Lopinavir/ritonavir monotherapy *versus* lopinavir/ritonavir and two nucleosides for maintenance therapy of HIV. Ninety-six week results of a randomized, controlled, open-label clinical trial (OK04 Study).

Arribas JR, Pulido F, Delgado R, González-García J, Pérez-Elias MJ, Arranz A, Portilla J, Pasquau J, Iribarren JA, Rubio R, Ocampo A, Miralles P, Knobel H, Gaya F, Clotet B, Podzamcer D, for the OK04 Study Group

Oral Presentation at EACS2007 # PS3/1

OK04 trial design

- HIV-1 RNA < 50 c/mL for > 6 months
- No history of virological failure while taking a PI
- Receiving LPV/r for + 2 NRTIs > 1 month

LPV/r SGC 400/100 mg BID ("OK") (*n*=100)

LPV/r SGC 400/100 mg BID + 2 NRTIs ("Triple") (*n*=100)

Week 96

LPV/r Tablet ("OK") 400/100 mg BID

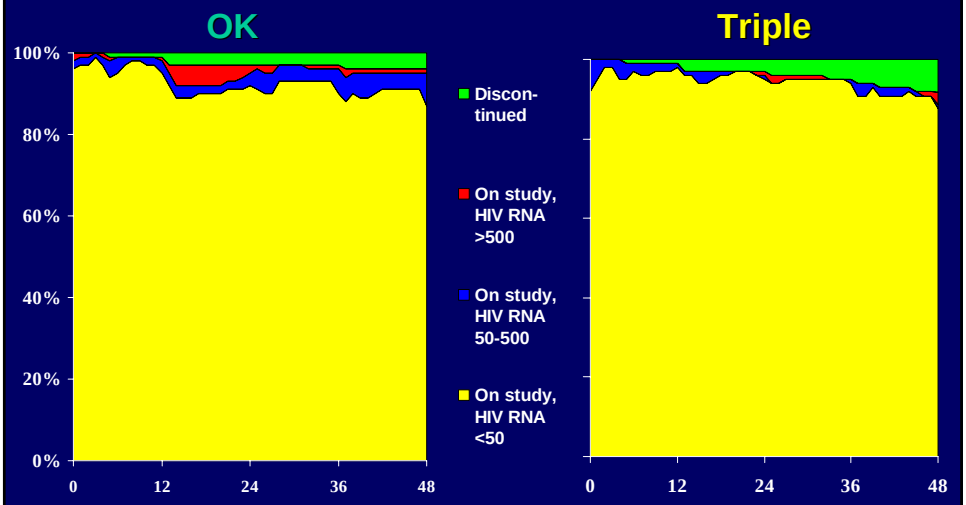
Visits: Screening, Baseline, Week 4 and 12, then every 12 weeks up to Week 96

Primary endpoint: Therapeutic failure at 48 weeks

- **2 viral loads > 500 c/mL 2 weeks apart* (without virological re-suppression after reinduction with NRTI in the OK arm)** OR
- Change of randomized therapy for reasons different from re-induction OR
- Treatment discontinuation OR
- Lost to follow-up

* OR decrease in HIV-1 RNA < 1 log 4 weeks after intensification OR failure to reach HIV-1 RNA < 50 c/mL 16 weeks after intensification

Point prevalence of discontinuations and virologic response through 48 weeks



Arribas JR. *et al., XVI IAC*, Toronto, 2006, # THLB0203

Protocol Amendment

- Based on the first year results, protocol was amended to allow intensification with nucleosides if patients developed HIV-1 RNA > 50 but < 500 copies/mL that was confirmed in three other samples within the following 8 weeks

Arribas JR. *et al*., *11th EACS,* Madrid, 2007, # PS3/1

OK04 trial design

- **Primary endpoint**
  Proportion of patients without therapeutic failure at 48 weeks
- **Secondary endpoint**
  Proportion of patients with undetectable viral load at 96 weeks
- **Study power**
  With 100 patients per arm, study has an 80% power to show the non-inferiority of the OK arm, assuming:
  - 10% therapeutic failure rate at 48 weeks in both arms
  - Non-inferiority would be demonstrated if the upper limit of the 95% CI of the difference in percent of patients without therapeutic failure (Triple – OK) is < 12%
- **Randomization stratification**
  - Nadir CD4 cell count (> or < 200 cells/μL)
  - Months with HIV-1 RNA < 50 c/mL prior to randomization (> or < 9 months)

Patient demographics and baseline characteristics

	OK	Triple
N	**103**	**102**
Male	**79 (78%)**	**84 (82%)**
Age, median (range)	**41 (28-78)**	**42 (26-65)**
HCV Ab+	**47 (46%)**	**52 (51%)**
AIDS Diagnosis	**46 (45%)**	**45 (44%)**
HIV-1 RNA (log_{10}c/mL) pre-HAART		
Median (IQR)	**5.1 (4.5-5.5)**	**5.2 (4.7-5.6)**
Months with HIV-1 RNA < 50 c/mL prior to randomization		
Median (IQR)	**19 (11-31)**	**17 (11-28)**
< 9 months, n (%)	**14 (14%)**	**16 (16%)**
CD4 (cells/μL) Median (IQR)		
Baseline	**474 (340-660)**	**473 (307-673)**
Nadir	**107 (28-216)**	**103 (32-214)**
Nadir < 200 cells/μL	**72 (70%)**	**74 (72%)**

Baseline characteristics: Prior HAART

	OK	Triple
Months on Lopinavir/r	26	25
Lopinavir/r 1st PI	59 (58%)	63 (62%)
2nd PI	35 (34%)	29 (29%)
3rd PI	7 (7%)	8 (8%)
4th PI	1 (1%)	1 (1%)
Other PIs prior to Lopinavir/r		
Nelfinavir	15 (15%)	9 (9%)
Indinavir	26 (25.5%)	23 (23%)
Ritonavir	6 (6%)	11 (11%)
Saquinavir	5 (5%)	5 (5%)
NRTIs pre-randomization		
AZT-3TC	31 (30%)	27 (27%)
d4T-3TC	20 (20%)	12 (12%)

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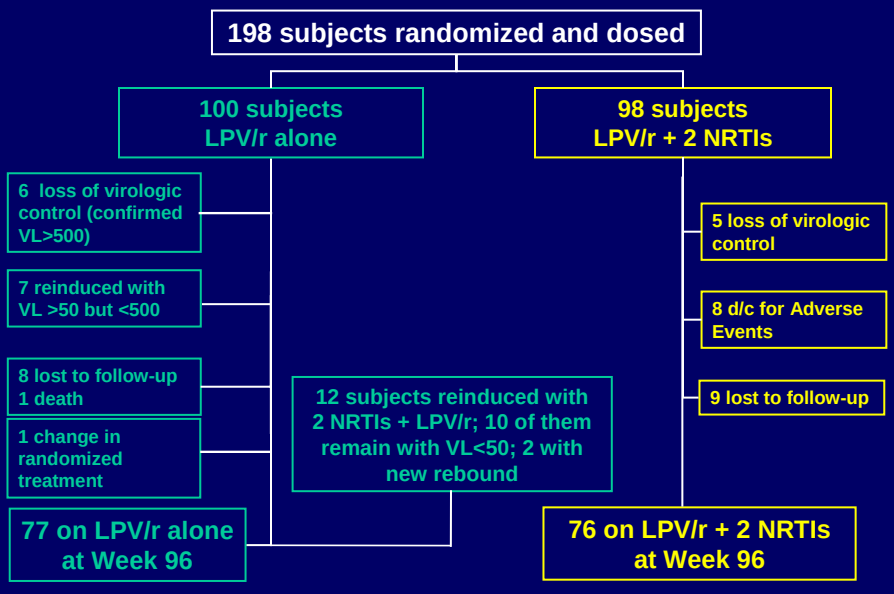
Subject disposition



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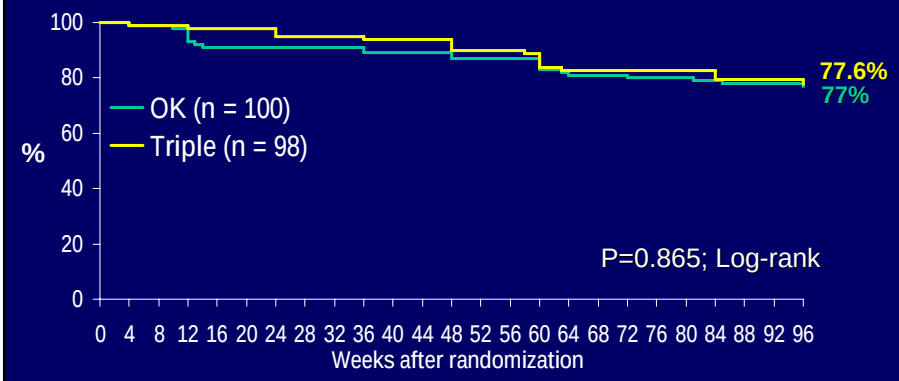
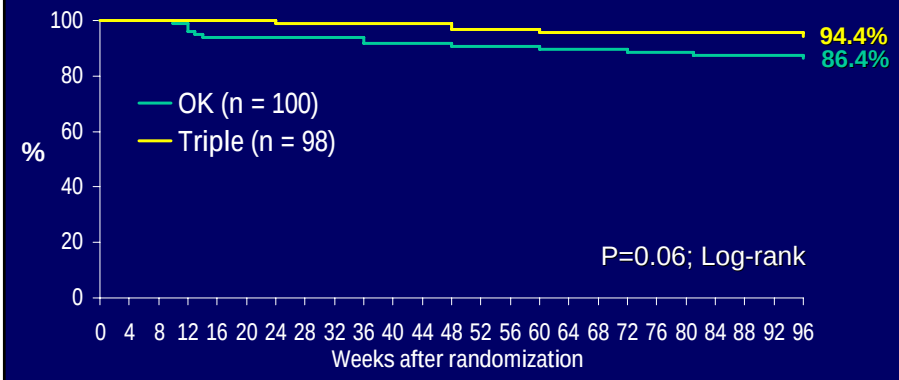
Time to HIV-1 RNA > 50 copies/mL
(ITT M = F, Reinduction = F)*



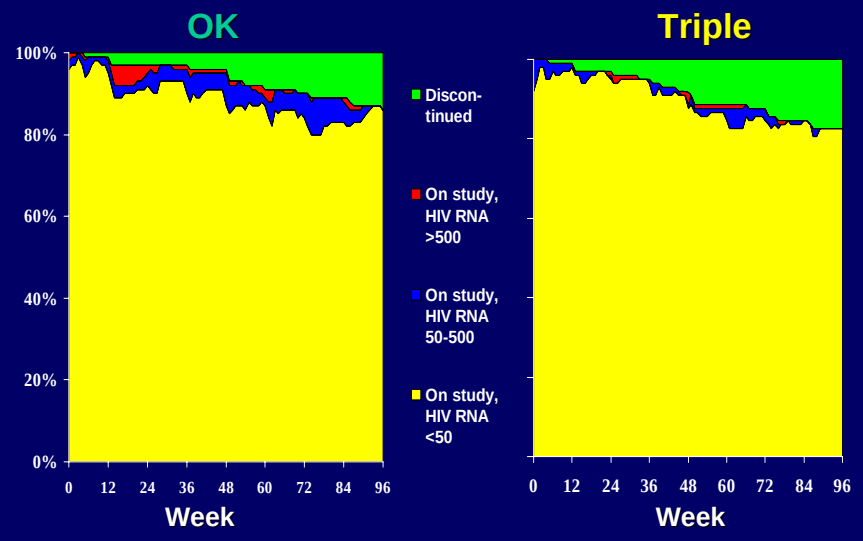
*** Patients in the monotherapy arm who reached and maintained < 50 c/mL after resuming baseline nucleosides are considered as failures (n = 10)**

Time to HIV-1 RNA > 50 copies/mL
(OT, Reinduction = F, Missing or Change in Therapy = Censored)*



*** Patients in the monotherapy arm who reached and maintained < 50 c/mL after resuming baseline nucleosides are considered as failures (n = 10)**

Point prevalence of discontinuations and virologic response through 96 weeks



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Reinductions (Monotherapy Group)

N (%)	Week		
	0-48	48-96	Total
Reinduced (> 500 c/mL)	5 (5)	0 (0)	5 (5)
Reinduced (> 50 & < 500 c/mL)	1 (1)	6 (6)	7 (7)
Not Reinduced	89 (89)	77 (77)	77 (77)

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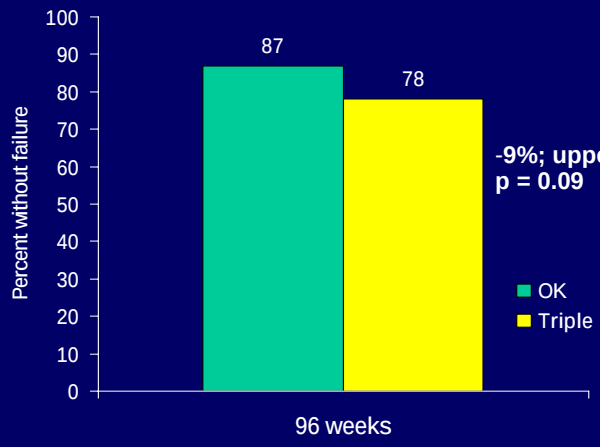
OK04

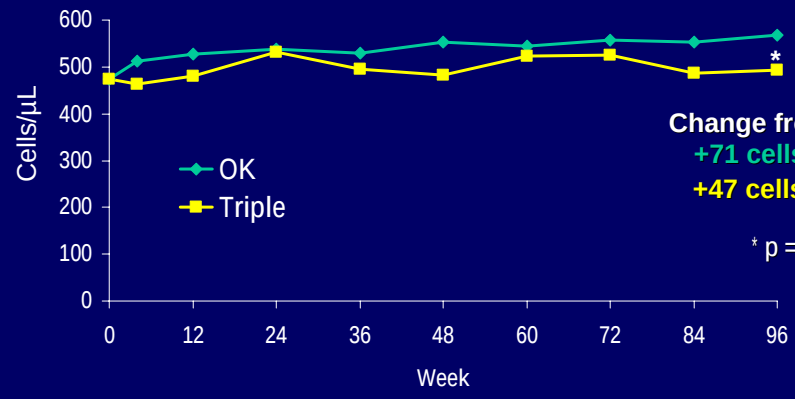
Proportion without therapeutic failure at Week 96*



-9%; upper-limit 95%CI: 1.2%.
p = 0.09

*** Patients in the monotherapy arm who reached and maintained < 50 c/mL after resuming baseline nucleosides are not considered as failures (n = 10)**

Median CD4 count values through 96 weeks



Change from BL
+71 cells/µL
+47 cells/µL

* p = NS

Adverse events leading to treatment discontinuation

Adverse Event	OK (n = 100)	Triple (n = 98)
Any	0	8 (8%)**
Diarrhea		2 (2 %)
Insomnia		1 (1%)
Severe lipoatrophy*		4 (4%)
Polyneuropathy		1 (1%)
Renal failure with hyperphosphaturia		1 (1%)

***Investigator-defined**
**** p = 0.003**

Adverse events leading to treatment discontinuation: Nucleosides combinations

Adverse event	Nucleosides
Diarrhea (2)	D4T+3TC, D4T+ABC
Insomnia	AZT+3TC
Severe lipoatrophy (4)	D4T+DDI, DDI+TDF (3)
Polyneuropathy (1)	DDI+3TC
Renal failure with hyperphosphaturia (1)	DDI+TDF

Genotypic testing through Week 96

	OK (n = 100)	Triple (n = 98)
Genotyping Population*	16 (16%)	4 (4%)
Number of samples	29	9
Patients with isolates with major PI mutations	2 (2%) [10F, 46I, 82A/V] [54V, 77I, 82A]	2 (2%) [54V, 63P, 71V, 82A] [**]

*** All patients with HIV-1 RNA > 500 copies/mL analyzed (blips > 500 copies/mL included)**
**** Genotypic/phylogenetic analysis ongoing to rule out super-infection**

Conclusions

- By intent-to-treat analysis, similar proportion of patients remain suppressed (< 50 copies/mL) at 96 weeks
  - In the monotherapy group, main cause for change in randomized therapy was low-level viremia. The majority of these patients resuppressed after restarting nucleosides
  - In the triple therapy group, adverse events leading to discontinuation were a more frequent cause of treatment failure
- This study supports the long-term efficacy and safety of LPV/r monotherapy with reinduction as needed for maintenance of HIV suppression

Arribas JR. *et al*., *11th EACS,* Madrid, 2007, # PS3/1 **OK04**

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