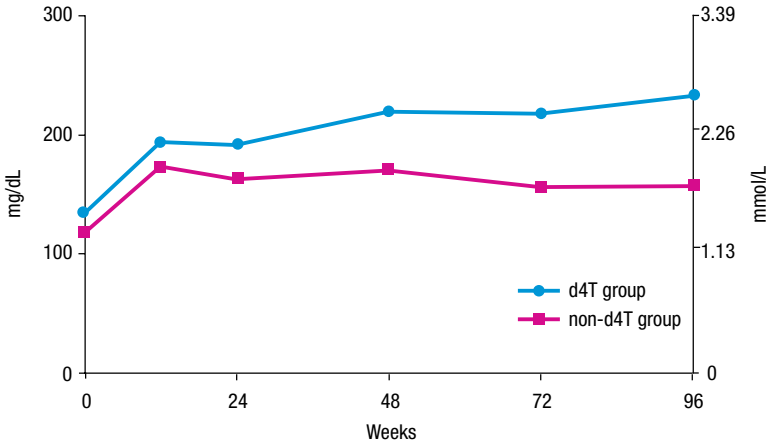


Figure 4. Median Cholesterol Values at Each Visit

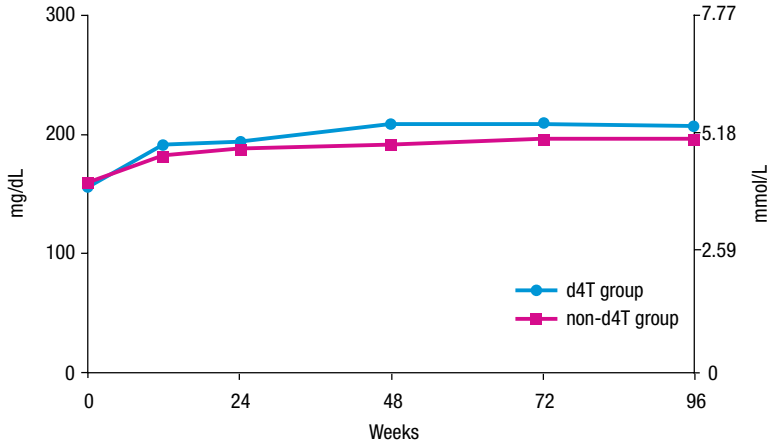


Figure 5. Incidence of Grade 3/4 Triglyceride and Cholesterol Elevations within 96 Weeks

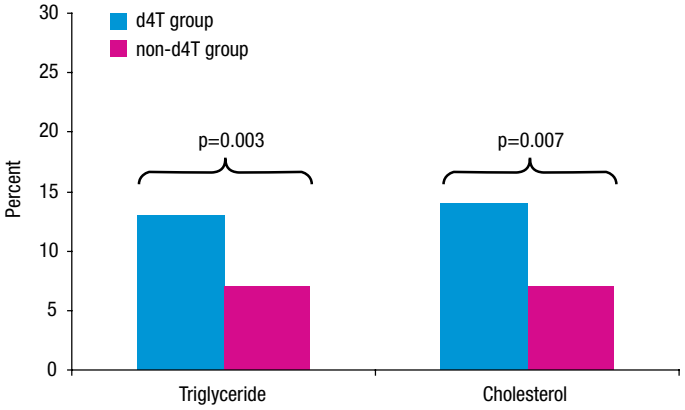
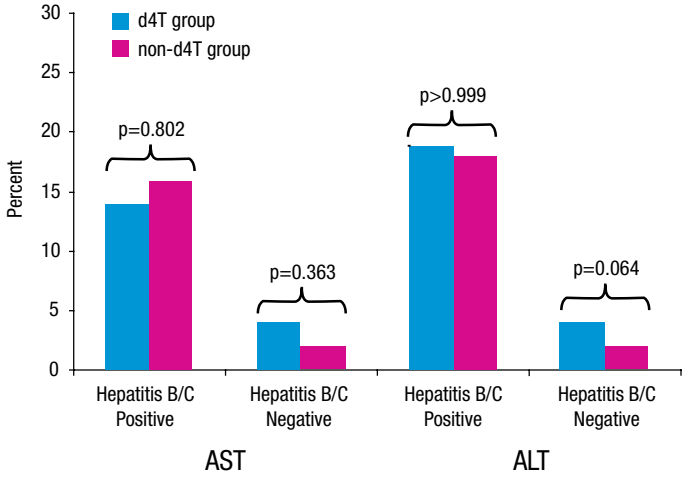


Figure 6. Incidence of Grade 3/4 AST and ALT Elevations within 96 Weeks by Baseline Hepatitis Status



- Through Week 96, the overall rate of grade 3+ AST and ALT elevations was 5% for both d4T and non-d4T groups, but more common in subjects with baseline seropositivity for hepatitis B/C compared with seronegative (AST: 15% vs. 3%, respectively, p<0.001; ALT: 19% vs. 3%, respectively, p<0.001). Within the seropositive and seronegative groups, no differences between the d4T and non-d4T groups were observed (p≥0.064 for each, Figure 6).

Conclusions

LPV/r is a safe and effective treatment for HIV-1 infection. Among antiretroviral-naïve subjects receiving LPV/r-based treatment, AEs were typically self-limiting and infrequently resulted in treatment-associated discontinuations. The risk of lipid and BFC changes was significantly lower in the non-d4T-containing vs. d4T-based regimens. These observations are particularly important in developing countries where use of d4T is still relatively common. Safety and efficacy studies of the heat-stable LPV/r tablet are ongoing, and this formulation will likely facilitate increased patient access to antiretroviral therapy in resource-limited settings.

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