

**Prospective trial to evaluate how
Therapeutic Drug Monitoring of protease
inhibitors increases virologic success
and tolerance of HAART
(COPHAR 2 – ANRS 111 trial)**

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Background

Due to the pharmacokinetic inter- and intra-variability of protease inhibitors (PI), Therapeutic Drug Monitoring (TDM) of PI has been proposed to improve the antiviral efficacy and tolerance of PI-containing HAART.

Objective

To evaluate the feasibility and the impact of an early Therapeutic Drug Monitoring in PI-naive HIV-1 infected patients in order to warrant virological success and safety of HAART.

Methods

- Open, non-comparative, multicenter, prospective trial
- PATIENTS
 - PI-naive HIV-1 infected patients
 - Initiating HAART containing one of the following PI:
 - indinavir (IDV) (400 to 800 mg bid) boosted by low-dose ritonavir (RTV) (100 mg bid)
 - lopinavir/ritonavir (LPV/RTV) (400/100 bid)
 - nelfinavir (NFV, new 625 mg formulation) (1250 mg bid)
- THERAPEUTIC DRUG MONITORING
 - Determinations of trough plasma concentrations (12 ± 2 h after the last drug intake) using HPLC assays at Week 2 (W2), W8 or W16, W24 and W48,
 - Interpretation and intervention according to predefined algorithms available for each PI dose adjustment,
 - Adjustment of PI doses once or more during the first 24 w if trough plasma concentrations out of the adequate predefined range (150-550, 2500-7000, 1500-5500 ng/ml for IDV, LPV and NFV, respectively).

- Adjustments made by increments of one pill bid: 200, 133/33 or 250 mg for IDV, LPV/RTV or NFV, respectively.

- Even with the usual food recommendations provided at the initiation of the trial, the high rate of low NFV trough plasma concentrations led to amend the protocol and propose a RTV boost in pts with low concentrations

- PRIMARY END POINT :

- failure of the strategy defined by either

- two plasma HIV-RNA > 200 cp/ml between W16 and W48,

- or a validated PI-related adverse event grade III or IV or a grade II diarrhoea or renal lithiasis.

- ASSESSABLE PATIENTS :

- pts with > 1 viral load available at or after W16

- or a pts experiencing a PI-related adverse event

- ANALYSIS

- Intent to treat (ITT) including all pts and only assessable pts

- On treatment analysis (OT)

Results

Patients characteristics at baseline

PI regimens

	IDV/RTV	LPV/RTV	Nelfinavir	Total
Patients (n)	42	38	35	115
Age (mean)	37	39	35	37 [19-63]
% male	66	71	43	61%
% CDC stage C	26	34	14	25%
ARV naive/pretreated*	39/3	36/2	34/1	119/6
Mean HIV-RNA (log ₁₀ cop/ml)	5.3	5.3	5.6	5.5 (3.5-5.1)
Mean CD4/mm ³	207	141	142	167 [10-980]
HBV/HCV chronically infected (%)	14.3	10.5	5.7	12/115 (10%)

* All pts were PI-naive

Sucess rate of the strategy

i-e virological success and no PI-related adverse event

	ITT	ITT in assessable patients	On treatment
IDV/RTV 42 patients (%, n)	50% (21/42)	70% (21/30)	87% (21/24)
LPV /RTV 38 patients (%, n)	58% (22/38)	69% (22/32)	81% (22/27)
NFV 35 patients (%, n)	40% (14/35)	44% (14/32)	56% (14/25)

Discontinuations before and after W16 for reasons other than PI related AE or virological failure

	IDV		LPV		NFV		Total
	< W16	> W16	< W16	> W16	< W16	> W16	
Lost to follow-up	2	3	2	1		1	9
Consent withdrawal	1				1	1	3
AIDS defining event	3		2	1			6
PI genotypic resistance at BL	1						1
Algorithm not followed						2	2
Non PI-related AE	5	1		2	1	1	10
Low adherence						1	1
Unallowed Rx or modification of ARV		2	2	1	1	1	7
Total	12	6	6	5	3	7	40

Dose adjustments and final PI doses in assessable patients

IDV/RTV group (n=30)

57% patients had doses modifications during the trial

IDV/RTV doses (mg bid)	Baseline (n pts)	Dose modifications during the trial (n pts)	Final doses (n pts)
200/100	0		5
400/100	21	13	13
600/100	6	1	12
800/100	3	3	

LPV/RTV group (n=32)

69% patients had doses modifications during the trial

LPV/RTV doses(mg bid)	Baseline (N pts)	dose modifications during the trial (N pts)	Final doses (N pts)
266/66	0		11
400/100	32	22	15
533/133	0		6

NFV group (n=32)

84% patients had doses modifications during the trial

NFV/RTV doses (mg bid)	Baseline (n pts)	dose modifications during the trial (n pts)	Final doses (n pts)
1250/0	32	26	6
1500/0	0		10
1750/0	0		5
NFV/100 mg bid RTV boosting*	0		10

* systematically prescribed in pts not achieving predefined ranges

Description of the failures

	PI-related adverse events (N pts)		Virological failure** (two VL > 200 copies/ml after W16)
	Before W 16	After W16*	
IDV/RTV	0	2	1
LPV/RTV	3 (before W2)	1	1
NFV	1 (before W2)	0	10

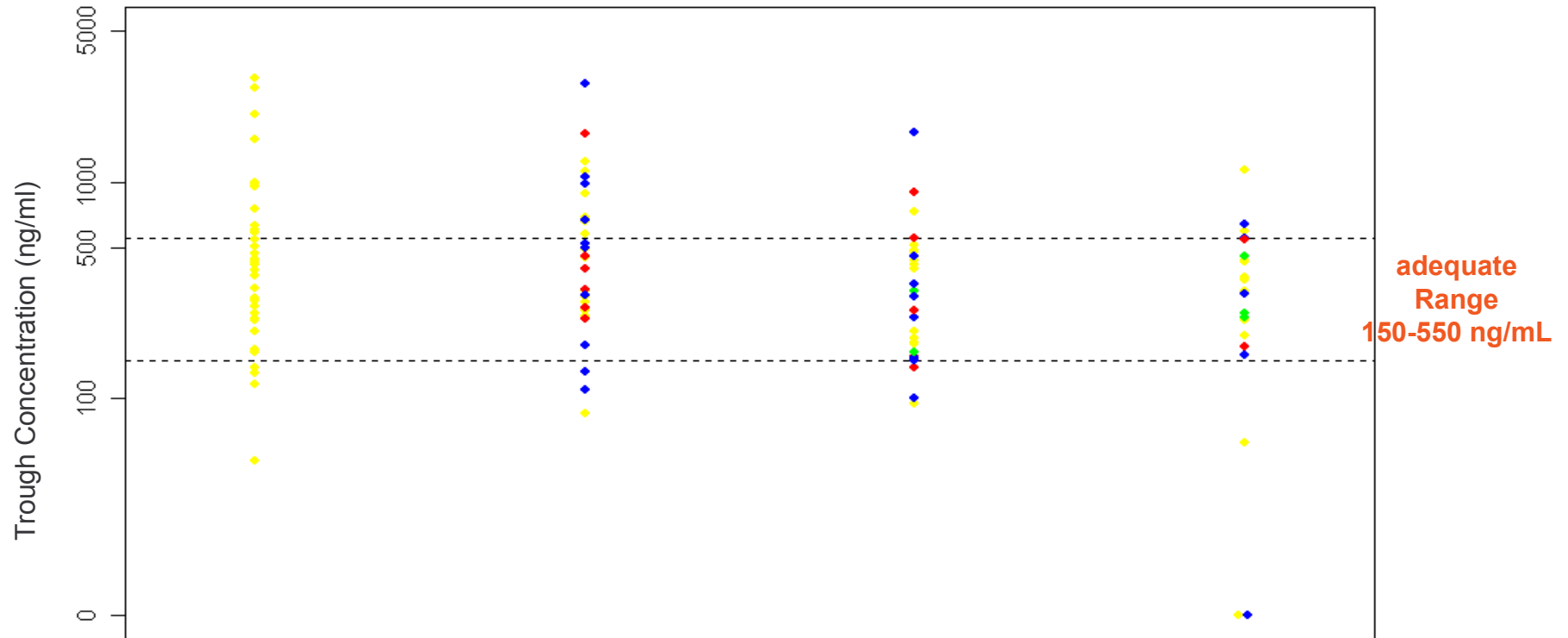
*All pts had concentrations within the range

**Among the 12 pts with virological failures, 8 had concentrations below the range (7 in NFV group)

PI trough plasma concentrations and % of concentrations within the predefined ranges during the trial

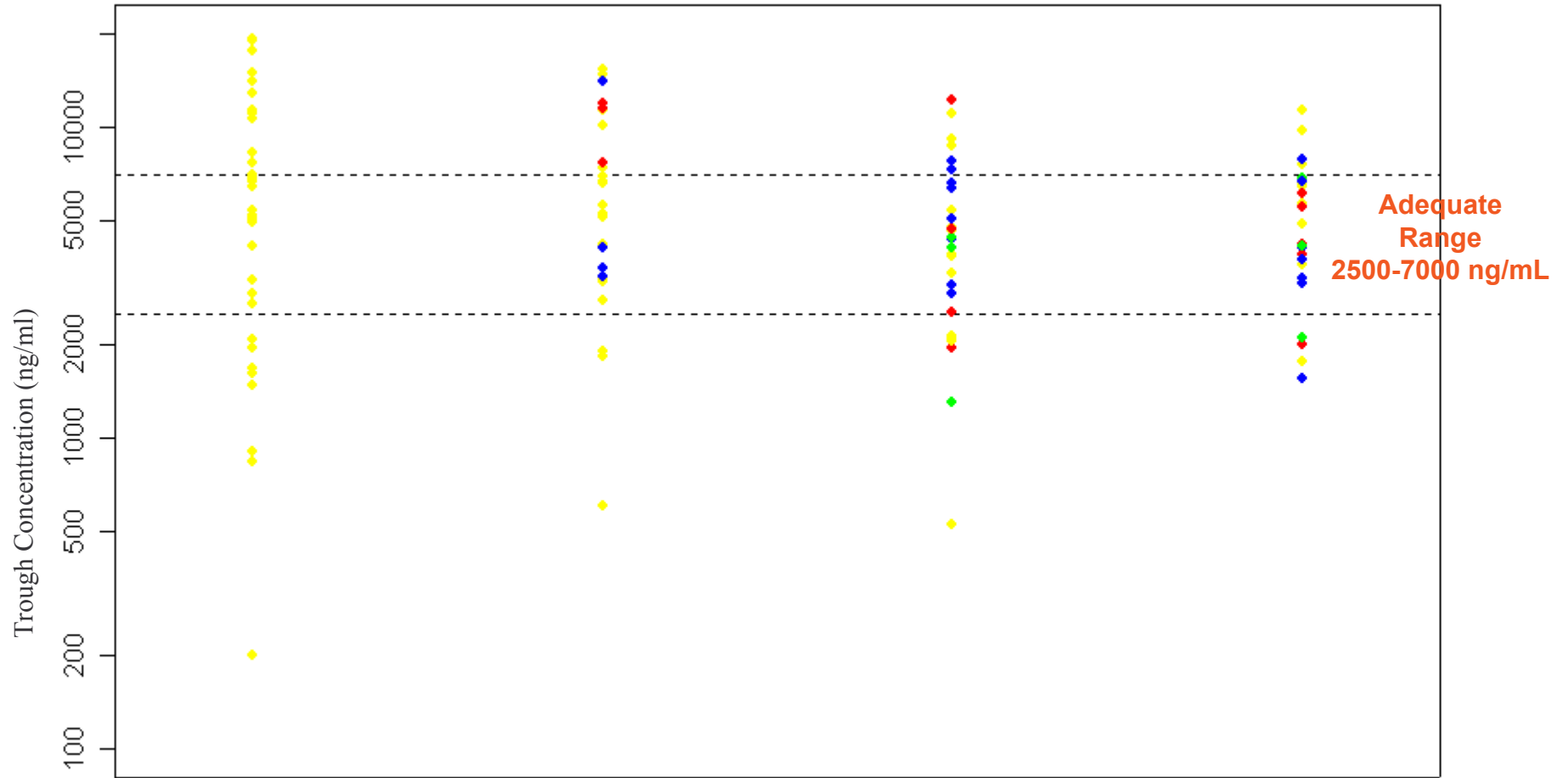
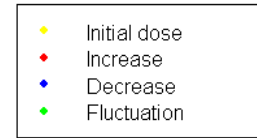
IDV trough plasma concentrations

- ◆ Initial dose
- ◆ Increase
- ◆ Decrease
- ◆ Fluctuation



	W2	W6/8	W24	W48
n=	39	34	27	21
% in the range	51.3	48.7	70.4	66.7
% Low	15.4	11.8	11.1	14.3

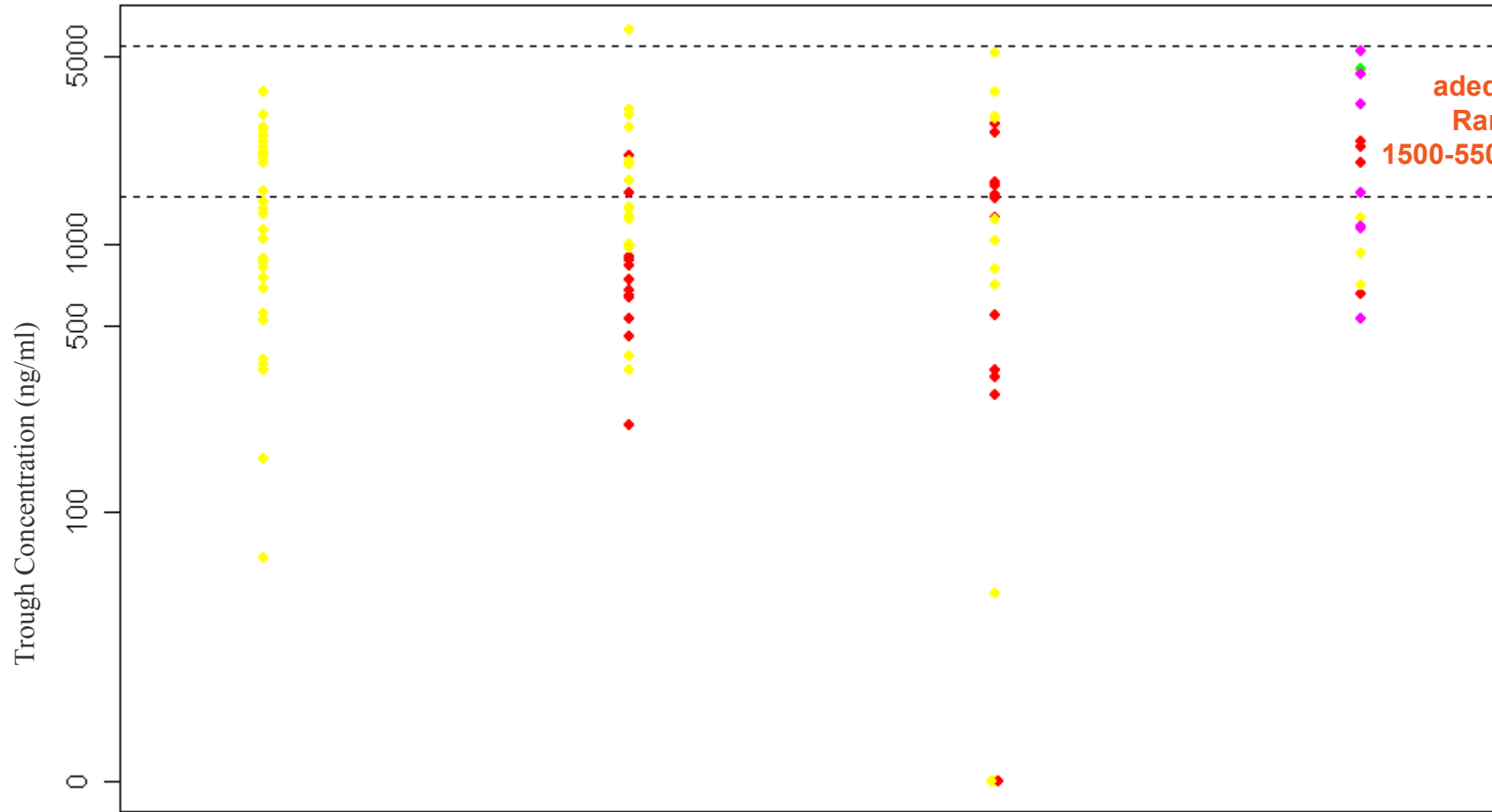
LPV trough plasma concentrations



	W2	W6/8	W24	W48
n=	34	32	29	26
% in the range	38.2	53.1	58.6	69.2
% Low	23.5	12.5	20.7	15.4

Nelfinavir trough Plasma concentrations

- ◆ Initial dose
- ◆ Increase
- ◆ Decrease
- ◆ Fluctuation
- ◆ Plus ritonavir

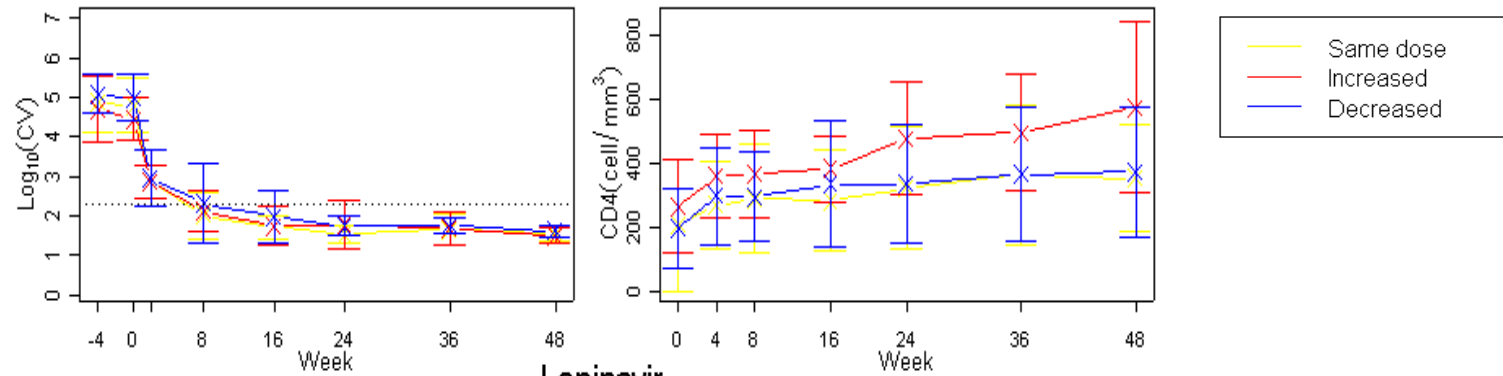


adequate
Range
1500-5500 ng/mL

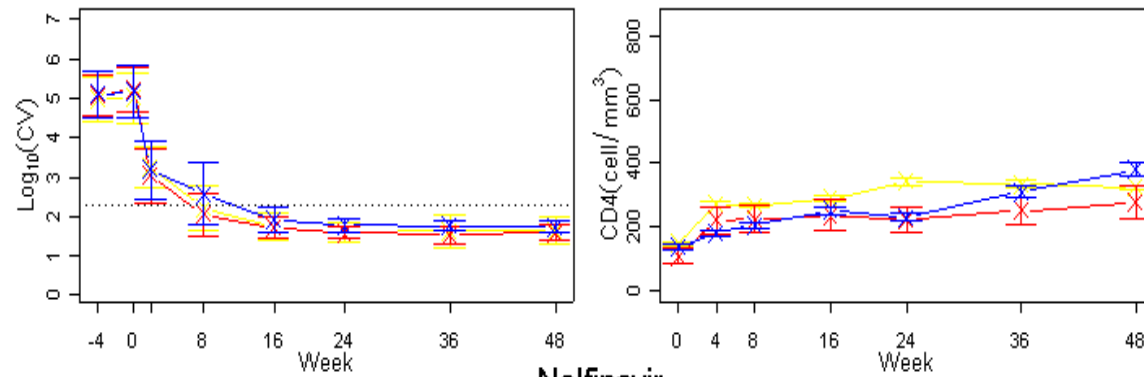
	W2	W6/8	W24	W48
n=	34	29	24	16
% in the range	44.1	31.0	41.7	56.3
% Low	55.9	65.5	58.3	43.8

HIV-RNA and CD4 during the study

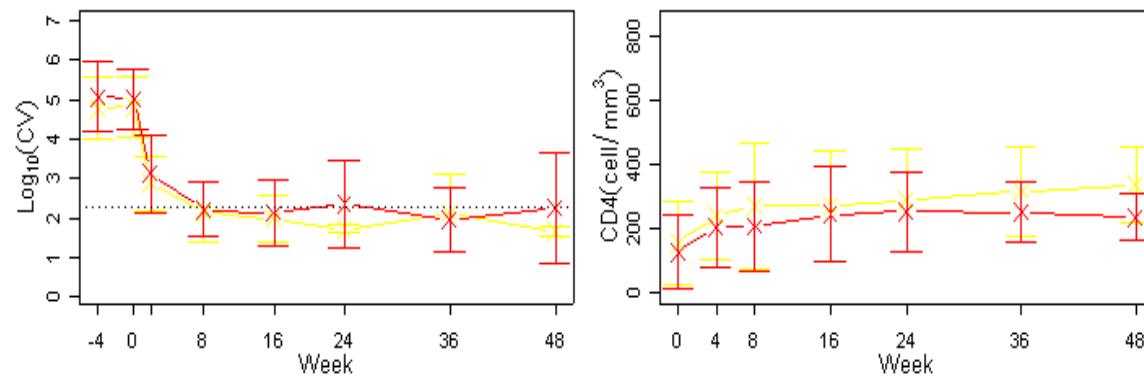
Indinavir



Lopinavir



Nelfinavir



Conclusion

- The feasibility of achieving trough plasma concentrations into predefined ranges has been demonstrated for IDV and LPV boosted PI
- To achieve the predefined concentrations ranges, a dose adjustment was necessary in 69% of the patients. A wide variability of final doses was prescribed (in 53% of LPV treated pts for example, the final dose was different from the usual recommended dose).
- These doses modifications did not compromise virological efficacy in IDV and LPV treated patients and probably reduced the occurrence of severe adverse events since the success rate of the strategy was around 70% at W48 in assessable PI-naïve patients of both groups.
- This strategy failed to move NFV concentrations into the predefined range and to ensure the expected virological success, despite food recommendations that were difficult to control. In NFV pts with low concentrations, a ritonavir boost was efficient in 6/10 pts to increase concentrations within the predefined range and an early systematic ritonavir boost should be further evaluated.

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