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# Lipid and lipoprotein profile in HIV-infected patients treated with lopinavir/ritonavir as a component of the first combination antiretroviral therapy

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## ABSTRACT

**Objective:** To characterize lipid and lipoprotein changes associated with a lopinavir/ritonavir-containing regimen.

**Methods:** We enrolled previously antiretroviral-naïve patients participating in the Swiss HIV Cohort Study. Fasting blood samples (baseline) were retrieved retrospectively from stored frozen plasma and post treatment (follow-up) samples were collected prospectively at two separate visits. Lipids and lipoproteins were analysed at a single reference laboratory.

**Results:** 65 patients had two post treatment lipid profile measurements, 9 only one. Most of the measured lipids and lipoprotein plasma concentrations increased on lopinavir/ritonavir-based treatment. The percentage of patients with hypertriglyceridemia (TG > 150 mg/dl) increased from 28/74 (38%) at baseline to 37/65 (57%) at the second follow-up. We did not find any correlation between lopinavir plasma levels and the concentration of triglycerides. There was weak evidence of an increase in small dense LDL-apoB during the first year of treatment but not beyond one year (odds ratio 4.5, 90% CI 0.7 to 29 and 0.9, 90% CI 0.5 to 1.5 respectively). However, 69% of our patients still had undetectable small dense LDL-apoB levels while on treatment. LDL-cholesterol increased by a mean of 17 mg/dl (90% CI -3 to 37) during the first year of treatment, but mean values remained below the cut-off for therapeutic intervention.

**Conclusions:** Despite an increase in the majority of measured lipids and lipoproteins particularly in the first year after initiation, we could not detect an obvious increase of cardiovascular risk resulting from the observed lipid changes.

## INTRODUCTION

Lopinavir/ritonavir (LPV/r) is a boosted protease inhibitor (PI) widely used at each stage of HIV disease due to its antiviral activity, very low selection rate of resistant mutants and good tolerance (1). However, several studies have shown a significant increase in triglycerides (TG) and total cholesterol (TC) on LPV/r-based therapy (2-5). In general combination antiretroviral treatments (cART), in particular PI-containing regimens, are thought to be involved in the genesis of lipid abnormalities, especially hypertriglyceridemia (6-8). Yet it is not clear whether changes in lipids and lipoproteins are a direct effect of cART or the result of a more complex scenario involving also genetic, virologic, immunologic, and inflammatory factors (9-11). Independent from their origin, lipid changes have lead to concern about increased cardiovascular risk in HIV-infected patients (12-14). In addition to well established coronary heart disease (CHD) lipid risk factors, such as increased low density lipoprotein (LDL) and reduced high density lipoprotein (HDL), the US National Cholesterol Education Program (NCEP) states that certain hypertriglyceridemic lipid disorders are strong risk factors for CHD. In particular slightly triglyceride-enriched very low density lipoprotein (VLDL) and small dense LDL-apolipoprotein B-100 (sdLDL-apoB) are regarded as emerging CHD lipid risk factors associated with hypertriglyceridemia (15).

Most previous studies of lipid abnormalities in patients treated with a LPV/r-based cART have some limitations: either cART experienced patients were also recruited (4;16-21), measurements were made irrespective of fasting status (2), or not all relevant lipid and lipoproteins were measured (3;22-24).

The aim of our study was a detailed assessment of lipids and lipoproteins in fasting cART naive patients before and twice during a LPV/r-based therapy. In particular, we investigated risk factors associated with development of hypertriglyceridemia and possible association between TG and slightly triglyceride-enriched VLDL, sdLDL and LPV plasma levels.

## METHODS

### Study design and population

The Swiss HIV Cohort Study (SHCS) is a prospective multicentric cohort study that enrolled more than 15'600 HIV-infected persons aged 16 years or older at seven outpatient clinics or specialized private practices (<http://www.shcs.ch>). Each SHCS patient undergoes a clinical visit every 6 months with collection of clinical data and storage of plasma and cells. In our study we included all the caucasian SHCS patients, previously antiretroviral-naïve, who started a LPV/r-based cART between March 2001 and January 2006. Only patients in a fasting state (defined as  $\geq 8$  h without caloric intake) were included in the study. Patients were taking LPV/r at the standard daily dose (800/200 mg) together with 2 or 3 nucleoside reverse transcriptase inhibitors (NRTI) for more than 3 months. The exclusion criteria were previous antiretroviral therapy, use of lipid-lowering drugs, TG > 500 mg/dl and no familial combined hyperlipidemia. To characterize the lipid and lipoprotein profile of patients we collected blood samples before initiation of treatment (baseline) and twice during a LPV/r-based therapy (follow-up 1 and 2). Baseline lipid profile was assessed retrospectively using retrieved frozen plasma samples from the SHCS collection, whereas follow-up samples were prospectively collected at two consecutive SHCS visits.

### Laboratory parameters

Citrate plasma was obtained by centrifugation of blood for 20 minutes at 1500 g and deep-frozen at  $-80^{\circ}\text{C}$  until analysis. VLDL were separated by ultracentrifugation (Airfuge, Beckman Coulter, Krefeld, Germany) at a density of 1.006 g/ml (4 hours,  $20^{\circ}\text{C}$ , 95 000 rpm) using an A-95 rotor with 8 x 20 mm Ultra-Clear tubes. LDL-cholesterol (LDL-C) was determined after removal of VLDL in the resulting infranantant by subtracting HDL-cholesterol (HDL-C) from total cholesterol (TC) concentration. TC, HDL-C, and TG in plasma and lipoprotein fractions were determined with commercially available enzymatic assays (Synchron CX5, Beckman Coulter, Krefeld, Germany),

apolipoprotein B (apo-B) and lipoprotein (a) [Lp(a)] by turbimetry using the same equipment. The antibody against Lp(a) used for the assay was purchased from Technoclone, Vienna, Austria, antibodies against apo-B from Beckman Coulter, Krefeld, Germany. SdLDL-apoB was determined after ultracentrifugation at a density  $> 1.044$  g/ml in the resulting infranant. All procedures and methods were checked for their compatibility with citrate plasma. The obtained values were corrected according to the dilution of blood with sodium citrate. All determinations were performed in a central laboratory. The presence of slightly triglyceride-enriched VLDL was detected by a VLDL-triglyceride/VLDL-apolipoprotein B ratio between 6 and 8. A ratio below 6 defined normally composed VLDL, while a ratio  $> 8.0$  triglyceride-rich VLDL. A concentration  $> 13.5$  mg/dl of sdLDL-apoB was regarded as abnormally high, while the detection limit was 5.3 mg/dl. Lipid and lipoprotein values were defined according to the thresholds established by the US NCEP. CD4 T lymphocytes were quantified by flow cytometry. Plasma HIV-1 RNA level was measured by a PCR assay (Amplicor HIV monitor; Roche Diagnostic System; limit of detection  $< 50$  copies/ml). LPV concentrations were measured in plasma extracted before the morning dose (C through), using a validated high-performance liquid chromatography (HPLC) method.

### Statistical Analysis

A paired t-test is appropriate if there is a constant difference between baseline and follow up measurements on the same patient. We fit models that assume that this difference (between baseline and follow up) was not constant but varied with time on LPV/r. In our models, time on LPV/r was represented by a linear spline (25) and this allows us to estimate the rate of change (per year) during the first year after starting and beyond one year. We give 90% confidence intervals for these estimates in order to focus on the clinical implications of the range of values in the interval (26). Because most patients contributed two data to each model (most have two follow up measurements), we estimated intervals using robust standard errors calculated using generalised estimating equations (and assuming an independent working correlation (27)). We also adjusted



estimates for a set of pre-specified covariates (gender, smoking status, and baseline age, BMI, CD4 counts per 100 and log 10 viral RNA) in order to estimate the rate of change for a ‘reference patient’ – a male smoker with other covariates set at typical values (40 years, 25 kg/m<sup>2</sup>, 200 cells /μL, 5 log 10 copies/mL – see Table 1).

For most lipid parameters, the outcome was the difference between baseline and follow up measurements with models fit by linear regression. However for two parameters, models were fit using logistic regression. For sdLDL-apoB, more than half of the values were below the limit of detection; therefore the response for this parameter was whether the follow up measurement was known to be higher than at baseline. For the ratio of VLDL-TG to VLDL-apoB, the response was whether the follow-up measurement was more atherogenic than at baseline, with the absolute difference between the observed ratio and 7.0 used as a measure of atherogenic risk.

We also tested a limited number of pre-specified hypotheses about associations between increases in TG and changes in other parameters. These were tested by replacing time on LPV/r in our models with the level of another parameter and we illustrate these associations using graphs. We used Intercooled Stata Version 9.2 for analyses and R 2.5.1 for graphics.

## RESULTS

### Population and treatment outcome

We identified 84 patients initiating a LPV/r-based therapy. Ten of these patients were excluded due to previous use of nucleoside or non-nucleoside reverse transcriptase inhibitors. 65 (88%) patients had lipid profile measured prospectively at two consecutive SHCS visits, while 9 (12%) had only one follow-up measurement (due to a change of antiretroviral therapy). The median time between start of LPV/r and the first follow-up was 15 months (range 1-51 months), while the median time between the first and the second follow-up was 6 months (range 1-13 months), resulting in a median time between start of LPV/r and the second follow-up of 22 months (range 5-58 months). Baseline characteristics of patients are shown in Table 1.

LPV/r-based therapy led to a reduction of median viral load from 5.1 (range 1.7-7.8) to 1.7 (range 1.7-3.3)  $\log_{10}$  copies/ml at follow up 1 and 2. Of note 66 (89%) patients at follow-up 1 and 62 (95%) at follow-up 2 had an undetectable HIV-1 RNA (< 50 copies/ml). Meanwhile median CD4 cell count increased from 179 (range 2-675) at baseline to 363 (range 51-915) and 411 (range 32-827) at follow-up 1 and 2, respectively (Table 2).

### Lipids and lipoproteins

Lipids and lipoproteins values before and changes after the initiation of a LPV/r-based cART are summarized in Table 3.

At baseline the mean values of TC, HDL-C, LDL-C and TG were 113 (SD 30) mg/dl, 28 (SD 8) mg/dl, 61 (SD 21) mg/dl, 141 (SD 74) mg/dl, respectively. LDL-C  $\geq$  130 mg/dl (a threshold regarded as significantly atherogenic according to US NCEP guidelines) was present in 1/74 patients (1%). Low HDL-C levels (< 40 mg/dl) were found in 69/74 patients (93%). Moreover 28/74 patients (38%) had TG > 150 mg/dl. Atherogenic slightly triglyceride-enriched VLDL (defined by a VLDL-TG to VLDL-apoB ratio between 6 and 8) were present in 13/74 patients (18%). SdLDL-apoB values were below detection limit in 66/74 patients (89%) and 1/74 patients

(1%) had elevated concentrations ( $> 13.5$  mg/dl). Elevated levels of Lp(a) ( $>30$  mg/dl) were present in 11/74 patients (15%).

After initiation of LPV/r-based cART TG had a mean increase of 110 mg/dl (90% CI 15 to 210) during the first year of treatment followed by little change beyond one year of treatment (a decrease of 7 mg/dl, 90% CI -42 to 28, Figure 1a). The percentage of patients with hypertriglyceridemia (TG  $> 150$  mg/dl) increased from 28/74 (38%) at baseline to 38/74 (51%) and 37/65 (57%) at follow-up 1 and 2, respectively. We also tested a pre-specified hypothesis that hypertriglyceridemia on treatment represents a worsening of a pre-existing condition by adding an interaction term to our model between TG at baseline and time on treatment. This interaction term was estimated to be negative implying that higher baseline values of TG show smaller increases over time than lower baseline values of TG (Figure 1b). Moreover, we found a small decrease in TG for patients with higher HDL-C levels (-5.5 mg/dl in TG, 90% CI -8.8 to -2.1, for each mg/dl increase in HDL-C, see also Figure 2a). There was no obvious increase in the atherogenicity of the VLDL-TG to VLDL-apoB ratio, in either the first or subsequent years (odds ratio 0.6, 90% CI 0.2 to 2.6, and 1.1, 90% CI 0.7 to 1.8 respectively). Consistent with these estimates, the percentage of patients with an atherogenic ratio of VLDL-TG to VLDL-apoB was relatively constant with 13/74 (18%) patients at baseline and 14/74 (19%) and 13/65 (20%) patients at follow-up 1 and 2 respectively. Moreover, we observed a roughly linear relationship between TG and VLDL-TG/ VLDL-apoB ratio (Figure 2b). The ApoCII to ApoCIII ratio declined by a mean 0.22 (90% CI -0.39 to -0.05) during the first year of treatment and remained stable thereafter. The decline of this ratio was driven by a sizeable increase in ApoCIII during the first year of treatment (7.5 mg/dl, 90% CI 4.1 to 11). There was weak evidence of a small decrease in TG for patients with higher ApoCII to ApoCIII ratios (-25 mg/dl, 90% CI -62 to 12 change in TG per unit change in the ApoCII to ApoCIII ratio, see also Figure 2c). There was weak evidence of an increase in sdLDL-apoB during the first year of treatment but not beyond one year (odds ratios 4.5, 90% CI 0.7 to 29, and 0.9, 90% CI 0.5 to 1.5). Consistent with these estimates, 66/74 patients (89%) had a concentration of sdLDL-apoB below

the detection limit at baseline compared with 51/74 (69%) patients and 45/65 (69%) patients at follow-up 1 and 2 respectively. Accordingly, few follow-up measurements (40/139) showed an increase in the level of sdLDL-apoB; most of them (99/139) showed no discernible change or a decrease. However, in patients with detectable sdLDL-apoB at follow-up, we found a higher increase in TG from baseline to follow-up compared to patients with sdLDL-apoB below detection limit at follow-up (by 144 mg/dl 90% CI 83 to 205, see also Figure 2d). Highly atherogenic concentrations of sdLDL-apoB (> 13.5 mg/dl) were found in 2/74 (3%) and 0/65 patients at follow-up 1 and 2 respectively compared to 1/74 (1%) at baseline.

TC had a mean increase of 45 mg/dl (90% CI 20 to 71) during the first year of treatment followed by little change beyond one year of treatment (a mean decrease of 3.1 mg/dl, 90% CI -10 to 4.3).

LDL-C had a mean increase of 17 mg/dl (90% CI -3 to 37) during the first year of treatment followed by little change beyond one year of treatment (a mean increase of 0.3 mg/dl, 90% CI -5.1 to 5.6). LDL-C  $\geq$  130 mg/dl was found in 2/74 (3%) and 1/65 patients (2%) at follow-up 1 and 2 respectively compared with 1/74 (1%) at baseline.

HDL-C had a mean increase of 6.7 mg/dl (90% CI 0.3 to 13) during the first year of treatment followed by little change beyond one year of treatment (a mean decrease of 0.7 mg/dl, 95% CI -2.9 to 1.5). The number of patients with HDL-C > 40 mg/dl increased from 5/74 (7%) at baseline, to 9/74 (12%) and 7/65 (11%) at follow-up 1 and 2, respectively.

Lp(a) had a mean increase of 3.2 mg/dl (95% CI -5.7 to 12) during the first year of treatment followed by little change beyond one year of treatment (a mean decrease of 0.7 mg/dl, 90% CI -2.4 to 1.0). Elevated plasma levels of Lp(a) (>30 mg/dl) were found in 13/74 (18%) and 11/65 patients (17%) at follow-up 1 and 2, respectively, compared to 11/74 patients (15%) at baseline.

#### Lopinavir plasma level and triglycerides.

During the study period 9 patients had only one measurement of LPV through plasma concentration, while 65 had two. The mean through plasma concentrations of LPV were 5.9 (SD 3)

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µg/ml and 6.2 (SD 4) µg/ml at the first and the second follow-up, respectively. We did not observe any obvious increase in TG with increasing plasma levels of LPV (0.1 mg/dl increase in TG, 90% CI -7.7 to 7.9, Figure 3).

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## DISCUSSION

HIV infection has itself a profound impact on lipid and lipoprotein metabolism that is further influenced by antiretroviral drugs. In a population of 74 previously treatment naive HIV infected patients we found that most of the lipid and lipoprotein plasma levels increased after initiation of a LPV/r based cART. When time on treatment was considered most of these increases tended to occur during the first year of cART and reached a plateau in the following years, as in previous reports (3;5;19).

As expected in a fairly advanced and untreated HIV population (10;28), TG were already elevated at baseline in more than one third of our patients, with further increase of the percentage of patients with hypertriglyceridemia (TG > 150 mg/dl) at follow-up. Triglycerides markedly increased only during the first year of a LPV/r-based cART. However, higher baseline values of TG were followed by a lower increase over time. In other words the odds of having elevated triglycerides on LPV/r therapy was lower in those patients who already had elevated triglycerides at baseline. This result is in contrast with data from other publications (3-5;19), but consistent with the results of a previous SHCS study involving patients on a PI other than LPV/r (7).

We could not confirm a correlation between increase in TG and higher LPV plasma concentration as reported in some (18;24;29), but not all studies (21;30).

Hypertriglyceridemia is characterized either by a normal number of large, triglyceride-rich VLDL or an increased number of small VLDL which are relatively poor in TG and rich in cholesterol (slightly triglyceride-enriched VLDL). The latter particles carry a strongly increased risk of coronary heart disease as shown in patients with familial combined hyperlipidemia. As one VLDL contains one molecule of apolipoprotein B, the ratio of VLDL-TG to VLDL-apoB can be used to determine VLDL composition (31-33) and to better estimate atherogenicity in patients with hypertriglyceridemia. In this study, there was no obvious increase in the atherogenicity of the VLDL-TG to VLDL-apoB ratio, in either the first or subsequent years of treatment. The percentage of patients with atherogenic slightly triglyceride-enriched VLDL did not change appreciably after

initiation of LPV/r-based cART. Moreover, we found a positive correlation between the increase in TG and an higher VLDL-TG to VLDL-apoB ratio. This suggests that in HIV positive patients treated with antiretroviral therapy there is a predominance of large, triglyceride-rich VLDL, similarly to the VLDL pattern seen in familial hypertriglyceridemia associated with a low cardiovascular risk (31).

We observed an important increase in Apo C3 concentration and a concomitant decrease of the Apo C2 to Apo C3 ratio after the initiation of a LPV/r-based cART, in agreement with previous studies (16;17;34). Since Apo C2 stimulates the catabolism of VLDL via lipoprotein lipase, while Apo C3 inhibits this pathway, our data support the hypothesis of a decreased activation of lipoprotein lipase as a key factor in the observed increase of TG (16;17;35). Moreover, genetic variants of ApoC3 have been found to be associated with extreme hypertriglyceridemia in patients treated with ritonavir boosted PIs, introducing genetic variability as an additional factor in the pathogenesis of cART-associated hypertriglyceridemia (11).

SdLDL-apoB, an emerging atherogenetic risk factor (15), is thought to mediate cardiovascular risk of certain hypertriglyceridemias (36;37). Atherogenicity of sdLDL-apoB is due to a great capacity to infiltrate the arterial wall, a reduced affinity for the LDL receptors and an increased susceptibility to ex-vivo oxidation (38). Although most of our population had undetectable values of sdLDL-apoB (below 5.3 mg/dl) before and after initiation of a LPV/r-based cART, patients with detectable sdLDL-apoB had, on average, a higher increase in TG from baseline to follow-up. Yet highly atherogenic concentrations of sdLDL-apoB were found only in a small proportion of subjects before and after a LPV/r-based cART (39;40). Other studies reporting on elevated sdLDL-apoB before and after starting a cART with LPV/r may be influenced by a previous treatment, since they were conducted on patients who switched to a new regimen because of virological failure or drug intolerance (16;17).

The majority of our study population had low TC and LDL-C mean values before starting antiretroviral treatment. Although both TC and LDL-C increased in the first year after the initiation

of LPV/r, the mean follow-up values remained far below the recommended therapeutic goal for LDL-C according to the US NCEP guidelines. Moreover, after the initiation of a LPV/r based cART only < 3% of our population had LDL-C values regarded as significantly atherogenic ( $\geq 130$  mg/dl).

We found a minimal increase of HDL-C in the first year after initiation of a LPV/r-based cART. Nevertheless, the percentage of patients with protective HDL-C values ( $> 40$  mg/dl) increased from 7% at baseline to 12% on cART.

Lp(a), another emerging atherogenic risk factor (15), tended to increase in the first year after the initiation of LPV/r. However, the percentage of patients with elevated values associated with premature development of atherosclerosis ( $> 30$  mg/dl) did not increase on LPV/r-based cART.

The well characterized population of cART naive HIV infected patients enabled us to obtain an extensive assessment of lipids and lipoproteins before and after the initiation of a LPV/r-based cART. Laboratory samples were collected in a fasting status and analyzed in a single reference laboratory. However, the size of our population was relatively small, although larger than the majority of previous studies that have reported on this topic. The different NRTIs used in combination with LPV/r could have influenced the lipid profile, as it has been shown for zidovudine and stavudine (41). Finally, the use of frozen plasma samples prevented standardization of the intervals between baseline and follow up assessment of lipid and lipoproteins. However, our models allowed for variation in the timing of assessments. Similarly we were not able to measure additional laboratory parameters, i.e. lipoprotein lipase and hepatic lipase, that could have been valuable to clarify some of the pathogenic pathways.

In conclusion, the majority of the measured lipids and lipoproteins were shown to increase on a LPV/r-based cART. We could not demonstrate a significant change in the percentage of patients with atherogenic plasma levels of lipoproteins commonly associated to hypertriglyceridemia, such



as slightly triglyceride-enriched VLDL and sdLDL-apoB. However, the risk of cardiovascular events in our population remains a concern mainly due to the high percentage of patients with low HDL (42), frequent smoking (43), and inflammatory factors associated with HIV infection (44).

## ACKNOWLEDGMENTS

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**Table 1** Baseline characteristics of 74 antiretroviral-naïve patients initiating a LPV/r-based cART.

Characteristic	n (%)
Age [mean (SD)]	40 (10)
Male gender	65 (88%)
Route of HIV transmission	
intravenous drug user	11 (15%)
homosexual	31 (42%)
heterosexual	29 (39%)
other	3 (4%)
Baseline BMI (kg/m <sup>2</sup> ) [mean (SD)]	23 (4)
Current or ex-smokers	48 (65%)
HCV coinfecting	11 (15%)
Concurrent NRTI backbone	
ABC / 3 TC	3 (4%)
AZT / 3TC	60 (81%)
AZT / ABC / 3TC	1 (1%)
DDI / D4T	1 (1%)
TNV / 3TC	4 (5%)
TNV / AZT / 3TC	1 (1%)
TNV / DDI	2 (3%)
TNV / ETC	2 (3%)
Nadir CD4+ < 200 cells / microliter	50 (68%)
HIV1-RNA (log <sub>10</sub> copies/ml) [mean (SD)]	5.2 (0.82)
CD4+ (cells/microliter) [median (range)]	179 (2-675)

**Table 2** CD4+ cell count, HIV1-RNA and body-mass index (BMI) at baseline and after the initiation of a LPV/r-based cART

Variable	Baseline (n=74)	Follow-up 1 (n=74)	Follow-up 2 (n=65)
CD4+ cells	179 (2-675)	363 (51-915)	411 (32-827)
HIV-1 RNA (log <sub>10</sub> copies/ml)	5.1 (1.7-7.8)	1.7 (1.7-3.3)	1.7 (1.7-3.3)
BMI (kg/m <sup>2</sup> )	22.4 (14.4-37.8)	24.0 (15.7-37.9)	24.2 (15.7-39.4)

All values are given as median and range

**Table 3**

Mean (SD) lipid and lipoprotein levels at baseline and estimated mean change per year (90% CI) after the initiation of a LPV/r-based cART. Change was modelled as two slopes, during the first year and beyond the first year, and estimates were adjusted for 6 covariates (gender, smoking status, and baseline age, BMI, CD4 counts per 100 and log 10 HIV-1 RNA)

Variable	Baseline level	Mean change per year (90% CI)	
	mean (SD)	During first year	Beyond first year
HDL-cholesterol	28 (8)	6.7 (0.3, 13)	-0.7 (-2.9, 1.5)
Apolipoprotein A-I	94 (22)	24 (6, 42)	3.9 (-1.2, 8.9)
Apolipoprotein A-II	22 (4)	3.0 (0.1, 5.8)	0.6 (-0.2, 1.4)
Total cholesterol	113 (30)	45 (20, 71)	-3.1 (-10, 4.3)
LDL-cholesterol	61 (21)	17 (-3, 37)	0.3 (-5.1, 5.6)
LDL apolipoprotein B	37 (12)	12 (2, 23)	1.2 (-1.7, 4.2)
Apolipoprotein B	50 (15)	17 (4.7, 29)	0.4 (-3.2, 4.0)
Small dense LDL- apolipoprotein B*	8/74 (11%)	4.5 (0.7, 29)	0.9 (0.5, 1.5)
Lipoprotein (a)	14 (21)	3.2 (-5.7, 12)	-0.7 (-2.4, 1.0)
Triglycerides	141 (74)	110 (15, 210)	-7 (-42, 28)
VLDL-cholesterol	24 (9)	22 (10, 34)	-2.7 (-7.0, 1.6)
VLDL-triglycerides	75 (50)	110 (21, 190)	0 (-33, 32)
VLDL apolipoproteinB	12 (5)	4.2 (0.7, 7.7)	-1.6 (-2.7, -0.5)
VLDL-triglycerides/ VLDL-apoB-ratio <sup>†</sup>	13 (18%)	0.6 (0.2, 2.6)	1.1 (0.7, 1.8)
Apolipoprotein CII	2.7 (0.8)	1.1 (0.1, 2.2)	-0.1 (-0.4, 0.2)



Apolipoprotein CIII	7 (3)	7.5 (4.1, 11)	-0.2 (-1.4, 1.0)
Apolipoprotein CII/CIII ratio	0.5 (0.4)	-0.22 (-0.39, -0.05)	-0.03 (-0.07, 0.01)
Glucose	86 (21)	3.5 (-8.7, 16)	6.1 (-1.1, 13)

All values are mg/dl (except ratios and proportions)

\* Since most patients were below the detection limit, we report the percentage of patients with a detectable level at baseline and adjusted odds ratio for whether follow-up measurements were known to be higher than at baseline.

† Here we report the percentage of patients with an atherogenic VLDL-triglycerides/VLDL-apoB ratio at baseline and estimate the adjusted odds ratio of having a more atherogenic ratio over time on treatment, with the absolute difference between the observed ratio and 7.0 used as a measure of atherogenic risk.

**Figure legends:****Figure 1:**

Triglyceride levels over time for 74 patients treated with a LPV/r containing regimen. Figure 1a (left) shows a non-parametric average response curve (calculated using the default LOESS function in R 2.5.1) and individual response profiles for a random sample of 19 (25%) patients. Figure 1b (right) shows non-parametric average response curves for patients with baseline triglycerides  $\leq 150$  mg/dl (+ , - - -) and for patients with baseline triglycerides  $>150$  mg/dl (o , ---).

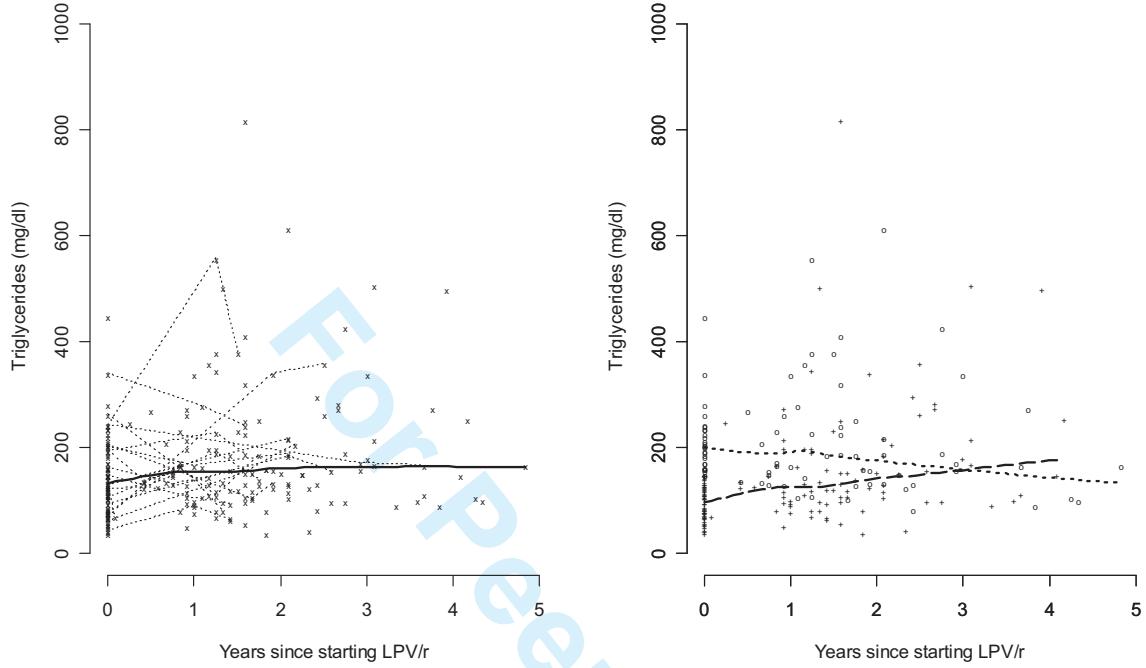
**Figure 2:**

Triglyceride versus other lipid levels for 74 patients on a LPV/r containing regimen. Non-parametric average response curves are shown (calculated using the default LOESS function in R 2.5.1) and the two values per patient are connected for each patient. In Figure 2b (top right) the atherogenic range of the VLDL triglyceride to VLDL apolipoprotein B ratio is indicated by vertical lines (between 6 and 8).

**Figure 3:**

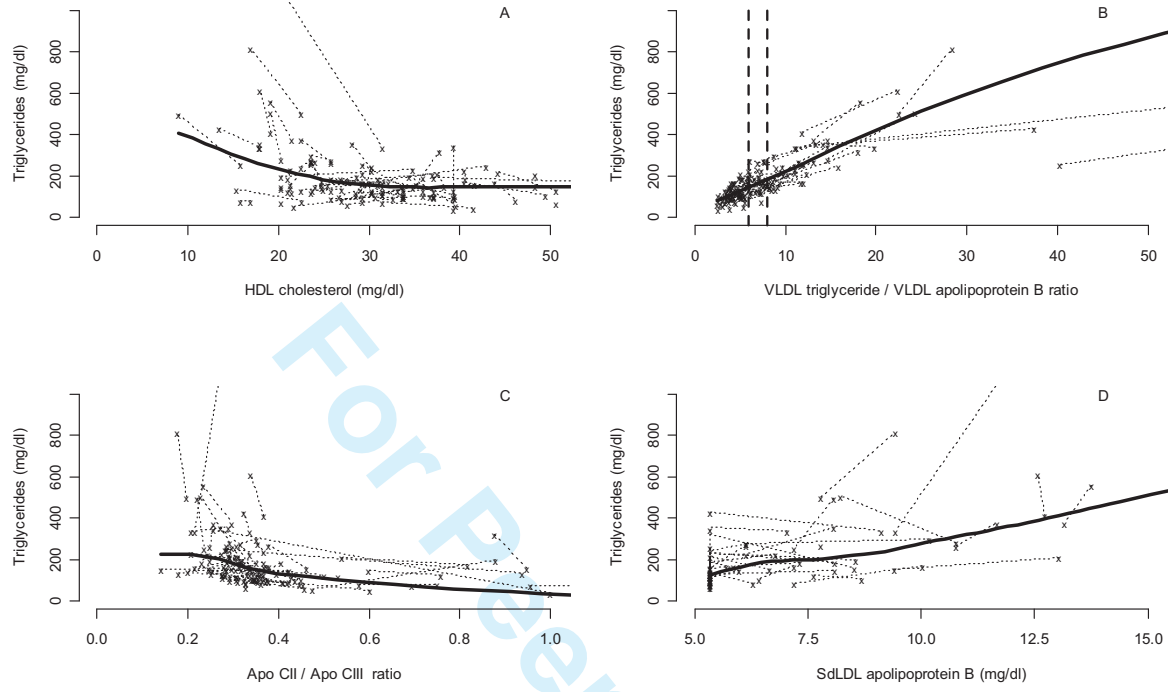
Lopinavir plasma levels and triglyceride for 74 patients treated with a LPV/r containing regimen. A non-parametric average response curve is shown (calculated using the default LOESS function in R 2.5.1) and the two values per patient are connected for each patient.

Figure 1



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Figure 2



AIDS Research and Human Retroviruses  
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Figure 3

