

Differentiation of Hypercholesterolemia associated with Antiretroviral Therapy

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BACKGROUND

Hypercholesterolemia frequently associated with antiretroviral treatment led to concerns about an increased cardiovascular risk in treated HIV+ patients. Previously it has been shown that the hypercholesterolemia found in HIV-positive patients is caused frequently by the elevation of very low density lipoprotein (VLDL). This type of hypercholesterolemia may be associated with a lower cardiovascular risk compared to hypercholesterolemia caused by an increase in low density lipoprotein LDL. To further estimate the cardiovascular risk we analysed the lipoprotein particles of HIV+ patients with antiretroviral treatment and compared the pattern with HIV-seronegative patients with familial combined

hyperlipidemia (high cardiovascular risk) and familial hypertriglyceridemia (low cardiovascular risk).

Familial combined hyperlipidemia (high cardiovascular risk) is caused by production of an increased number of small VLDL-particles in the liver – leading to a parallel increase in apolipoprotein B. Familial hypertriglyceridemia (low cardiovascular risk) is characterised by production of a normal number of large VLDL-particles containing more triglycerides than normal. As one VLDL particle contains one apolipoprotein B molecule the ratio of VLDL-triglycerides to VLDL-apolipoprotein B differs in these two lipoprotein disorders.

METHODS

Fasting serum samples were drawn from 187 consecutive HIV+ patients, 14 patients with familial hypertriglyceridemia and 10 patients with familial combined hyperlipidemia. Total cholesterol, LDL-, HDL-cholesterol, triglycerides, apolipoprotein

A1 and B were determined in serum. VLDL was prepared by ultracentrifugation and analysed for cholesterol, triglyceride and apolipoprotein B. Age, sex, CD4+, CD8+ cell status, CDC-stage, viral load, body mass index and antiretroviral therapy were recorded.

RESULTS

32/187 patients (17%) were treatment-naive, 20/187 (11%) received NRTIs only, 68/187 (36%) an NNRTI containing regimen and 64/187 (34%) a PI containing regimen (Fig. 1).

85/187 patients (45%) had hypercholesterolemia (>200 mg/dl). The classification according to Fredrickson is shown in Fig. 2. 12 of these 85 patients (14%) had an elevated LDL-cholesterol (Fredrickson type IIa), 14/85 (16%) high LDL- and VLDL-cholesterol (Fredrickson type IIb, 56/85 (66%) had an elevated VLDL-cholesterol (Fredrickson type IV) and 3/85 (4%) high HDL-cholesterol (Fig. 3).

PI treatment resulted in elevated total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides compared to patients without antiretroviral treatment. NNRTI treatment led to higher total cholesterol, LDL-cholesterol and HDL-cholesterol. NRTI-regimen were associated only with increased HDL-cholesterol (Tab. 1).

In a multivariate analysis an elevated total cholesterol was associated with ritonavir (p=0.002), age >40 years (p=0.004), efavirenz (p=0.007) and indinavir (p=0.03). An elevated LDL-

cholesterol was associated with fortovase (p=0.02), indinavir (p=0.02) and efavirenz (p=0.04). An increased HDL-cholesterol was associated with female sex (p=0.003) and didanosine (p=0.01). Hypertriglyceridemia was associated with stavudine and abacavir in a univariate analysis, but no variable survived in the multivariate model.

HDL-cholesterol in HIV+ patients is generally lower than in the general population, however compared to patients with familial combined hyperlipidemia or familial hypertriglyceridemia, HIV+ patients had higher HDL-levels (p<0.05) (Tab. 2).

VLDL composition was analysed in 34 HIV+ patients with elevated total cholesterol due to high VLDL-cholesterol (Fredrickson type 4). The ratio of VLDL-triglycerides to VLDL-apolipoprotein B was 16.2 ± 6.0 . This ratio was not different from 14 patients with familial hypertriglyceridemia (16.9 ± 6.0 , p = 0.61). But the ratio differed markedly from 10 patients with familial combined hyperlipidemia (6.8 ± 1.0 , p < 0.0001). The range of the individual measurements did not even show an overlap between familial combined hyperlipidemia and the other groups (Tab. 3).

Antiretroviral therapy n = 187

■ NNRTI 37%
■ NRTIs only 11%
■ PI 35%
■ naive 17%

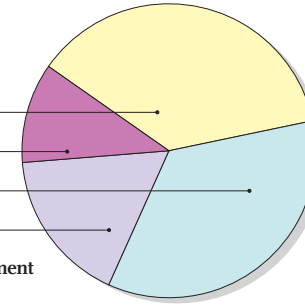


Fig. 1: Distribution of antiretroviral treatment regimen in the HIV+ study cohort

Fredrickson classification of lipoprotein pattern in HIV+ patients n=187

■ no lipoprotein disorder 39%
■ type IV 46%
■ type IIa 7%
■ type IIb 8%

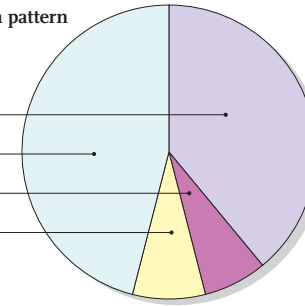


Fig. 2: Fredrickson classification of lipoprotein pattern in HIV+ patients

Lipoprotein pattern in HIV+ patients with hypercholesterolemia n = 85

■ VLDL 66%
■ HDL 4%
■ VLDL/LDL 16%
■ LDL 14%

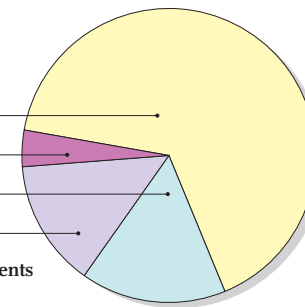


Fig. 3: Lipoprotein pattern in HIV+ patients with hypercholesterolemia

	total cholesterol (mg/dl)	LDL-cholesterol (mg/dl)	HDL-cholesterol (mg/dl)	triglycerides (mg/dl)
PI	221 ± 85**	113 ± 49*	43 ± 15*	352 ± 354*
NNRTI	214 ± 49**	116 ± 50*	47 ± 14**	314 ± 380
NRTI	179 ± 55	90 ± 45	45 ± 12*	237 ± 170
noART	175 ± 47	98 ± 43	38 ± 16	209 ± 122

Tab. 1: Lipid profiles in patients according to antiretroviral treatment group (PI = protease inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitors, NRTI = nucleoside reverse transcriptase inhibitors, noART = antiretroviral treatment naive), * p < 0.05, ** p < 0.001

	HIV+ patients (n = 34)	familial hypertriglyceridemia (n = 14)	familial combined hyperlipidemia (n = 10)
total cholesterol (mg/dl)	215 ± 65	238 ± 55	241 ± 30
LDL-cholesterol (mg/dl)	94 ± 45	88 ± 33	123 ± 25
HDL-cholesterol (mg/dl)	45 ± 11	31 ± 10*	36 ± 4*
triglycerides (mg/dl)	452 ± 446	552 ± 274	373 ± 150

Tab. 2: Lipid profiles in HIV+ patients with hypercholesterolemia due to increased VLDL (Fredrickson type IV), HIV-negative patients with familial hypertriglyceridemia and HIV-negative patients with familial combined hyperlipidemia, * p < 0.05.

	HIV+ patients with VLDL-hypercholesterolemia (n = 34)	familial hypertriglyceridemia (n = 14)	familial combined hyperlipidemia (n = 10)
mean ratio VLDL-TG / VLDL-Apo B	16,17	16,95	6,752**
Standard deviation	± 5,98	± 5,97	± 1,03
Range (min – max)	9,41 – 42,5	8,82 – 24,3	5,3 – 8,5

Tab. 3: VLDL-triglyceride / VLDL-apolipoprotein B ratio in HIV+ patients under ART, patients with familial hypertriglyceridemia (low cardiovascular risk) and patients with familial combined hyperlipidemia (high cardiovascular risk). The range of the ratio between HIV+ patients vs. familial combined hyperlipidemia or familial hypertriglyceridemia vs. familial combined hyperlipidemia shows no overlap and is highly significant (p < 0.0001).

CONCLUSION

The multivariate analysis of the data from the HIV+ cohort demonstrated, that PI treatment was associated with elevated total cholesterol and triglyceride levels, which seemed to be driven particularly by ritonavir and indinavir. Efavirenz was associated with both an increase in total and LDL-cholesterol. NRTIs seemed not to have a profound effect on the lipid profile.

The most common cause for high total cholesterol in HIV+ patients under ART was an elevation of VLDL. As VLDL contains 80% triglycerides and 20% of the mass of cholesterol the increased concentration of triglyceride-rich VLDL leads to an elevated total cholesterol. Less than a third of the patients with high total cholesterol had an elevated LDL-cholesterol, which is in contrast to the general HIV-negative population. This may be due to

genetically transmitted hypercholesterolemia (as in the general population) or an increased catabolism of VLDL to LDL.

The analysis of the VLDL-composition in HIV+ patients with Fredrickson type IV hyperlipidemia revealed the presence of large VLDL-particles with no increase in number. This pattern resembles familial hypertriglyceridemia. It is different from familial combined hyperlipidemia, where an increase in number of small, dense VLDL-particles occurs. In addition HDL-cholesterol was higher in HIV+ patients than in both HIV-negative groups. This indicates that the large subgroup of HIV+ patients under ART with hypercholesterolemia due to VLDL-cholesterol may have a lower cardiovascular risk than generally expected.