LPV/r-based 2-drug HAART vs LPV/r-based 3-drug HAART: Comparable virological efficacy and tolerability in HIV-1-infected naïve subjects (Kalead1 study) – 48-Week results

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4th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Sydney, Australia, 22-25 July 2007
Poster # WEPEB035

Background

Current guidelines for the management of HIV-1 infected subjects recommend the use of 3-drug combination therapy. The use of 3-drug HAART may not always be feasible. Patients can have specific contraindications that make the incorporation of 3 drugs difficult. They may have drug resistance that can reduce the antiviral activity of a drug in the 3 drug regimen. Therefore a rationale exists to consider drug regimens using less than 3 drugs.

A virologically suppressive 2-drug regimen, which does not harbour an increased risk of drug resistance, which reduces the economic cost of requiring a third drug for HIV treatment, and eliminates any toxicity associated with a third drug, would be attractive for the treatment of HIV-1 infection. Kalead1 is the first study of the combination of Lopinavir/ritonavir soft gel capsules (LPV/r SGC) and Tenofovir DF (TDF) as first-line HAART.

Objectives

Kalead1 was designed to compare the antiviral activity and safety of the combination of LPV/r SGC and TDF as first-line 2-drug regimen, versus a standard-of-care 3-drug regimen of LPV/r SGC in combination with 2 nucleoside analogues.

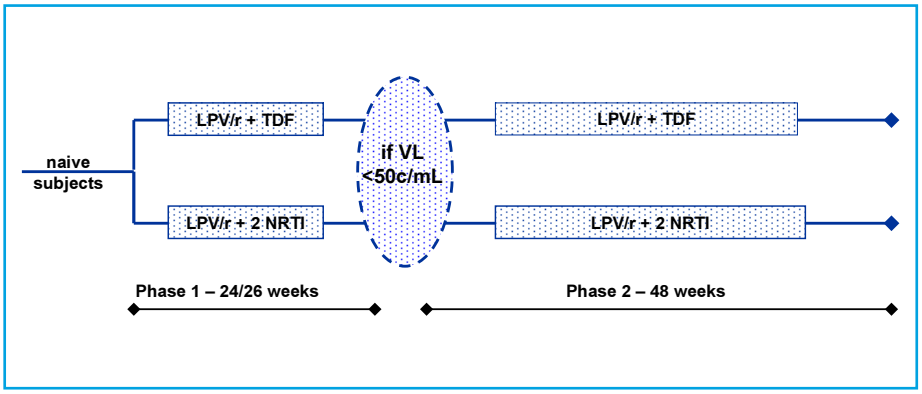
Methods

Study Design

Kalead1 is a 72-week, phase III, open-label, randomized, comparative, multi-center trial comparing the antiviral efficacy of two-drug therapy with LPV/r in combination with TDF versus the SOC three-drug therapy (LPV/r in combination with 2 NRTI's) in antiretroviral naïve, HIV-1 infected adults.

The study consists of two phases. The first phase of 24 - 26 weeks was built into the study design to gauge initial virologic safety of a 2-drug regimen. If virologic suppression was successful during Phase 1 (HIV-RNA <50c/mL), then the subject continued in the trial for further 48 weeks of Phase 2. (Fig. 1)

Figure 1. Kalead1 study design



Antiretroviral naïve male and female subjects, >18 years of age, with plasma HIV-1 RNA > 400 copies/mL and any CD4 count were eligible for study entry. The subjects were randomized to receive LPV/r SGC 400/100 mg BID + TDF 300 mg QD or LPV/r SGC 400/100 mg BID + 2 NRTIs chosen by the Investigator. The subjects were monitored for plasma HIV-1 RNA, CD4 cell count, adverse events and routine clinical laboratory studies.

All randomized subjects who received at least one dose of study drug are included in this interim 48-weeks efficacy analysis for non-inferiority.

Baseline data

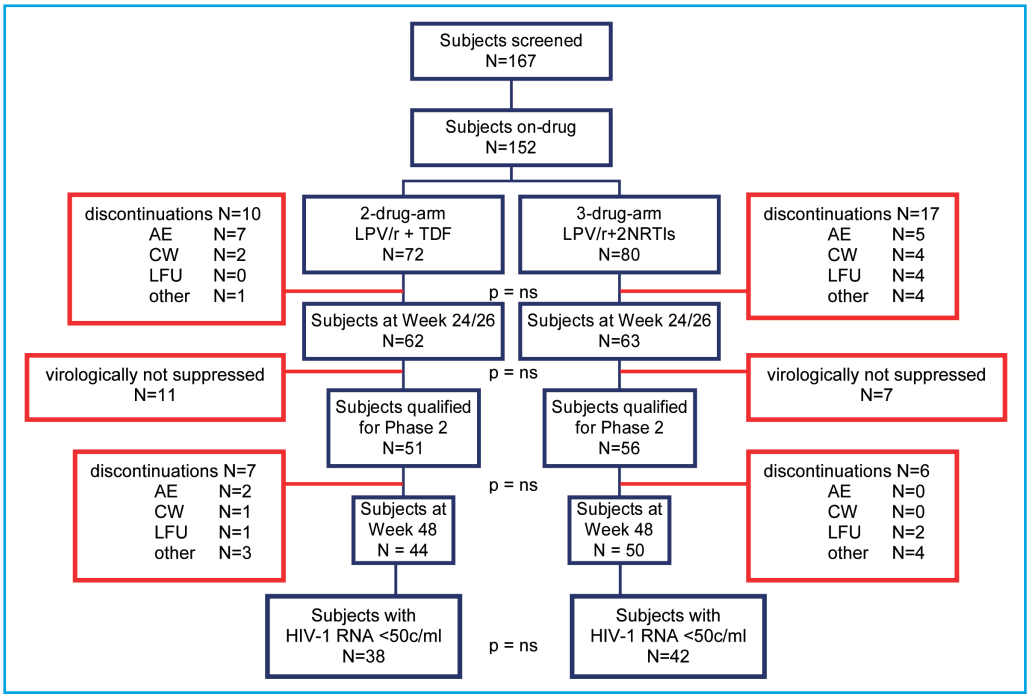
The two treatment arms were comparable at baseline for all criteria except CD4 cell count. CD4 count was significantly lower (p=0.019) in the Triple Arm (LPV/r + 2NRTIs). The difference between the two treatment arms was no longer evident when the subjects were stratified for CD4 cell counts ≤ 200 cells/mm3 vs >200 cells/mm3 (p = ns).

Table 1. Baseline data

	LPV/r + TDF	LPV/r + 2 NRTIs	total	p value
male gender	87.5%	76.3%	81.6%	ns
age mean (range)	39.92 (24-69)	40.44 (23-66)	40.19 (23-69)	ns
CD4 cell count median (range) [CI 95%]	231 (2-580) [215.5, 274.05]	199 (3-639) [171.26, 224.49]	220.5 (2-639) [200.23, 239.92]	0.019
CD4 cell count ≤200 median (range) [CI 95%]	152 (2-200) [104.55, 150.87]	116 (3-200) [88.53, 126.98]	125 (2-200) [101.25, 130.46]	ns
CD4 cell count >200 median (range) [CI 95%]	321 (208-580) [293.28, 348.72]	265.5 (209-639) [267.52, 322.69]	290 (208-639) [289.47, 328.24]	ns
HIV-1 RNA (log) mean (range) [CI 95%]	4.81 (2.73-6.0) [4.64, 4.98]	4.92 (2.81-6.16) [4.76, 5.07]	4.87 (2.73-6.16) [4.75, 4.98]	ns

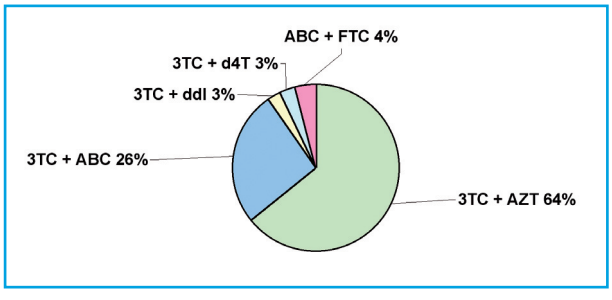
72 subjects were randomized to LPV/r+TDF (Dual Arm) and 80 to LPV/r+2NRTIs (Triple Arm). 62/72 (86.1%) and 63/80 (78.8%) of the subjects in Dual Arm and Triple Arm, respectively, reached the end of phase 1.
51 (82.3%) and 56 (88.9%) of the subjects who reached the end of Phase 1 did so with two consecutive HIV RNA values below 50 copies and thus qualified to enter Phase 2 of the study.
Of the 51 subjects in the dual and 56 subjects in the triple arm, further 7 (13.7%) and 6 (10.7%) subjects discontinued before Week 48 *(see Figure 2 for details).*

Figure 2. Kalead1 Subject Summary



The distribution of the Investigator-prescribed NRTIs in the Triple Arm (LPV/r + 2NRTIs) is presented in *Figure 3.*

Figure 3. Investigator-prescribed NRTI combinations in the 3-drug-arm

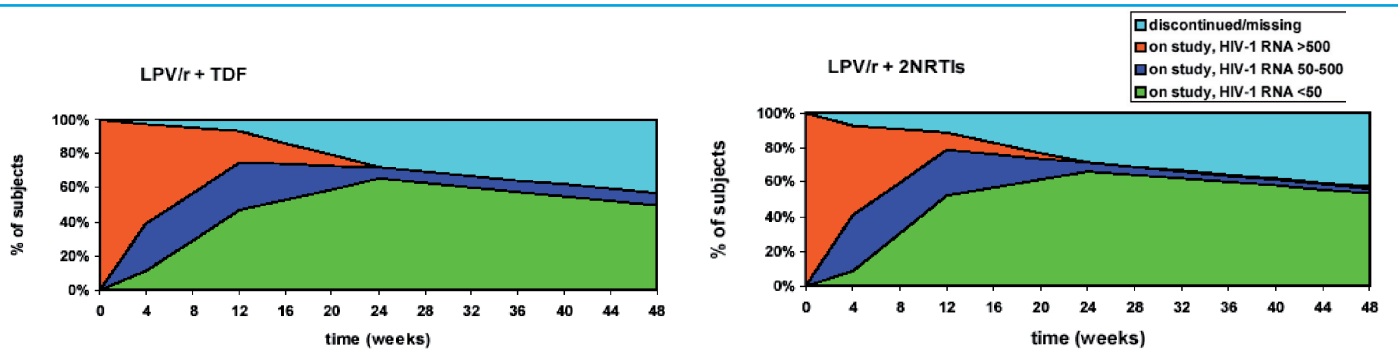


Results

Efficacy

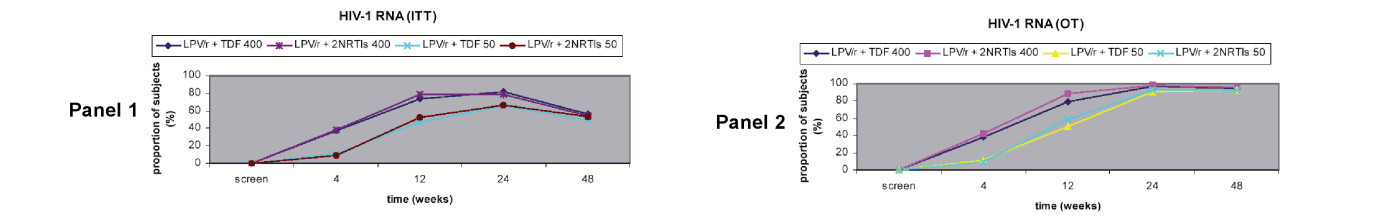
The reduction in HIV-1 RNA from baseline to Week 48 was comparable between the two treatment arms. *(Fig. 4).*

Figure 4. HIV-1 RNA through Week 48



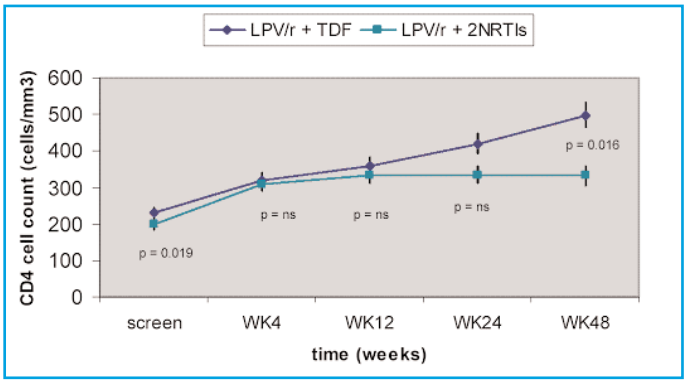
The proportion of subjects with viral load <400 copies/mL and <50 copies/mL from Screening through Week 48 in Intention-To-Treat (ITT) and On-Treatment (OT) populations is presented in Figure 5, Panel 1 & 2, respectively:

Figure 5. HIV-1 RNA through Week 48 – ITT and OT populations



5 subjects (6.94%) in the dual arm had a viral blip at Week 48, the values ranging from 51 to 91 copies/mL, whereas in the triple arm the viral blips were 3 (3.75%; p=ns), ranging from 72 to 1000 copies. No resistance testing was performed.
The change in CD4 counts through Week 48 is presented in Figure 6.

Figure 6. Evolution of CD4 cell count from Screening through Week 48



Safety

Discontinuations

The number of discontinuations due to various reasons was comparable in the two treatment arms through Week 48 (see Fig. 2 for details).

Adverse Events

The incidence of adverse events through Week 48 was comparable in the two groups, except Investigator-reported lipid elevations (dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia) which were less frequent in the dual arm (p=0.086).

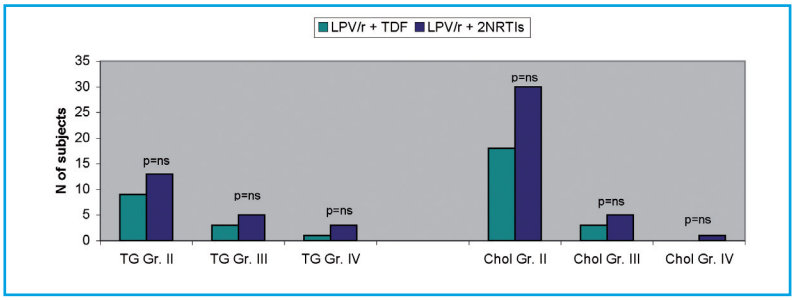
Table 2. Adverse events through Week 48

	LPV/r + TDF (N=72)	LPV/r + 2NRTIs (N=80)	p value
any AE	59 (81.9%)	65 (81.3%)	0.912
any related AE	38 (52.8%)	52 (65.0%)	0.126
any serious AE [#]	8 (11.1%)	8 (10.0%)	0.824
any gastrointestinal AE	34 (47.2%)	33 (41.3%)	0.459
any dyslipidemia	10 (13.9%)	20 (25.0%)	0.086

[#] of all SAEs only 1 in the triple arm was judged correlated to the Study Drugs by the Investigator

When laboratory values of fasting serum lipids were compared, the differences between Grade II-III-IV elevations of triglycerides and total cholesterol were not significant between the two treatment arms *(Fig. 7).*

Figure 7. Fasting serum lipid values



Conclusions

48-week results demonstrated comparable virologic efficacy and tolerability when a dual regimen of LPV/r + TDF was compared to LPV/r + 2 NRTIs in ARV-naïve patients. CD4 increases were significantly greater in the dual therapy arm at Week 48. Finally, while not reaching statistical significance, there was a trend for lower incidence of lipid elevations in the dual therapy arm.

Discussion

Kalead1 is the first study to compare dual ART therapy with standard-of-care triple therapy in HIV-infected adults naïve to ARV therapy. The results of the Kalead1 study suggest that a dual therapy with LPV/r + TDF may be equally effective and tolerable, when compared to three-drug HAART.

Monotherapy strategy with LPV/r has been compared to triple therapy with LPV/r + 2 NRTIs employing various approaches (ARV naïve, induction-maintenance, simplification to LPV/r monotherapy among virologically suppressed). LPV/r monotherapy while effective, does carry an increased risk of selecting protease resistance mutations, a greater incidence of viral blips and viral failure when compared to triple therapy with LPV/r as the anchor. In our Kalead1 study, through 48 weeks, there was no difference between the dual and the triple arm with regard to the incidence of viral blips, emergence of PI resistance, nor virologic failure.

The limitations of Kalead1 study include the choice to use Investigator-selected NRTIs in the triple arm instead of a standard comparative arm. Also, the dosing of LPV/r was not QD in neither of the treatment arms, due to the lack of QD labelling in Italy. Obviously the attractiveness of dual therapy would be enhanced if the LPV/r was dosed QD, thereby making the entire regimen QD. Furthermore, the new tablet formulation of LPV/r was only used in the Kalead1 study by a few subjects near the end of the trial (none prior to week 48).

Further study of dual therapy HAART with LPV/r employing QD dosing, with the tablet formulation, and with other NRTI partners (3TC, FTC, ABC) is warranted.

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Acknowledgements

Patients

We wholeheartedly wish to express our gratitude to all the People Living With HIV/AIDS who participated in the Kalead1 Study, thus permitting further advancement in the fight against HIV/AIDS.

Investigators

The Kalead1 Study Group: Principal Investigators Prof. Andrea Antinori, Rome; Prof. Antonietta Cargnel, Milan; Dr Amedeo Capetti, Milan; Prof. Giampiero Carosi*, Brescia; Prof. Roberto Cauda, Rome; Prof. Francesco Chiodo, Bologna; Prof. Ercole Concia, Verona; Prof. Giovanni Di Perri*, Turin; Prof. Adriano Lazzarin*, Milan; Prof. Francesco Leoncini, Florence; Prof. Francesco Mazzotta, Florence; Dr. Paola Meraviglia, Milan; Prof. Mauro Moroni*, Milan; Dr. Pasquale Narciso, Rome, Prof. Giuseppe Pastore, Bari, Dr. Tiziana Quirino, Busto Arsizio; Dr. Giuliano Rizzardini, Busto Arsizio; Prof. Gian Marco Vigevani, Milan; Prof. Vincenzo Vullo*, Rome.

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Gilead Sciences

The collaboration of Gilead Sciences, Foster City, CA, USA is gratefully acknowledged.