Lopinavir/ritonavir as single-drug therapy for maintenance of HIV-1 viral suppression. A randomized, controlled, open-label, pilot clinical trial

OK Study: 48 Weeks

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BACKGROUND

The concept of induction and maintenance therapy is attractive:

- Less exposure to potentially harmful drugs.
- Preserving future treatment options.
- Minimising both risk of side-effects and/or resistance.
- Fewer tablets to take, helping with compliance.
- Less expensive.

Three previous trials (ACTG 343, Trilege, ADAMS) performed

- Single or dual drug regimens associated with a very high risk of virological failure. Trials prematurely terminated.

Lopinavir/r is an appropriate candidate for single-drug HAART

- High potency.
- High genetic and pharmacological barriers to resistance.
- Extremely low risk of resistance in antiretroviral-naïve patients.
- Non-controlled experiences suggest a possible use of lopinavir/r as single-drug HAART (Pierone, Gathe).

OBJECTIVES

PRIMARY

- To determine the feasibility of maintaining virological control with lopinavir/ritonavir monotherapy in patients who have had undetectable viral load for 6 months.

SECONDARY

- Proportion of subjects with plasma HIV-RNA< 500 copies/mL at 6 and 12 months.
- Proportion of subjects with plasma HIV-RNA < 50 copies/mL at 6 and 12 months.
- Incidence of resistance to lopinavir/ritonavir.
- To determine the basis for sample size estimations for a subsequent comparative trial with appropriate statistical power.

PATIENTS AND METHODS

Design

- Investigator-initiated, randomized, open-label, multi-center, pilot study.
- 42 patients receiving lopinavir/r + 2 NRTIs (or 1 NRTI + TDF) were randomized 1:1 to continue or to stop the NRTIs (or 1 NRTI + TDF)

Main Inclusion Criteria

- Continuous antiretroviral treatment during at least the prior 6 months.
- Receiving lopinavir/r + 2 NRTIs (or 1 NRTI + TDF) ≥ 4 weeks.
- No history of virological failure while receiving a PI.
- Change of PIs for adverse events or other reasons is allowed if changes had been made while viral load was < 50 copies/mL
- HIV viral load < 50 copies/mL for at least 6 months prior to study entry.
- HBsAg negative.

Figure 1. **OK Study design**

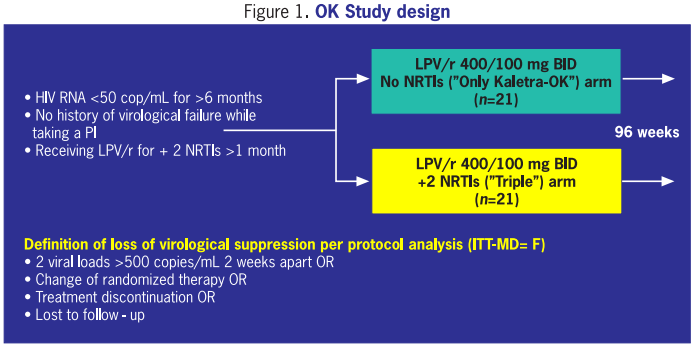


Table 1. **Demographics**

	OK	Triple*
N	21	21
Male	17 (81%)	18 (86%)
Age, median (range)	42 (25-54)	42 (31-48)
Risk factor		
IVDU	8 (38%)	6 (29%)
MSM	5 (24%)	8 (38%)
Heterosexual	8 (38%)	7 (33%)
CDC CIII	11 (52%)	7 (33%)
AIDS	15 (71%)	14 (67%)

*No statistical difference between arms.

Table 1.1. **Baseline characteristics: Disease**

	OK	Triple*
pre-HAART HIV-RNA		
Median (Log_{10} c/ml)	5.11	4.93
(IQR)	(4.7-5.5)	(4.5-5.6)
Months HIV-RNA <50 copies/mL prior to randomization		
Median	28.6	15.7
(IQR)	(11.3-44.9)	(8.6-27.5)
CD4 (cells/μL). Median (IQR)		
Baseline	662 (446-740)	585 (331-721)
Nadir	139 (53-248)	90 (29-261)
HCV co-infection	10 (48%)	10 (48%)

*No statistical difference between arms.

Table 1.2. **Baseline characteristics: Prior HAART**

	OK	Triple
Months on Lopinavir/r	13	13
Lopinavir/r 1st PI	7 (33%)	6 (29%)
Lopinavir/r 2nd PI	14 (67%)	10 (47%)
Lopinavir/r 3rd PI	0 (0)	5 (24%)
Other PIs prior to Lopinavir/r		
Nelfinavir	3 (14%)	7 (33%)
Indinavir	4 (19%)	9 (43%)
Ritonavir	5 (24%)	3 (14%)
Saquinavir/RTV	2 (10 %)	1 (5%)
NRTIs pre-randomization		
AZT-3TC	7 (33%)	9 (43%)
d4T-3TC	8 (38%)	6 (29%)
Others	6 (29%)	6 (29%)

Table 1.3. **Baseline characteristics: Fasting lipidids (Median, IQR)**

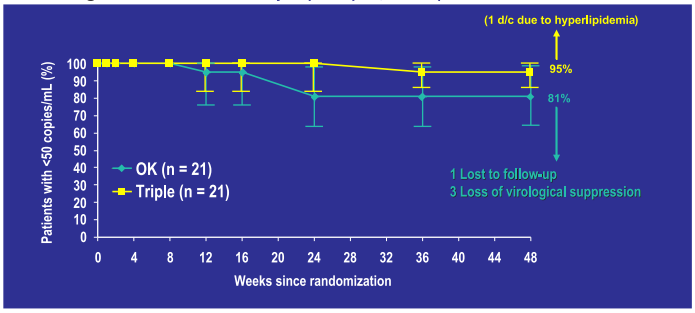
	OK	Triple
Total Cholesterol (mg/dL)	176 (131-211)	193 (173-236)
LDL Cholesterol (mg/dL)	84 (56-121)	104 (84-126)
HDL Cholesterol (mg/dL)	44 (31-53)	43 (37-49)
Triglycerides (mg/dL)	186 (121-244)	208 (160-310)

Table 2. **Patient disposition at Week 48**

	OK	Triple
N	21	21
Discontinuation (non-compliance)	1	0
Discontinuation due to adverse event	0	1*
Loss of virological suppression	3	0
Still on study at 48 weeks	20**	20

*Hyperlipidemia associated with multiple cardiovascular risk factors and despite treatment with a lipid-lowering drug. At week 24 his fasting Total Cholesterol was 282 mg/dL, LDL-Cholesterol 164 mg/dL and serum triglycerides 421 mg/dL
**3 patients with loss of virological suppression are still actively followed.

Figure 2. **HIV-RNA <50 copies/mL (ITT, MD=F) BY TREATMENT ARM**



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OK Sudy: 48 Weeks

Table 3. **BLIPS throughout the study (w48)**

Week	OK	Triple
1	0	0
2	1 (202 c/mL)	0
4	0	0
8	1 (61 c/mL)	0
12	0	0
16	0	0
24	0	0
36	1 (94 c/mL)	0
48	0	1 (1020 copies/mL)

- Blip = HIV RNA >50 copies/mL with subsequent sample < 50 copies/mL. Each blip corresponds to a different patient
- Maintenance failure per protocol = 2 viral loads >500 copies/mL 2 weeks apart or change of randomized therapy or treatment discontinuation or lost to follow-up.

Figure 3. **CD4 Cell count. Mean change from baseline**

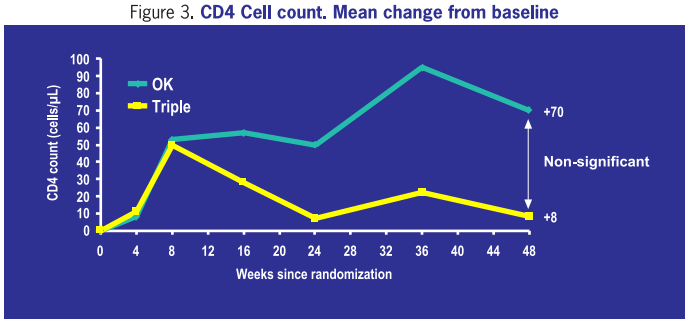


Figure 4.1. **Loss of virological suppression (OK arm, Patient DO-17)**

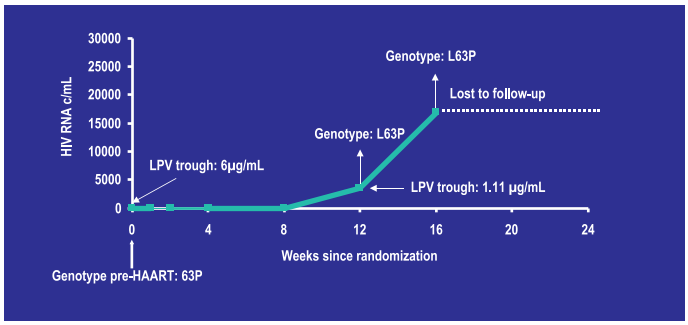
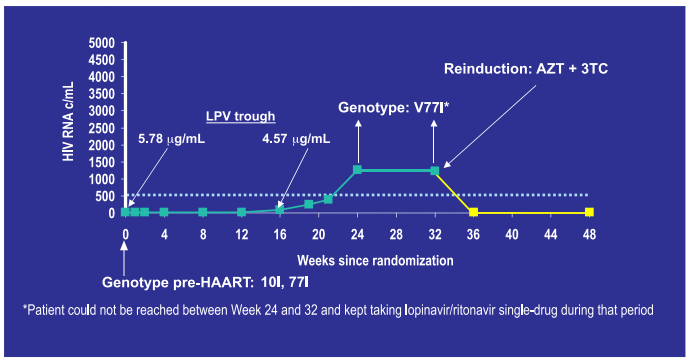


Figure 4.2. **Loss of virological suppression (OK arm, Patient DO-14)**



*Patient could not be reached between Week 24 and 32 and kept taking lopinavir/ritonavir single-drug during that period

Figure 4.3. **Loss of virological suppression (OK arm, Patient LP-12)**

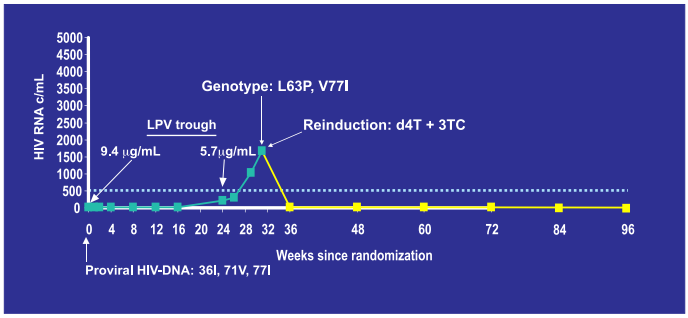


Figure 4.4. **Loss of virological suppression (OK arm, Patient DO-10)**

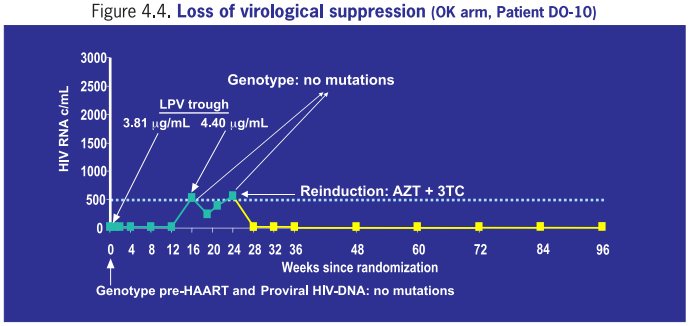


Tabla 4. **Mean change in fasting serum lipids at w48 (mg/dL)**

	OK	Triple	p
Total Cholesterol	+17	+7	NS
LDL-Cholesterol	+18	+11	NS
HDL-Cholesterol	+2	-3	NS
Triglycerides	-3	-6	NS

NOTE: Baseline values were not significantly different between arms (See Table 1.3)

CONCLUSIONS

- A large proportion of patients (81%) simplified to lopinavir/ritonavir single-drug therapy remain virologically supressed after 48 weeks of follow-up, which is in clear contrast to previous trials of induction-maintenance strategies.
- Preliminary data show that failure of lopinavir/ritonavir single-drug HAART is not associated with the development of primary resistance mutations.
- Patients with maintenance failure on lopinavir/ritonavir single-drug HAART in our study could be succesfully resuppressed by adding NRTIs back into the regimen.
- A larger clinical trial (200 patients) with a design similar to this OK pilot trial finished enrollment in July/2005. (ClinicalTrials.gov Identifier: NCT00114933)

ACKNOWLEDGMENTS

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