Unexpectedly high failure rate in LPV/r monotherapy arm, involving CNS, and association with low nadir CD4 count in the MOST study

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BACKGROUND

Strategies to simplify HIV treatment were motivated by concerns about side effects of nucleoside analogues, such as lipodystrophy, mitochondrial toxicity, as well as renal and cardiovascular complications.
The results of the SMART study argue against treatment interruption[1]. However, little effort has been conducted so far to test the hypothesis that under optimal viral suppression less active drugs might be required to prevent the occurrence of resistance. Treatment simplification using mono-maintenance is a potential method to reduce toxicity while maintaining full viral suppression.
Previous monotherapy maintenance using boosted protease inhibitors have demonstrated continued viral load (VL) suppression for more than one year[2]. Although previous studies have shown that monotherapy might result in insufficient VL suppression in a subset of patients, the risk factors for mono-maintenance failure are not well described. In addition, concerns remain regarding compartmental HIV replication due to limited drug penetration into the central nervous system and the genital tract.
We therefore conducted a randomized controlled study to evaluate the activity of monotherapy in the central nervous system and in the genital tract.

OBJECTIVES

This study evaluated ritonavir-boosted Lopinavir (LPV/r) mono-maintenance with respect to:

- The ability of LPV/r to suppress viral replication in CNS and genital compartments
- Safety and efficacy of monotherapy
- Identification of predictors of mono-maintenance failure

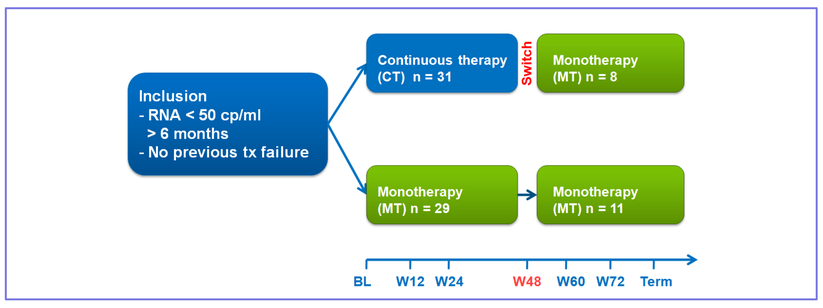
METHODS and STUDY DESIGN

- Randomized controlled open label trial comparing LPV/r monotherapy (MT) with continuation of triple therapy (CT) for 48 weeks, followed by
- An additional observation period of 48 weeks with all patients. At week 48, patients in the CT arm had the option to switch to monotherapy (delayed-switch group, DS) **Figure 1**.
- Patients were included from the participating SHCS sites (Zurich, St. Gallen, Berne, Lausanne and Geneva).
- Primary endpoint was treatment failure in the compartment CSF and / or genital tract.
- HIV RNA in blood was measured at week 6/12/18/24/32/40/48/54/60/66/72/80/88 and 96 at the local laboratory. All confirmation tests in cases of HIV-RNA failure were performed in one central laboratory.
- At baseline, week 48 and termination of the study, CSF and genital secretion were collected and DEXA scans as well as neuropsychological tests were performed.

Definition of failure, analysis plan and sample size calculation

- Treatment failure in blood was defined as two consecutive HIV RNA detections > 400 cp/ml.
- Treatment failure in CSF and genital compartment was defined as an HIV RNA level one log above the respective value at baseline.
- The study was powered to detect a difference of 12% failures in CSF.
- Premature study termination was mandated by a predefined stopping rule, i.e. when more than 6 patients (20%) of the first 30 patients on MT fail.
- For the analysis of risk factors for MT failure patients who switched from CT arm to MT arm at week 48 were combined with the immediate MT arm group.

Figure 1: Study design and patient allocation



RESULTS

The per protocol defined analysis of the primary endpoint (compartment failure) could not be performed due to the premature termination of the study according to the predefined stopping criteria.
On September 24, 2008 the protocol committee decided to stop the trial when 6 patients under MT demonstrated a viral failure in blood as opposed to none of the CT patients. At this time, 60 patients were included, 29 randomized to MT.

Baseline characteristics, patient disposition and follow up:

- Among 19 patients in the CT arm reaching wk 48, eight switched to MT
- Median follow up 48 weeks (MT: 43 wk, CT: 43 wk, DS: 19 wk)
- Baseline characteristics: similar in both arms **Table 1**

Description of failing patients

- See key characteristics of the six failing patients in **Table 2**
- No failure was observed in the CT arm.
- All failures in patients under MT occurred within the first 24 weeks of failure.
- All failures had a CD 4 nadir of < 200/µl.
- Failure of LPV/r monotherapy was significantly associated with low nadir CD 4 ($p < 0.01$) **Figure 2**.
- All 5 blood failures who were tested for HIV RNA in CSF had higher HIV RNA counts in CSF than in blood (mean difference 0.8 $\log_{10}$ cp/ml).

Analysis of risk factors of mono-maintenance failure

- All patients included in the analysis had at least 6 weeks of MT (MT and DS Group).
- Only nadir CD4 count was a predictor of treatment failure (Cox-regression).
- The following parameters were not associated with failure: Age, gender, pre-treatment, CDC classification, RNA setpoint, HCV Co-infection, length of therapy until baseline, Hb, platelets, CD4 at baseline.

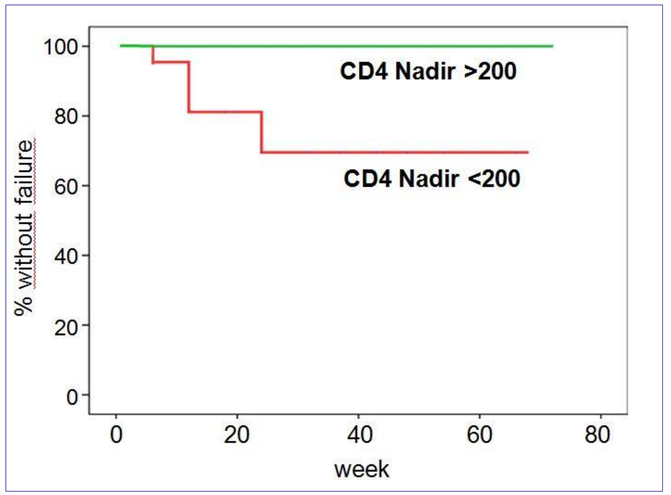
HIV RNA in CSF and genital compartment

- CSF analysis in patients consenting to additional lumbar punctures after baseline was performed in 54 patients at termination visit and in 32 patients at week 48, respectively.
- Results of compartment testing in the genital tract are pending.
- With the exception of one patient (CSF HIV RNA 82 cp/ml, randomized to CT) all patients had undetectable HIV RNA in CSF at baseline.

Isolated CSF failure:

- At study termination, 3 patients had increased CSF VL while blood VL was < 400cp/ml **Table 3**.
- All isolated CSF failures had detectable HIV RNA in blood, but <400cp/ml.
- All detectable viral isolates were wildtype in CSF and blood.
- CSF VL was more than 1log above blood VL in the three isolated CSF failure cases.
- Cases with isolated CSF failures were not associated with low nadir CD4 count.

Fig 2: Kaplan Meier Analysis of failure by nadir CD4



Tab. 1 **Baseline Characteristics**

		CT n = 31	MT n = 29
Pretreatment (%)	PI	74	73
	NNRTI	23	24
	Triple N	3	3
CD 4 Nadir	absolute	160	160
	%	12	12
CD 4 Baseline	absolute	517	519
	%	28	29
Gender (%)	female	23	34
	male	77	66
Age (years)		44	44
HIV RNA setpoint (log)		4.8	4.8
Follow up (weeks)		48	48
Length of therapy until baseline (years)		3.9	3.9

Tab 2: Characteristics of the six failing patients

ID	Weeks on MT	Pre-Study Therapy	VL Blood	VL CSF	CD4 Nadir (abs.)	CD4 Nadir (%)	LPV/r ng/ml (percentile)
101	12	ATV/r + 2N	4.3 log	5.1 log	57	13	87 (<1)
108	12	LPV/r + 2N	2.7 log	3.1 log	5	1	6777 (50)
126	12	LPV/r + 2N	4.1 log	5.0 log	149	26	6388 (25-50)
302	24	EFV + 2N	3.0 log	4.1 log	7	3	6438 (50)
303	6	LPV/r + 2N	5.0 log	Refused	54	2	4661 (25)
713	24	EFV + 2N	3.0 log	3.7 log	160	5	< LoD

Tab 3: Parameters at the time of virological failure in CSF only

ID	Weeks on MT	Pre-Study Therapy	VL Blood	VL CSF	CD4 Nadir (abs.)	CD4 Nadir (%)	LPV/r ng/ml (percentile)
703	18	ATV/r + 2N	2.2 log	3.4 log	370	17	pending
704	60	LPV/r + 2N	2.3 log	4.3 log	100	12	pending
707	20	EFV + 2N	2.1 log	3.4 log	130	10	pending

DISCUSSION

- Suboptimal HIV RNA suppression in CSF is a relevant concern in HIV monotherapy with ritonavir boosted lopinavir or atazanavir (PI/r)[3].
- There is some indication that low activity of monotherapy in CSF is also associated with decreased antiviral activity in blood.
- As shown in previous studies of monotherapy, failure of monotherapy - if detected early - is not associated with overt drug resistance and intensification with the previous treatment regimen results in complete VL suppression [4].
- Patients under monotherapy should be monitored carefully by HIV RNA in blood, at least during the first year of therapy.
- The safety of PI/r monotherapy in terms of compartment activity has not yet been established and careful monitoring of CSF should be considered.
- PI/r monotherapy should probably not be initiated in patients who experienced a nadir CD 4 count below 200/µl.

CONCLUSION

- Monotherapy failure appears to occur in the first 6 months after switch to mono-maintenance.
- No development of drug resistance was detected in patients failing monotherapy.
- LPV/r monotherapy results in suboptimal HIV RNA suppression in the CSF compartment in approx. 10% of cases.
- A high failure rate of monotherapy was associated with low nadir CD 4 count.

References:

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