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Single-drug HAART (Lopinavir/r) for maintenance of HIV viral supression

Week 24 results of a randomized, open-label, pilot clinical trial

Only Kaletra Study (OK)

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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 risk of side-effects 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 feasability 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 <400 copies/mL at 6 and 12 months.
- Proportion of subjects with plasma HIV <50 copies/mL at 6 and 12 months.
- Incidence of resistance to lopinavir/ritonavir.
- Impact on lipid values (WePeB5925. Hall 3-Track B).
- To determine sample size estimations for a subsequent comparative trial with appropriate power.

Patients and Methods

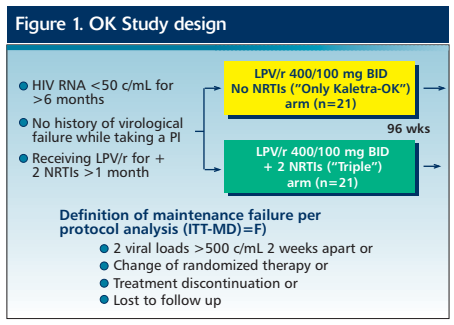
Design

- 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 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.

Figure 1. OK Study design



Results

Table 1a. Demographics

	OK	Triple*
N	21	21
Male	17 (81%)	18 (86%)
Age, mean (range)	42 (25-54)	42 (31-48)
Risk factor (%)		
IVDU	8 (38%)	6 (29%)
MSM	5 (24%)	8 (38%)
Heterosexual	9 (43%)	7 (33%)
CDC CIII	11 (52%)	7 (33%)
AIDS	12 (57%)	6 (29%)

*No statistical difference between arms.

Table 1b. Disease baseline characteristics

	OK	Triple*
HIV-RNA (log_{10} c/mL) pre-HAART		
Median	5.11	4.93
(IQR)	(4.7-5.5)	(4.5-5.6)
Months HIV-RNA <50 c/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 1c. Baseline characteristics: Prior HAART

	OK	Triple
Months on Lopinavir/r	13	13
Lopinavir/r 1st PI	6 (29%)	6 (29%)
Lopinavir/r 2nd PI	13 (62%)	10 (48%)
Lopinavir/r 3rd PI	2 (9.5%)	5 (24%)
Other PIs prior to Lopinavir/r		
Nelfinavir	3 (14%)	6 (29%)
Indinavir	4 (19%)	9 (43%)
Ritonavir	6 (29%)	3 (14%)
Saquinavir/r	2 (9.5%)	
NRTIs pre-randomization		
AZT-3TC	7 (33%)	9 (43%)
d4T-3TC	8 (38%)	6 (29%)
Others	6 (29%)	6 (29%)

Table 2. Patient disposition. Week 24

	OK	Triple
N	21	21
Lost to follow-up	1	0
Maintenance failure per protocol	3	0
Discontinuation for adverse events	0	0
Still on study	20*	21

*Patients with maintenance failure are still actively followed.

Figure 2. HIV-RNA <50 copies/mL (ITT, MD=F) by treatment arm

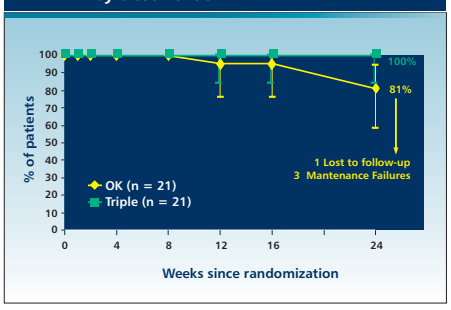


Table 3. BLIPS

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	1 (94 c/mL)	0

Blip = HIV RNA >50 c/mL with subsequent sample <50 c/mL.
Maintenance failure per protocol = 2 viral loads >500 c/mL 2 weeks apart or change of randomized therapy or treatment discontinuation or lost to follow up.

Figure 3. CD4 Cell Count Mean (±SE) Change from Baseline

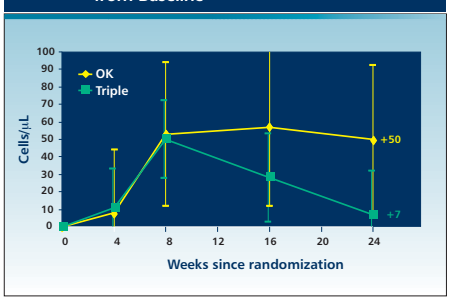


Figure 4. Hematocrit (mean)

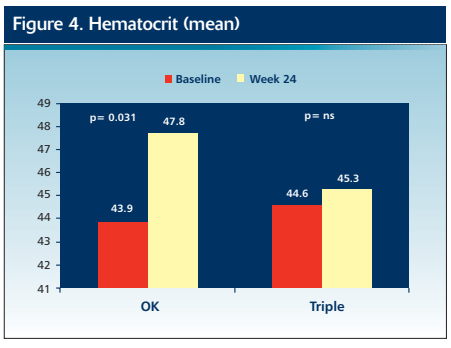


Figure 5. OK maintenance failures (Patient DO-17)

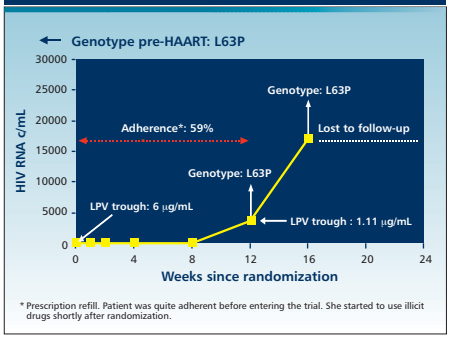


Figure 6. OK maintenance failures (Patient DO-10)

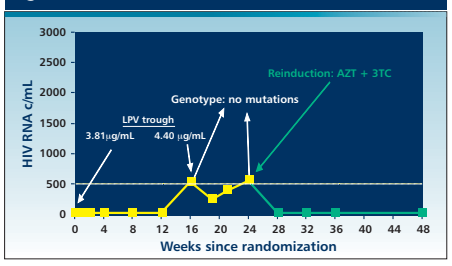


Figure 7. OK maintenance failures (Patient DO-14)

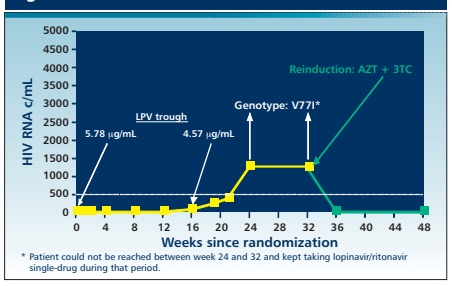


Figure 8. OK maintenance failures (Patient LP-12)

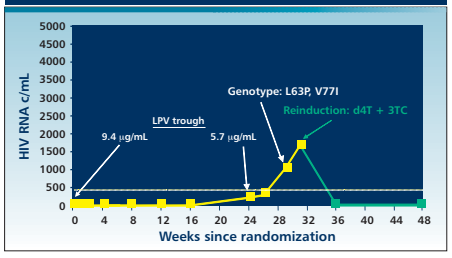
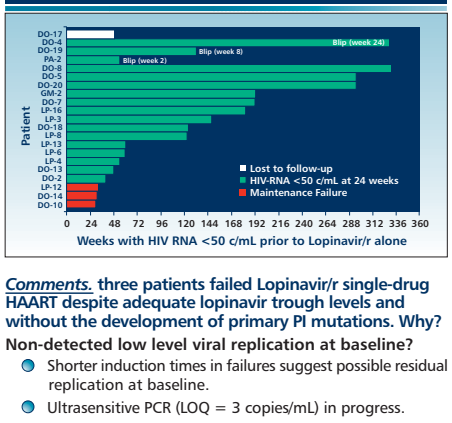


Table 4. Comparison of treatment factors in patients treated with Only Kaletra with and without protocol defined maintenance failure

	HIV-RNA <50 at week 24	Maintenance failures	p
N	17	3*	
AIDS, n (%)	10 (58)	2 (67)	ns
HIV-RNA pre-HAART. Mean (range)	218,730 (500-500,000)	57,357 (53,776-60,938)	ns
Days HIV-RNA <50 c/mL prior to LPV/r alone. Mean (range)	1,095 (277-2,316)	218 (208-229)	0.002
CD4 cells/μL. Mean (range)			
Baseline	658 (196-1037)	437 (293-722)	ns
Nadir	158 (6-416)	43 (8-62)	ns
4 weeks increase	9 (-198 +258)	127 (86-208)	ns
Total months on lopinavir/r prior to			
Lopinavir/r alone. Mean (range)	17 (2.6-48)	17.3 (10.8-27.9)	ns
Lopinavir/r 1st PI, n (%)	4 (23.5)	2 (67)	ns

Pt DO-17 (lost to follow-up, poor adherence) excluded from the analysis

Figure 9. Maintenance outcome (Only Kaletra arm) according to time with virological supression prior to randomization



Comments. **three patients failed Lopinavir/r single-drug HAART despite adequate lopinavir trough levels and without the development of primary PI mutations. Why?**

Non-detected low level viral replication at baseline?

- Shorter induction times in failures suggest possible residual replication at baseline.
- Ultrasensitive PCR (LOQ = 3 copies/mL) in progress.

Minority populations of HIV-resistant virus?

- Single genome sequencing in progress, but rebound in viral load would likely have been accompanied by resistant virus as the majority species if resistance were the primary cause of failure.
- Active follow-up of patients after reinduction in progress.

Host issues?

- Anatomically protected site in which PIs do not penetrate.
- Overexpression of cellular efflux pumps.

Other?

- Please send ideas to: jrarribas.hulp@salud.madrid.org & fpulido.hdoc@salud.madrid.org

Conclusions

- In contrast to previous trials of induction-maintenance strategies, a large proportion of patients (81%) simplified to lopinavir/ritonavir single-drug HAART remain virologically supressed after 24 weeks of follow up.
- Preliminary data show that failure of lopinavir/ritonavir single-drug HAART is not associated with the development of resistance mutations.
- Patients with maintenance failure on lopinavir/ritonavir single-drug HAART in our study could be safely reinduced with previous NRTIs.
- The OK Trial continues. Full 48 weeks results will be available by the end of July-04.

Aknowledgments

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