Risk factors for loss of virological suppression at 48 weeks in patients receiving lopinavir/ritonavir monotherapy in the OK clinical trial.

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BACKGROUND

- The OK Study is a randomized, controlled, open label, 42 patients-pilot clinical trial of lopinavir/ritonavir (LPV/r) monotherapy (MT) for maintenance of HIV viral suppression.
- Patients were eligible for the trial if they had no history of virological failure while receiving a protease inhibitor, were receiving 2 NRTIs + LPV/r and had serum HIV RNA <50 copies/mL for >6 months prior to randomization.
- (See poster WePe12.3C05 for complete details).
- During the first year of follow-up, 4 patients in the monotherapy arm did not maintain virological suppression, including one patient lost to follow-up.
- Genotypic resistance to lopinavir/ritonavir was not found as none of these patients presented primary genotypic mutations in the protease gene (See poster WePe12.3C05 for further details).
- In addition, the persistent residual viremia level (replication below 50 copies/mL) between virologic failures and non-failures was not different at baseline (See oral presentation WeOa0203).

OBJECTIVE

- The aim of this exploratory sub-analysis was to identify potential risk factors for maintenance failure in patients receiving lopinavir/ritonavir monotherapy (LPV/r MT) after more than six months with virological suppression (HIV-RNA < 50 copies/mL).

PATIENTS AND METHODS

We compared the following risk factors for loss of virological suppression at 48 weeks in the 21 patients randomized to MT with LPV/r:

- AIDS diagnosis,
- Pre-HAART HIV RNA (copies/mL),
- CD4 (cells/ìL), baseline and nadir,
- Time with HIV RNA < 50 copies/mL prior to MT,
- Time on LPV/r prior to MT,
- Use of LPV/r as first protease inhibitor,
- Adherence by drug refill score [(number of total days of antiretroviral dispensation / number of total days until next dispensation) x 100].
- Adherence by self-report using the GEEMA adherence questionnaire.

METHODS: GEEMA adherence questionnaire

- **The GEEMA adherence questionnaire (AIDS.2002;16:605) has 6 individual questions:**

1. Do you ever forget to take your medicine?
2. Are you careless at times about taking your medicine?
3. Sometimes if you feel worse, do you stop taking your medicines?
4. Thinking about the last week: How often have you not taken your medicine?
5. Did you not take any of your medicine over the past weekend?
6. Over the past 3 months, how many days have you not taken any medicine at all?

- **In this questionnaire, we quantified responses to the questions number 4 and 6.**
- **In addition, we classified patients as adherent or non-adherent when there was a positive response to any of the four qualitative questions included in the questionnaire.**

RESULTS (1)

Patients with loss of virological suppression had:

- significantly shorter time with HIV RNA < 50 copies/mL before starting LPV/r MT(Table 1) and
- significantly lower adherence as measured by the GEEMA questionnaire (Table 2)

3 out of 4 patients who lost virological suppression had adherence rates (by drug refill scores) that could justify the outcome (59%, 60%, 79%).

There were non-signficant differences in the rest of characteristics studied (Tables 1 and 2).

RESULTS (2)

- **Only 1 out 10 patients with drug refill scores between 70 and 95% lost virological suppression (drug refill score = 79%) Table 2, Figure 2.**
- **In one patient, loss of virological suppression was observed despite good adherence (drug refill score = 100%, Figure 4), suggesting that other unusual mechanism for failure might be implicated.**
- **No genotypic mutations were found and HIV RNA remains supressed 72 weeks after re-introducting the same NRTIs that had been used before the start of the study.**

Table 1. **Comparison of therapy factors in patients treated with LPV/r-MT**

	Suppression maintained N=17	Suppression lost N=4	p
AIDS, n (%)	7 (41)	2 (50)	ns
Intravenous drug users, n (%)	5 (29%)	3 (75%)	0.25
Pre-HAART HIV RNA, c/mL, mean (range)	218,730 (500-500,000)	47,384 (27,438-60,938)	0.13
Weeks with HIV RNA < 50 c/mL prior-MT, median (range)	132 (40-331)	40 (30-84)	0.02
CD4, cells/L, mean (range)			
Baseline	658 (196-1037)	437 (293-722)	ns
Nadir	158 (6-416)	95 (8-252)	ns
Months with LPV/r before MT, mean (range)	17 (2.6-48)	16 (10.8-27.9)	ns
Lopinavir/r as 1st PI , n (%)	4 (23.5)	2 (50)	ns

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Table 2. **Comparison of therapy factors in patients treated with LPV/r-MT**

	Suppression maintained N=17		Suppression lost N=4		p
Adherence % by drug-refill score, median (range)	94	(71-100)	70	(59-100)	0.14
"Adherent" patients*, n (%)	7	(41)	0	(0)	0.25
Total days without medication* median (range)	0	(0-31)	3	(1-65)	0.008
Total missed doses in week prior to the study visit*, median (range)	0	(0-4)	3	(2-10)	0.013

* Data based on GEEMA adherence questionnaire

Figure 1. **Loss of virological suppression** (OK arm, Patient DO-17)

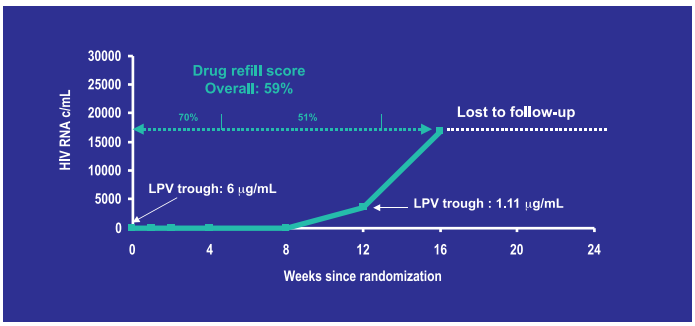
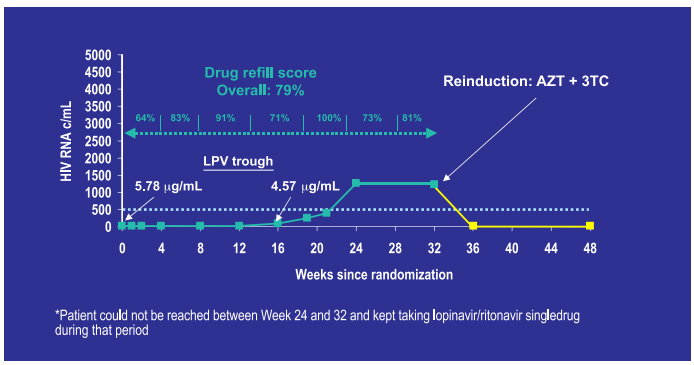


Figure 2. **Loss of virological suppression** (OK arm, Patient DO-14)



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

Figure 3. **Loss of virological suppression** (OK arm, Patient LP-12)

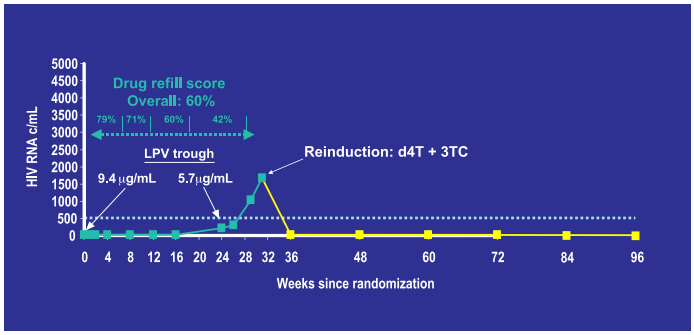
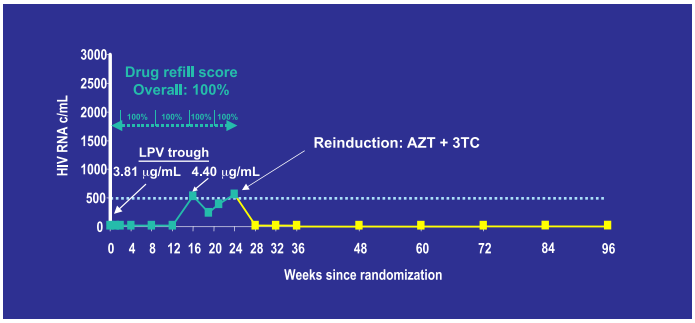


Figure 4. **Loss of virological suppression** (OK arm, Patient DO-10)



CONCLUSIONS

- Suboptimal adherence and a short time with undetectable viral load (<50 copies/mL) before MT (probably also a proxy for suboptimal adherence) appear to be the main risk factors for losing virological suppression in patients randomised to MT with LPV/r.
- Although suboptimal adherence seems to facilitate loss of virological suppression while receiving LPV/r MT, it should be noted that perfect adherence does not appear to be an absolute requirement for success of of LPV/r monotherapy. Actually, half of the patients who did not lose virological suppression had drug refill scores of 70-94%.

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