Metabolic complications of antiretroviral therapy
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Lipid profiles associated with antiretroviral drug choices

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Introduction

Since the introduction in 1996 of triple drug potent antiretroviral therapy (ART) including protease inhibitors (PIs) for the treatment of HIV infection there has been a dramatic decline in the mortality and morbidity of people living with HIV in developed countries.[1,2] Unfortunately these novel treatments are frequently associated with side effects. One of the most mysterious of these side effects related to the use of current ART is the lipodystrophy syndrome.[3,4] The syndrome includes a redistribution of fat, with loss of fat from the extremities, buttocks and face (so called lipoatrophy), with or without fat accumulation in the abdomen due to an increase in visceral fat or, more rarely, an increase in the amount of fat in the neck (buffalo hump) or breasts. Besides these phenotypic changes a large proportion of patients develop insulin resistance and elevated plasma concentrations of LDL-cholesterol, total cholesterol and triglycerides. The combination of hyperlipidemia, insulin resistance and visceral fat accumulation closely resembles the abnormalities seen in 'the metabolic syndrome X' and has raised the concern that HIV-infected patients treated with ART may be at increased risk of developing premature coronary artery disease (CAD).[5-10] In this review we will discuss the recent finding that different drug classes/ART regimens may importantly differ with respect to their effect on the plasma lipid profile. Based on this we will illustrate how such differences, together with knowledge of the presence of other classic CAD risk factors, opens the door for individualised treatment, based on criteria in addition to HIV-1 viral load and CD4-cell count.

Lipid changes in the natural course of HIV infection

Early in the natural course of HIV infection, as seen in other infections and chronic inflammatory conditions, HDL-cholesterol slightly decreases.[11,12] This decrease is followed by a decrease in the size of LDL particles leading to a rise in more artherogenic small dense LDL
particles (LDL type B).[13] Late in the infection when patients progress to the clinical diagnosis of AIDS triglyceride concentrations exhibit a slight rise.[11] This rise is probably due to an increased production of triglyceride rich VLDL particles and a decreased clearance of VLDL by the liver.[14] In a study performed in patients using zidovudine monotherapy triglycerides decreased.[15] For more details concerning metabolic disturbances in the natural course of HIV infection we would like to refer to a very comprehensive review written by Sellmeyer and Grunfeld. [16]

**Antiretroviral therapy-induced lipid changes**

Numerous studies have demonstrated that patients using PI-based ART develop atherogenic changes in their lipoprotein profile, consisting of elevations in triglyceride rich lipoproteins, total cholesterol and LDL-cholesterol. On top of this hyperlipidemia there is also considerable evidence for a decrease in endothelial function[17,18], an increase in intima media thickness[5,19] and impaired fibrinolysis[20] when using PI-based therapy, warranting the concern for an increased risk of CAD in HIV-infected patients. A very elegant in vitro study recently showed that several protease inhibitors selectively inhibit the proteasomal degradation of apolipoprotein B.[21] This protein is crucial for the formation of triglyceride- and cholesterol rich lipoprotein particles. A decreased clearance of apolipoprotein B may lead to an elevation of very low-density lipoproteins (VLDL) and low density lipoproteins (LDL). In healthy volunteers treatment with the protease inhibitor ritonavir indeed led to elevations of triglycerides, apolipoprotein B and VLDL-cholesterol.[22] Taken together these findings suggest that protease inhibitors, independently of HIV, directly contribute to the potentially deleterious effects on lipids. Another study showed that certain genetic ApoC-III polymorphisms are associated with higher PI-induced elevations in triglycerides, demonstrating that genetic predisposition may also play a role in the development of the hyperlipidemia associated with the use of PIs.[23]
There seem to be important differences in the extent of lipid elevations induced by the different PIs. This has been nicely reviewed for most of the currently licensed PIs by Penzak and Chuck.[24] The most pronounced elevations in triglycerides are seen with ritonavir-based regimens while all PIs to some extent lead to elevations in total- and LDL-cholesterol. An intriguing exception to this rule is the novel PI atazanavir which is currently in clinical development. No significant effects on the lipid profile were found when atazanavir was administered in clinical trials, either as the only PI in the regimen or together with saquinavir, nor were any changes observed on triglyceride secretion from adipocytes in vitro. [25-27] Elucidating which pathways atazanavir does not but currently available PIs do affect may provide important clues to the pathogenesis of PI-induced hyperlipidemia.

In contrast, in treatment naïve patients commencing non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens so far no atherogenic changes in the lipoprotein profile has been described. One study showed that with an efavirenz (EFV) based regimen total cholesterol and HDL cholesterol tend to rise after 48 weeks of treatment.[28] A nevirapine (NVP) based regimen in treatment naïve patients after 24 weeks of treatment however, led to a more prominent increase in HDL-cholesterol (+49%), accompanied with a rise in apolipoprotein AI and a decrease of the ratio of total cholesterol over HDL-cholesterol.[29] This effect on HDL-c was sustained after 96 weeks of treatment. [30] Many epidemiological studies have indicated that lipoprotein metabolism and in particular plasma levels of high-density lipoprotein (HDL) are strongly and independently inversely correlated with the risk of CAD[31,32]. In fact, in many of these studies the level of HDL-c and the ratio of total cholesterol over HDL-c (TC/ HDL-c ratio) have been the most powerful predictors of future coronary events. This inverse relationship between the level of HDL-c and the risk of developing premature CAD has been a consistent finding in a large number of prospective studies, such as the Framingham Heart Study[33,34], the PROCAM Study [35], the Helsinki Heart Study[36]
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and the Lipid Research Clinics Prevalence Mortality Follow-up Study[37]. Overall, it has been estimated from these studies that for every 0.025 mmol/l increase in HDL-c, the risk for CAD is reduced by 2-5%. The answer to the question whether different types of ART regimens will indeed result in clinically meaningful differences in CAD risk for patients receiving treatment for their HIV infection we must await the results of large studies such as the “Data collection of adverse events of anti-HIV Drugs “ (DAD) study which have been designed to prospectively address this issue.

“Switch” studies

Several studies have been conducted focussing on the effects of replacing the PI component in a regimen by antiretrovirals from another class to see to which extent the PI-induced hyperlipidemia may be reversed. The details of almost all of these switch studies have recently been nicely reviewed by R. Murphy ea.[38]

Replacing PIs by a nucleoside reverse transcriptase inhibitor (NRTI) in general leads to a decrease in total cholesterol and triglyceride concentrations. This has been demonstrated in several studies randomly comparing continuation of PI-containing ART with replacement of the PIs by abacavir. [39,40][41,42]. Although switching to the NNRTI NVP or EFV at first glance seems to reduce total cholesterol to a lesser extent, when examining the lipoprotein profile in more detail a rise in HDL-cholesterol is observed very similar to what was seen in ART-naïve patients commencing a NVP-based regimen. In a head to head comparison of replacing PIs by either NVP or EFV, the effect of increasing HDL-cholesterol was more pronounced when switching to NVP than EFV.[42] Recently a study with the novel PI atazanavir was presented demonstrating an improvement in total cholesterol, LDL-cholesterol and triglycerides, 12 weeks after replacing nelfinavir by atazanavir.[43] Without discussing each of the numerous switch studies in detail, it seems to be clear that the removal of PIs
from a regimen improves plasma lipids, and replacement by NVP in particular may result in a lipid and lipoprotein profile that may be expected to be associated with a reduced risk of CAD when compared to continued use of PIs. [44]

**Interpretation and consequences**

In the preceding paragraphs we have briefly summarised the distinguishing effects in HIV-infected patients of different initial types of ART as well as of switches to non-PI regimens on the lipid profile. Assuming that these differences in effect on lipids will translate into differences in risk of CAD, it becomes important to take this into account when choosing a first line regimen in a treatment-naïve patient. When doing so, it is however essential to at the same time account for other well-known CAD risk factors including age, smoking, etc. To illustrate how this could work in clinical practice, we have calculated the 10 year absolute CAD risk for two different 40 year old male subjects, using the PROCAM risk calculator[45] which is also available online at [www.CHD-taskforce.com](http://www.CHD-taskforce.com). Patient 1 is normotensive (tension 120/80 mmhg), does not suffer from diabetes, has never touched a cigarette in his life, but has developed hyperlipidemia (fasting total cholesterol 7.4 mmol/l, triglycerides 4.5 mmol/l, HDL-cholesterol 0.9 mmol/l, LDL-cholesterol 4.7 mmol/l) following the start of a PI-containing regimen which was necessary based on a CD4-cell count of 300 cells/mm³. Prior to the initiation of ART his lipid concentrations were more or less normal except for a somewhat low HDL concentration (total cholesterol 5 mmol/l, triglycerides 1 mmol/l, HDL-cholesterol 0.9 mmol/l, LDL-cholesterol 2.9 mmol/l). Patient 2 is hypertensive, with a systolic BP of 160 mmHg, smokes 20 cigarettes daily, does not suffer from diabetes and has a positive family history for CAD. His lipids and CD4 cell count match patient 1’s profile both prior and following the initiation of PI-containing therapy. For patient 1 the calculated CAD risk increases from 1.1% pre-therapy to 3.5% after the initiation of protease inhibitor based therapy. The calculated risk for this patient
remains unchanged when the patient would have started on a NVP-based regimen (figure A). In contrast, patient 2 has a 10 yr absolute risk of 5.7% prior to therapy, that increases to as much as 17.5% after the initiation of PI-based therapy. (figure 1B) If patient 2 would manage to stop smoking his 10-yr CAD risk would drop to 8.8%. Control of his hypertension, resulting in a systolic blood pressure (BP) of 120 mmHg would decrease the risk further to 5.1%. Finally, if his LDL-cholesterol and triglyceride concentrations could also be significantly lowered using pravastatin to 3.5 and 3 mmol/l, respectively, his remaining risk becomes 3.5%. In the event that patient 2 would have started NVP-containing rather than PI-containing ART, resulting in a 0.44 mmol/l rise in HDL-c and a 0.41 mmol/l rise in LDL-c, without being able to change any of the other risk factors his CAD risk lowers to 2.4%. (figure B)

**Figure A and B** The influence of traditional risk factors for coronary artery disease (CAD) in combination with different first line antiretroviral regimens on the calculated 10 yr. CAD risk using the PROCAM risk calculator (www.CHD-taskforce.com)

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**Figure A** represents the effects of either protease inhibitor- (PI) or nevirapine- (NVP) based first line antiretroviral therapy (ART) in a patient without additional risk factors known to increase the CAD risk. **Figure B** represents these effects in a patient with the same age and HIV parameters, but who smokes, has hypertension (systolic blood pressure (BP) of 160 mmHg) and a positive family history for CAD. It also shows the effects on the calculated 10 yr. CAD risk when one is able to modify traditional risk factors.
These two cases demonstrate the importance of assessing the CAD risk in each patient prior to the initiation of ART as well as to try to modify traditional CAD risk factors as much as possible. Successfully intervening with risk factors such as smoking and blood pressure unfortunately often may be easier said than done. As illustrated, under such circumstances initiation of treatment with regimens without a PI should be strongly considered, if permitted by a patient's viral and immunological markers. In such a context treatment with a NVP-containing regimen may be the preferred option given the most pronounced effects on HDL cholesterol.

HIV-associated mortality has dramatically decreased since the introduction of potent combination ART. This will result in an ageing patient population which will inevitably be followed by an increase in CAD risk factors, particularly the development of obesity, hypertension and type II diabetes mellitus. An assessment of such conditions should probably be repeated approximately annually in patients attending outpatient clinics. If modifiable CAD risk factors are identified, relatively aggressive intervention should be attempted as this would result in considerable CAD risk reduction.

Apart from modifying the ART regimen, one may also try to influence PI-associated hyperlipidemia with the use of HMG-CoA reductase inhibitors (statins) or fibrates. When considering to do so, potential interactions between PI and statins at the level of hepatic cytochrome P450 isozymes must be taken into account. Many of the currently licensed PI to some extent are inhibitors of cypP4503A4 isozymes leading to an increase in statin plasma concentrations[46,47] thereby increasing the risk for statin-related side effects. The only two statins which can be used relatively safely are atorvastatin and particularly pravastatin. The latter was shown to be effective in modifying plasma lipids in combination with dietary intervention.[48]
Conclusions

To conclude we want to stress that it is becoming increasingly important to make an adequate CAD risk assessment in each patient both prior to and approximately annually after the initiation of ART. In patients with an already considerable risk of CAD based on traditional risk factors, particularly when it is expected to be difficult to modify these, starting with either a triple NRTI or an NNRTI-based regimen may be the preferred option, given the propensity of such regimens to have either no or potentially even beneficial effects on the lipoprotein profile.
References


