Abstract #74

Drug Resistance Outcomes in a Trial Comparing Lopinavir/ritonavir (LPV/r) Monotherapy to LPV/r + Zidovudine/Lamivudine (MONARK Trial)

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Background

LPV/r used as part of a 3-drug regimen in antiretroviral-naïve patients is highly effective in durably suppressing plasma HIV-1 RNA to <50 copies/mL.[1-2]

In antiretroviral-naïve patients, combination therapy with LPV/r only rarely selects for protease inhibitor (PI) resistance.

- An analysis of 4 Abbott clinical trials that enrolled 654 antiretroviral-naïve patients starting a LPV/r-based 3-drug regimen and followed for 2–7 years showed no selection of protease inhibitor (PI) resistance in patients experiencing viremia.[2-4]
- A single case of development of PI resistance during therapy with a LPV/r-based 3-drug regimen has been reported in the literature (Table 1)[5].

LPV/r monotherapy has shown promising short-term efficacy in small studies of relatively short duration.[6-8]

Little is known about the propensity of LPV/r monotherapy to select drug resistance. However, four case reports of PI-naive patients on LPV/r monotherapy developing primary PI resistance mutations with virologic failure have been presented (Table 1).

Table 1. Protease Inhibitor Resistance in Protease Inhibitor-Naïve Patients on LPV/r Regimens: Published Case Reports

Case Source	Prior ARV	Current ARV	Protease Genotype	LPV Phenotype
Three-Drug HAART Including LPV/r				
Conradie[5]	Naïve	LPV/r + AZT/3TC	BL: 36I 63P 93L Fail: **33F** 36I **54V** 63P **82A**	BL: N/A Fail: N/A
LPV/r Monotherapy				
Friend[9]	EFV AZT 3TC TDF	LPV/r	BL: 12S 13V 15V 19I/L 37N 61N/H Fail: 12S 13V 15V 19I 37S/N 61N **82V/A**	BL: N/A Fail: N/A
Pierone[10]	NNRTI + 2 NRTIs	LPV/r	BL: 41K 63C 93L Fail: 41K 63C **71V 76V** 93L	BL: N/A Fail: N/A
Wolf[11]	d4T 3TC	LPV/r	BL: 19I 37N 77I Fail: 19I 37N **46I 54V** 77I **84V**	BL: N/A Fail: N/A
Vanig[12]	AZT 3TC d4T ABC ddI NVP	LPV/r	BL: 10F Fail: 10F **32I 46I 47V 84V**	BL: N/A Fail: 39-fold

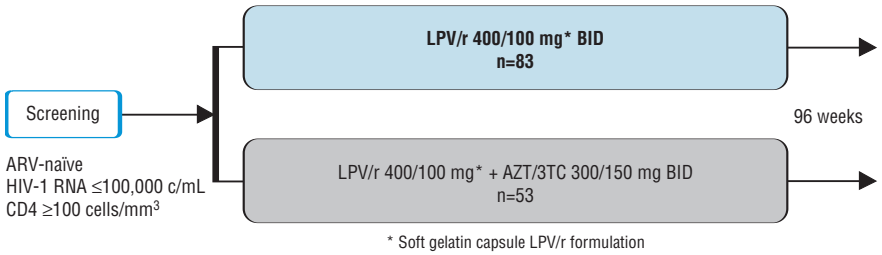
The relative risk of developing resistance with failure of LPV/r monotherapy versus 3-drug therapy is unknown. We evaluated the frequency of emergence of drug resistance among subjects on LPV/r monotherapy in a controlled, randomized trial of the safety and efficacy of LPV/r monotherapy compared to LPV/r + zidovudine/lamivudine (AZT/3TC) in antiretroviral-naïve patients.

Methods

Study Design

MONARK is an ongoing controlled, randomized, open-label, 96-week trial comparing the safety and efficacy of LPV/r + AZT/3TC to LPV/r monotherapy in antiretroviral-naive HIV-1 infected adults starting antiretroviral therapy.

Figure 1. MONARK Study Design



* Soft gelatin capsule LPV/r formulation

Inclusion criteria included:

- Antiretroviral-naïve
- Plasma HIV-1 RNA ≤100,000 copies/mL
- CD4+ T-cell count ≥100 cells/mm^3

No evidence of resistance to study drugs on screening HIV-1 drug resistance genotype. Resistance to study drugs was defined as follows:

- AZT: Presence of any mutation in reverse transcriptase (RT) gene leading to an amino acid substitution at codon 215
- 3TC: Presence of any mutation in RT gene leading to an amino acid substitution at codon 184
- LPV/r: Presence of any mutation in the protease gene leading to an amino acid substitution at the following codons: 32, 47, 48, 50, 82, 84 or 90; or >3 mutations at the following codons: 10, 20, 24, 46, 53, 54, 63 or 71

Subjects were randomized to either the LPV/r or LPV/r + AZT/3TC arm according to the following scheme: Randomization was 1:1 for the first 60 subjects, then 2:1 in favor of the monotherapy arm for the remaining subjects.

Subjects were monitored with plasma HIV-1 RNA levels at Weeks 1, 2 and 4, then every 4 weeks until Week 24, then every 8 weeks until Week 48, then every 12 weeks until Week 96.

Laboratory Evaluation

Plasma HIV-1 RNA quantitation (Amplicor 1.5, Roche, Indianapolis, Indiana, USA) with a lower level of quantitation of 50 copies/mL was performed at a central laboratory (MDS Central Lab, Baillet-en-France, France).

HIV-1 drug resistance genotype testing (PCR by C. Delaugerre via ANRS technique in the lab of C. Rouszioux, Centre Hospitalier Univeritaire, Necker, Paris, France) was performed at screening to determine study eligibility, and at time of plasma HIV-1 RNA >500 copies/mL after achieving <50 copies/mL, rebound of >1 $\log_{10}$ from nadir of <400 copies/mL, or study discontinuation.

Additional HIV-1 drug resistance phenotype and genotype testing (Phenosense GT, Monogram Biosciences, South San Francisco, CA) was performed on samples demonstrating changes in protease from Baseline.

Results

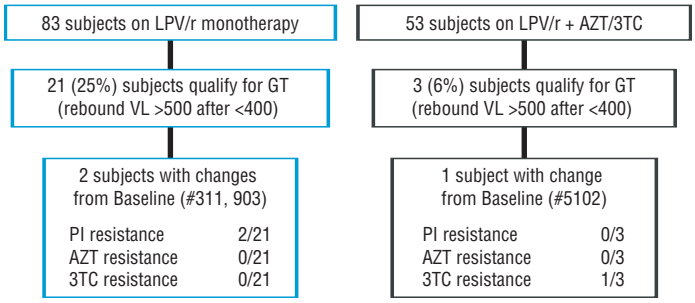
136 subjects were randomized, 83 to LPV/r monotherapy and 53 to LPV/r + AZT/3TC.

- Mean follow-up for this analysis is 64 weeks (range 48–96 weeks).

At the time of the present analysis, 24 subjects qualified for resistance testing: 3 on LPV/r + AZT/3TC and 21 on LPV/r monotherapy. Reasons for resistance testing included:

- Plasma HIV-1 RNA >500 copies/mL after nadir <400 copies/mL: 18 subjects (15 out of 18 had nadir <50 copies/mL)
- Plasma HIV-1 RNA >500 copies/mL at time of discontinuation from trial after nadir <400 copies/mL: 5 subjects (4 out of 5 had nadir <50 copies/mL)
- Investigator choice due to persistent low level viremia (below protocol-defined virologic failure): 1 subject

Figure 2. Genotypic Resistance Testing Results



- In the monotherapy arm, 2 subjects (311 and 903 described below) developed new resistance mutations and 19 did not.
- In the 3-drug arm, 1 subject (5102 described below) developed a new resistance mutation and 2 did not.

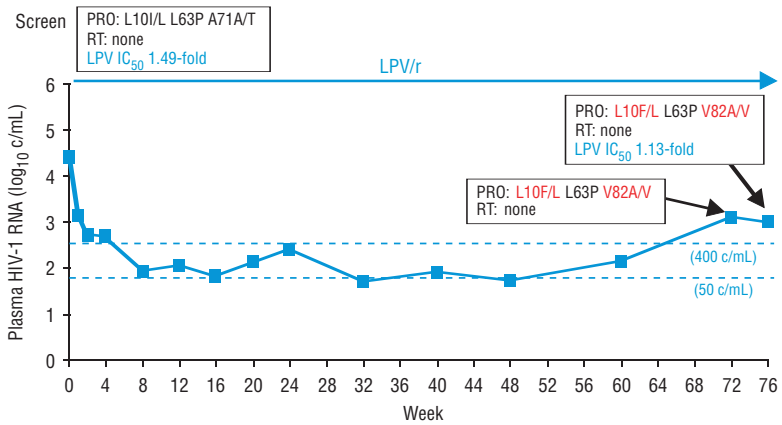
Subject 311 (LPV/r Monotherapy Arm)

Screening sample from Subject 311 showed wild-type RT, and protease L10I/L, L63P and A71A/T (secondary PI resistance mutations frequently noted as natural polymorphisms in wild-type HIV-1). Plasma HIV-1 RNA was 25,000 copies/mL at Baseline and dropped to <400 copies/mL by Week 8. However, with the exception of Week 32 when plasma HIV-1 RNA was undetectable (<50 copies/mL), subject remained with low-level viremia (50–400 copies/mL) until Week 72 when plasma HIV-1 RNA was 1,160 copies/mL.

Drug resistance testing at Week 72 showed the following:

- Genotype:
  - RT with no resistance mutations
  - Protease L10F/L and V82A/V, with persistence of L63P from Baseline
- Phenotype:
  - LPV IC_{50} 1.13-fold the reference wild-type HIV-1

Figure 3. Development of Resistance in Subject 311 (LPV/r Monotherapy Arm)



Subject 903 (LPV/r Monotherapy Arm)

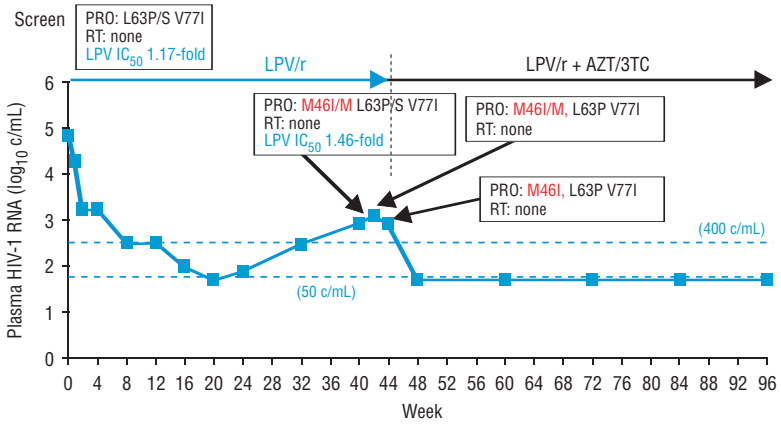
Screening sample from Subject 903 showed wild-type RT, and protease L63P/S and V77I (secondary PI resistance mutations frequently noted as natural polymorphisms in wild-type HIV-1). Plasma HIV-1 RNA was 66,400 copies/mL at Baseline and dropped to <50 copies/mL by Week 20. However, the subject subsequently was viremic with plasma HIV-1 RNA of 70, 281, 809, 1170 and 789 copies/mL at Weeks 24, 32, 40, 42 and 44, respectively.

Drug resistance testing at Week 40 showed the following:

- Genotype:
  - RT with no resistance mutations
  - Protease M46I/M, with persistence of L63P/S and V77I from Baseline
- Phenotype:
  - LPV IC_{50} 1.46-fold the reference wild-type HIV-1

Subject then added AZT/3TC to LPV/r with resuppression of plasma HIV-1 RNA to <50 copies/mL for the subsequent 48 weeks.

Figure 4. Development of Resistance in Subject 903 (LPV/r Monotherapy Arm)



Subject 5102 (LPV/r + ATZ/3TC Arm)

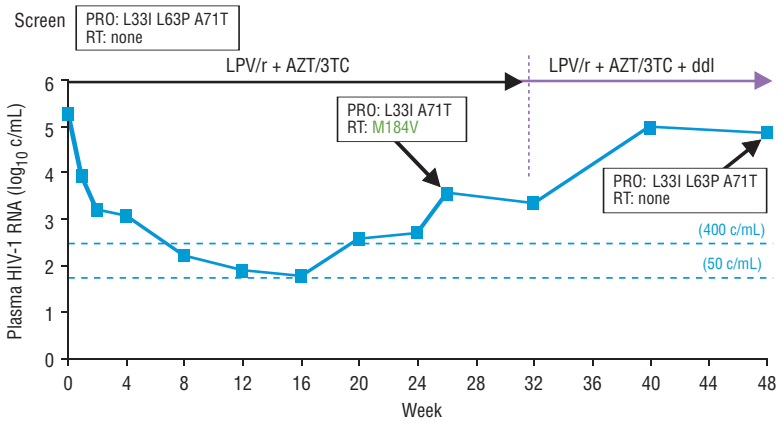
Screening sample from Subject 5102 showed wild-type RT, and protease L33I, L63P and A71T (secondary PI resistance mutations frequently noted as natural polymorphisms in wild-type HIV-1). Plasma HIV-1 RNA was 177,000 copies/mL at Baseline and dropped to a nadir of 57 copies/mL by Week 16. However, plasma HIV-1 RNA subsequently increased to 364, 482 and 3400 copies/mL at Weeks 20, 24 and 26, respectively.

Drug resistance testing at Week 26 showed the following:

- Genotype:
  - RT with M184V (3TC resistance mutation)
  - Protease with persistence of L33I and A71T from Baseline

At Week 32, plasma HIV-1 RNA was 2190 copies/mL and the subject changed antiretroviral regimen to LPV/r + AZT + didanosine. Subject remained persistently viremic through Week 48 when repeat drug resistance genotype showed RT and protease with no changes from the baseline genotype.

Figure 5. Development of Resistance in Subject 5102 (LPV/r + AZT/3TC Arm)



Conclusions

To date, 2 of 83 subjects starting LPV/r monotherapy and none of 53 subjects starting a LPV/r-based 3-drug regimen developed PI resistance mutations.

Although the incidence of development of PI resistance mutations with LPV/r monotherapy appears to be low, the barrier for the selection of PI resistance with LPV/r monotherapy may be lower than with LPV/r-based 3-drug regimens.

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