High concentrations of nelfinavir as an independent risk factor for lipodystrophy in HIV-infected patients

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Introduction
The use of new Highly Active Antiretroviral Therapies (HAART) has led to a dramatic decrease in HIV-1-related morbidity and mortality. Unfortunately, the widespread introduction of HAART has also been associated with adverse effects. Lipodystrophy syndrome is one of the most worrisome. Among the mechanisms suggested to have a role in the etiology of lipodystrophy, several could be drug concentration dependant such as inhibition of adipocyte differentiation or inhibition of steroids metabolism . If this hypothesis could be confirmed, therapeutic drug monitoring would help at preventing the occurrence of lipodystrophy in HIV-1 infected patients with high level of plasma drug concentrations. This study was designed to assess the relationship between antiretroviral drug exposure and lipodystrophy in a cohort of patients treated with highly active antiretroviral therapy regimens containing nelfinavir as a protease inhibitor.

Methods
69 HIV-1 patients receiving nelfinavir were investigated cross sectionally. Lipodystrophy was defined by patients' self report and classified as peripheral fat wasting, central accumulation or overall lipodystrophy. Plasma trough concentrations of nelfinavir and its main metabolite M8 were measured in the venous blood samples drawn in the morning after 12 hours overnight fasting.
Lipodystrophy was defined by patients' self report completed before the medical consultation as previously described by Carr . Patients rated the severity of peripheral fat wasting and central fat accumulation in six regions (face, arms, legs, buttocks, abdomen, neck) as none (score 0), mild (score 1) moderate (score 2) or severe (score 3). Scores for peripheral wasting (four sites : face, arms, buttocks, legs ; total score 0-12), central accumulation (two sites : abdomen, neck ; total score 0-6) and overall lipodystrophy (six sites, total scores 0-18) were assigned .

	Age (years)	Height (cm)	Weight (kg)	Viral load (cp/mL)	CD4 (cells/mm3)
Mean	40,2	172,4	68,8	26482,2	474,7
S.D.	10,6	8,6	11,6	120419,9	208,9
Minimum	26,4	150	41	25	7
Maximum	76,1	192	92	840000	1210

Table 1: Demographic characteristics of the population (n=69)

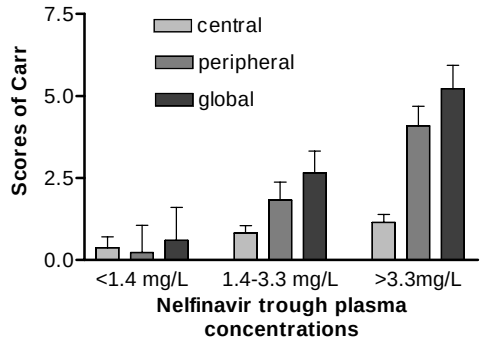
	Central accumulation		Peripheral wasting		Overall lipodystrophy	
	Odds ratio	P	Odds ratio	P	Odds ratio	P
Age		Removed		Removed		Removed
Sex		Removed	0.36	0.02	0.37	0.02
Nelfinavir trough level		Removed	1.08	0.01	1.04	0.001
D4T	2.09	0.16		Removed		Removed
3TC		Removed	0.27	0.14		Removed
NRTI duration treatment		Removed	1.03	0.001	1.03	0.03
PI duration treatment	1.03	0.06		Removed		Removed

Table 2: Risk factors of clinical lipodystrophy (logistic regression). A backward (step-down) variable selection was performed. In this procedure, all variables were included in the model. The variable that was the least significant was removed. This deleting of variables continued until all of the variables in the model were significant at a level below 0.20. Level of significance below 0.05 was underlined.

Results
Nelfinavir trough plasma concentrations were significantly related to overall lipodystrophy score (r=0.38, p=0.001) and peripheral fat wasting score (r=0.38, p=0.001) but not central fat accumulation score. Nelfinavir trough plasma concentration appeared to be an independent risk factor of overall lipodystrophy and peripheral fat wasting but not central fat accumulation in a multivariate analysis
The other risk factors of lipodystrophy evidenced using a logistic regression analysis were duration of NRTI treatmen and gender. These risk factors were significantly associated with overall lipodystrophy and peripheral wasting but not central accumulation. No significant relationship was detected between trough levels of nelfinavir and biological variables. We evidenced an association between the risk of hypercholesterolaemia and duration of protease inhibitor treatment.

	Central accumulation			Peripheral wasting			Overall lipodystrophy		
	Yes	No	P	Yes	No	P	Yes	No	P
Uricemia (mmol/L)	340±90	398±112	0.08	352±91	377±113	0.51	364±106	367±95	0.82
ALAT (UI/L)	32.4±25.1	24.3±18.1	0.05	32.8±25.4	23.2±16.6	0.06	32.3±24.7	21.5±14.6	0.03
ASAT (UI/L)	24.2±18.3	19.8±10.7	0.32	23.8±18.2	19.7±10.0	0.75	23.6±17.6	19.0±8.3	0.65
γGT (UI/L)	67.9±98.5	36.6±46.3	0.06	51.7±46.0	48.7±92.8	0.01	62.4±87.1	33.8±30.3	0.004
Triglyceride (mmol/L)	2.2±1.1	1.9±0.9	0.46	2.4±1.1	1.8±1.0	0.006	2.3±1.0	1.8±1.0	0.04
Cholesterol (mmol/L)	6.2±1.4	5.0±1.1	0.15	6.4±1.3	5.0±1.1	0.002	6.3±1.3	5.0±1.0	0.02
HDL-cholesterol (mmol/L)	1.3±0.3	1.3±0.5	0.39	1.2±0.4	1.4±0.5	0.67	1.2±0.3	1.4±0.6	0.26
Glycemia (mmol/L)	5.3±1.8	5.2±0.8	0.30	5.3±1.7	5.1±0.6	0.67	5.4±1.6	5.1±0.7	0.87
Insulinemia (mUI/L)	17.2±10.2	14.3±7.4	0.26	18.8±9.6	12.6±7.8	0.004	17.6±9.2	12.9±7.6	0.03
C-peptide (nmol/L)	3.0±1.8	2.3±0.9	0.18	3.0±1.6	2.3±1.4	0.09	2.8±1.4	2.3±1.3	0.08

Table 3: Metabolic data and body composition in patients according to lipodystrophy classification. Levels of significance below 0.05 are underlined.



: Scores of Lipodystrophy for overall lipodystrophy, central fat accumulation, peripheral wasting in patients with nelfinavir trough concentrations below the 25th percentile (1.4 mg/L) (group 1), between the 25th percentile (1.4 mg/L) and the 75th percentile (3.3 mg/L) (group 2) and above the 75h percentile (3.3 mg/L) (group 3). Using a Kruskal-Wallis Test, a significant difference was evidenced for overall lipodystrophy and peripheral fat wasting : overall lipodystrophy F=3.94, p=0.02, central fat accumulation F=1.32, p=0.27, peripheral wasting F=3.75, p=0.03). A Kruskal-Wallis Multiple-Comparison test found significant difference between group 1 and 3 (p<0.05) but not between group 2 and group 3 or between group 2 and group 1 for overall lipodystrophy and peripheral wasting.

	Hypercholesterolaemia (>6.5 mmol/L)		Hypertriglyceridaemia (>2.0 mmol/L)		Hyperinsulinaemia (>20 mmol/L)		High plasma concentration of C-peptide (>2.5 mmol/L)	
	Odds ratio	P	Odds ratio	P	Odds ratio	P	Odds ratio	P
Age		Removed		Removed		Removed		0.18
Sex		Removed		Removed		Removed		Removed
Nelfinavir trough level		Removed		Removed		Removed		Removed
D4T (yes/no)		Removed		Removed		Removed		Removed
AZT (yes/no)		Removed		Removed		Removed		Removed
NRTI duration of treatment	0.93	0.17		Removed	1.03	0.14		Removed
PI duration of treatment	1.1	0.05	1.41	0.05		Removed		Removed

Table 4: Risk factors of metabolic dysfunction (logistic regression). A backward (step-down) variable selection was performed. In this procedure, all variables were included in the model. The variable that was the least significant was removed. This deleting of variables continued until all of the variables in the model were significant at a level below 0.20. Level of significance below 0.05 was underlined.

Conclusions : Our results provide evidence that peripheral fat wasting is partly accounted by modifiable risk factors and warrant further evaluation of therapeutic drug monitoring to decrease the risk of lipodystrophy in HIV infected patients.