

Chapter 9

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Introduction

Since the introduction of combination antiretroviral therapy (cART) in 1996, the life expectancy of patients with HIV-1 infection who have access to antiretroviral drugs has greatly increased and the incidence of opportunistic infections has diminished considerably[1]. However, longer term side effects were soon recognized, including changes in body fat distribution, dyslipidemia, and insulin resistance, together often called lipodystrophy syndrome. In addition, reduced bone mineral density has been observed.

The potential consequences of these side effects are becoming more and more clear. Fat distribution changes often lead to stigma and psychological distress, and may have a negative impact on treatment adherence [2], potentially leading to therapy failure due to the emergence of drug resistant virus. Furthermore, several of these metabolic side effects may increase the risk of cardiovascular disease, thereby partly counteracting the beneficial effects of cART on life expectancy. Limiting the metabolic complications of cART is therefore of importance for quality of life, long-term viral suppression and, hopefully, reduction of the risk for cardiovascular disease in patients with HIV-1 infection.

The aim of this thesis was to evaluate the effects of two potential treatment strategies to limit the metabolic complications of treatment of HIV infection. The first strategy consists of a thymidine analogue nucleoside reverse transcriptase inhibitor (TA-NRTI) sparing first-line therapy in cART naïve patients. This was studied in the MEDICLAS (**M**etabolic **E**ffects of **D**ifferent **C**lasses of **A**ntiretroviral**S**) trial, a multicenter, randomized trial comparing the TA- NRTI-containing regimen of zidovudine/lamivudine + lopinavir/ritonavir (ZDV/3TC/LPV/r) with the TA-NRTI-sparing regimen of nevirapine + lopinavir/ritonavir (NVP/LPV/r) in antiretroviral-naïve HIV-1-infected men. This thesis describes the effects of these regimens on body composition, lipid profile, insulin sensitivity, bone mineral density and vascular properties during 24 months of follow-up. This study was designed to gain more insight into the pathophysiology of metabolic complications and specifically the role of the TA-NRTI zidovudine in combination with lamivudine (ZDV/3TC).

With the second strategy, consisting of switching effective cART to a regimen based on atazanavir, a protease inhibitor with no significant effect on lipid profile, we aimed to investigate the reversibility of drug-induced hyperlipidemia in

treatment- experienced patients. This was evaluated within the ATHENA cohort, a nationwide observational cohort study of HIV-infected individuals in the Netherlands. In a retrospective cohort study in patients with sustained viral suppression, we compared patients who switched to atazanavir with those not switching to this drug. We studied which factors influence changes in lipids after switching to atazanavir, including the degree of hyperlipidemia and the presence of lipodystrophy prior to the switch.

Summary of main findings

Body fat distribution (chapter 2)

In patients randomized to the TA-NRTI containing regimen of ZDV/3TC/LPV/r in the MEDICLAS study, a progressive loss of limb fat (subcutaneous fat in arms and legs) was observed, commencing after 3 months of treatment. During the same time period, these patients experienced selective gain of visceral abdominal adipose tissue without any change in subcutaneous abdominal fat. These changes, loss of peripheral subcutaneous fat and accumulation of abdominal (visceral) fat, are characteristic for HIV-associated lipodystrophy. In contrast, patients assigned to the TA-NRTI sparing regimen of NVP/LPV/r demonstrated a generalized increase in fat mass, which included both subcutaneous and deep adipose tissue compartments, and may be seen as a “restoration to health” phenomenon. Consistent with these observations, lipodystrophy as defined according to the International Case Definition in those patients with complete 24 months follow up was present in 3/18 patients allocated to ZDV/3TC/LPV/r, but in none of the 22 evaluable patients allocated to NVP/LPV/r.

Dyslipidemia (chapters 2 and 8)

Total cholesterol and triglycerides increased significantly in all patients using both regimens in the MEDICLAS study. Due to the concomitant rise in HDL cholesterol, the total/HDL cholesterol ratio did not increase over time in either of the study arms. However, patients using the TA- NRTI sparing regimen of NVP/LPV/r developed higher total cholesterol levels than patients using ZDV/3TC/LPV/r, and an increase in LDL cholesterol was observed only in those on NVP/LPV/r. Other than what may have been expected considering that the use of NVP has been

demonstrated to be associated with an HDL increase, the HDL cholesterol rise in the NVP/LPV/r arm was not significantly greater than in the ZDV/3TC/LPV/r arm. The potential reversibility of cART-related dyslipidemia was studied in the retrospective cohort study of cART-experienced patients with sustained virological suppression. A significant decrease in total cholesterol and triglycerides was observed in patients switching to atazanavir from other regimens, compared to those continuing cART. The greatest changes were seen in patients with higher total cholesterol and triglyceride levels prior to the switch. Patients with physician reported lipodystrophy had similar improvements in both total cholesterol and triglyceride levels after switch to atazanavir as patients without lipodystrophy, after adjusting for baseline lipid levels. The presence of diabetes mellitus however was associated with a reduced effect of switching to atazanavir on total cholesterol. Virological failure was observed more frequently in patients switching to atazanavir compared to those continuing cART.

Insulin resistance (chapters 3 and 4)

Glucose metabolism and lipolysis were studied in depth by hyperinsulinemic euglycemic clamps using stable isotopes in a substudy of the MEDICLAS trial. In patients randomised to ZDV/3TC/LPV/r, but not in those randomised to the TANNRTI-sparing regimen of NVP/LPV/r, an early decrease in insulin mediated peripheral glucose uptake was observed within three months of initiating cART, in the absence of any change in body fat distribution. This was accompanied by a transient increase in basal lipolysis. During further follow-up a persistence of this change was demonstrated, followed by a transient reduced insulin sensitivity regarding inhibition of lipolysis after 12 months. In the NVP/LPV/r arm, increased insulin-mediated inhibition of hepatic glucose production was observed after 24 months, probably explained by lower glucagon levels and possibly by the increased adiponectin.

Insulin sensitivity was also estimated in the whole study population of the MEDICLAS study by the homeostasis model assessment of insulin resistance (HOMA), calculated from fasting glucose and insulin. We found no difference between the treatment arms in this measure of insulin sensitivity in all study patients.

Bone mineral density (chapter 5)

In all patients in the MEDICLAS trial, lumbar spine and femoral neck bone mineral density decreased considerably in the first year after initiation of antiretroviral therapy, and appeared to stabilize thereafter. However, patients randomised to ZDV/3TC/LPV/r had significantly greater bone loss measured by DXA scan in both locations compared to patients allocated to NVP/LPV/r. The difference in bone loss of the lumbar spine between the two study arms was not visible when measured by quantitative CT scan. Furthermore, markers of bone formation (osteocalcin), and bone resorption (urine deoxypyridinoline /creatinine ratio) increased significantly after start of cART in all patients, indicating an increase in bone turnover. Parathyroid hormone also increased in all patients, but to a significantly greater degree in those randomized to NVP/LPV/r.

Vascular properties (chapters 6 and 7)

We first attempted to determine the relative contribution of HIV infection itself, antiretroviral therapy and lipodystrophy to cardiovascular disease risk in patients with HIV infection. In a cross-sectional study we evaluated carotid artery intima-media thickness (C-IMT), a surrogate measure of atherosclerosis, and arterial stiffness, an independent predictor of cardiovascular morbidity and mortality, in HIV-infected patients and in healthy controls. After adjustment for traditional cardiovascular risk factors, HIV infected patients had a 0.067 mm (10.8%) greater C-IMT compared to controls, and significantly greater stiffness of the carotid and femoral arteries. Patients exposed to ART had similar C-IMT compared to ART-naïve patients, but significantly increased stiffness of the femoral artery. Cumulative use of PI and NRTI was independently associated with femoral artery stiffness after adjustment for traditional cardiovascular risk factors while no such association was found for cumulative NNRTI use. Arterial properties did not differ between patients with and without objectively determined lipodystrophy.

To further explore the role of antiretroviral therapy, in particular ZDV/3TC containing versus TA-NRTI sparing regimens, on C-IMT and arterial stiffness, we investigated these markers in patients initiating antiretroviral treatment in the MEDICLAS study. In addition, biochemical markers of endothelial dysfunction, which are commonly employed as biomarkers of early stages of atherosclerosis, were evaluated. We found that patients initiating cART had a deterioration of arterial wall properties, characterized by an increase in c-IMT, which appears greater than expected in healthy controls, and in arterial stiffness of the femoral

artery. These changes appeared regardless of allocated treatment. In contrast, levels of von Willebrand factor (vWF), an endothelial cell molecule involved in coagulation, and the endothelial adhesion molecules soluble vascular cell adhesion molecule-1 (sVCAM-1) and soluble intercellular adhesion molecule-1 (sICAM-1) significantly decreased in both arms. PAI-1, a marker of fibrinolytic activity, increased only in the NVP/LPV/r arm.

In conclusion, we demonstrated a deterioration of structural and functional arterial properties, related to an increase in cardiovascular risk, in the first two years after initiation of cART, but an improvement in several markers of endothelial function.

Overall interpretation of main findings

Both regimens in the MEDICLAS study led to excellent and similar virological suppression and restoration of immunity, but to different metabolic profiles. As described, patients randomized to ZDV/3TC/LPV/r developed body composition changes consistent with lipodystrophy, insulin resistance, an increase in total and HDL cholesterol and triglycerides, bone loss and deterioration of vascular properties. In contrast, patients using NVP/LPV/r did not develop lipodystrophy or insulin resistance and lost bone mineral density to a lesser degree than patients using ZDV/3TC/LPV/r. However, one of the expected advantages of including nevirapine in the NRTI sparing regimen, a higher increase in HDL cholesterol, was not observed, and patients allocated to this regimen had higher increases in total and LDL cholesterol, but similar deterioration of arterial properties.

The prospective evaluation of all these parameters and the comparison between the two study arms may increase our understanding of the pathogenesis of the metabolic adverse effects of antiretroviral therapy, and more specifically, considering that nevirapine has not been implicated in the pathogenesis of these adverse effects, of the role of ZDV/3TC in the pathogenesis of these metabolic side effects. In addition, they may give insight into the possibilities and limitations of a TA-NRTI sparing regimen in general, and the combination of NVP/LPV/r in particular, to limit the occurrence of these metabolic changes. Furthermore, the advantages and limitations of the atazanavir switch strategy will be discussed.

Pathogenesis of metabolic complications and the role of ZDV/3TC

Our findings clearly suggest that ZDV/3TC contributes to limb fat loss. Whether this is a synergistic effect in combination with LPV/r cannot be formally determined from this study, but seems unlikely given that treatment with LPV/r without ZDV/3TC (in the NVP/LPV/r arm) did not lead to loss of limb fat, but rather to an increase in fat in both arms and legs. Also, the recent results from a randomized trial in which antiretroviral naive subjects treated with dual NRTI's plus LPV/r exhibited significantly less loss of limb fat than those treated with two NRTI's plus efavirenz argue against an important contribution from LPV/r towards limb fat loss[3]. The role of ZDV/3TC in visceral fat accumulation is less clear. As there was a trend for patients on ZDV/3TC to have gained more intra-abdominal fat after 24 months, a contribution from these NRTI to this feature of lipodystrophy cannot be ruled out. The finding that visceral fat accumulation in patients on ZDV/3TC/LPV/r was observed in the context of stable subcutaneous adipose tissue, whereas in patients on NVP/LPV/r subcutaneous adipose tissue increased in parallel with visceral fat would seem to support a contribution of ZDV/3TC to visceral fat accumulation. Potential mechanisms for ZDV/3TC associated adipose tissue toxicity include mitochondrial toxicity, leading to depletion of mitochondrial DNA and adipocyte apoptosis, and interference with cellular transcription factors that are essential for adipocyte function. Alternatively, a selective autonomic neuropathy, with predominant sympathetic activity in subcutaneous fat and parasympathetic activity in visceral fat, has been proposed as a mechanism[4], which, if a link with ZDV/3TC would be established, might explain both subcutaneous fat loss and visceral fat accumulation.

The increase in total cholesterol and triglycerides in all patients in the MEDICLAS study was an expected finding considering that all patients used LPV/r and this drug is known for its lipid raising effects. Less is known on the effects of ZDV/3TC on the lipid profile, but as total cholesterol and triglyceride levels have been shown to decrease in patients in whom ZDV is replaced by tenofovir[5], a negative effect on lipids may exist. NVP, on the other hand, has been associated with marked increases in HDL cholesterol[6]. Our findings that the combination of NVP/LPV/r led to the highest total and LDL cholesterol levels, without the expected beneficial difference in HDL cholesterol, were somewhat surprising. Concerning the higher total and LDL cholesterol, differences in plasma or intracellular levels of lopinavir or ritonavir (the two components of LPV/r) between the two study groups may be speculated to play a role. However, only lopinavir plasma levels were available and

adjustment for differences in these levels between the two study arms did not change the results. Our findings are consistent with the dyslipidaemia described in patients switching to regimens of LPV/r with efavirenz, another NNRTI[7], but contrast with results from another small trial which also included a regimen of NVP/LPV/r in treatment-naive subjects[8]. Concerning the absence of a difference in HDL cholesterol between the two study arms, we calculated that our sample size was only sufficient to demonstrate a statistically significant difference between arms if this was 33% (or 0.29 mmol/l) or greater. Therefore it is possible that the true difference is smaller and a larger sample size would be required to detect this. Our finding that the dyslipidemia associated with cART is (partially) reversible after switching to an atazanavir based regimen, is compatible with the current view that cART-associated dyslipidemia is at least partially caused by direct effects of antiretroviral drugs. This improvement in lipid profile was similar in patients with lipodystrophy, but the presence of diabetes mellitus was associated with a reduced effect of switching to atazanavir on total cholesterol, suggesting that a clinically important degree of insulin resistance rather than the presence of the body composition changes characteristic of lipodystrophy is more important for maintaining or aggravating the dyslipidemia in these patients.

Concerning the early decrease in peripheral insulin sensitivity observed in patients using ZDV/3TC/LPV/r, we hypothesize that this also is a direct effect of ZDV/3TC since no changes in body fat distribution occurred at that time. The fat distribution changes occurring later on may have contributed to the persistence of this peripheral insulin resistance. Again, a synergistic effect with LPV/r cannot be excluded, but patients treated with LPV/r without ZDV/3TC (in the NVP/LPV/r arm) did not develop any reduced insulin sensitivity during two years after start of cART. Several mechanisms may be responsible for the effects of ZDV/3TC on peripheral insulin sensitivity, of which the most plausible is ZDV- induced mitochondrial dysfunction. This hypothesis is supported by a study in healthy volunteers, in which a similar effect on peripheral glucose uptake without changes in body composition was observed after treatment with stavudine for 4 weeks and was associated with a significant reduction in muscle mitochondrial DNA and reduced mitochondrial function[9]. How mitochondrial dysfunction interferes with peripheral insulin sensitivity has not been fully clarified yet, but accumulation of intracellular lipids due to reduced oxidative capacity may be one mechanism[10]. The transient increase in basal lipolysis and the transient decrease in insulin-mediated inhibition

of lipolysis may also be explained by direct effects of NRTI on adipocytes, either through mitochondrial dysfunction leading to oxidative stress or via inflammatory changes with production of pro-inflammatory cytokines, both resulting in enhanced lipolysis.

The apparent discrepancy between the clamp results in the sub-study and HOMA in the whole study population may imply that HOMA as a marker of insulin resistance may not be sensitive enough to detect the development of reduced insulin sensitivity in this population. Also, it should be kept in mind that the hyperinsulinemic euglycemic clamp measures insulin stimulated glucose disposal at high insulin levels, whereas HOMA reflects insulin sensitivity at basal insulin levels. Comparisons between these indices in non HIV infected populations have had heterogeneous results, ranging from high to non-significant correlation[11-13].

The mechanism of the rapid bone loss in patients initiating cART, as observed in all patients in the MEDICLAS study, has not been fully clarified. The contribution of antiretroviral drugs to reduced bone mineral density in HIV- infected patients is controversial. Different drugs appear to have heterogeneous effects on osteoblasts and osteoclasts in vitro[14-16]. On the other hand, as HIV infection has been associated with disturbed bone formation and resorption, and restoration of the bone remodelling process was observed after start of cART[17], suppression of HIV by cART may even have a beneficial effect on bone mineral density. The design of our study does not enable us to discern between direct effects of cART in general or any effect of suppression of HIV. In particular, the role of LPV/r in this process cannot be determined. Previous studies on the role of PI, including LPV/r, in bone loss have had conflicting results[18-20]. However, the greater bone loss in patients in the ZDV/3TC/LPV/r arm in the MEDICLAS study suggests that ZDV/3TC contributes to this feature. Both zidovudine and lamivudine have been shown to enhance osteoclastogenesis in vitro[16], which may lead to bone loss. Lactic acidemia due to NRTI related mitochondrial dysfunction has also been suggested to play a role in reduced BMD[21]. The increase in PTH does not appear to explain the greater degree of bone loss on ZDV/3TC/LPV/r, as parathyroid hormone actually increased to a significantly greater degree in patients randomized to NVP/LPV/r.

There was an apparent contrast between the results of the DXA scan and the quantitative CT scan concerning bone mineral density loss in the lumbar spine. It should be noted that quantitative CT scan in our study measured the central part of the vertebral body, i.e. trabecular bone, whereas a DXA scan cannot differentiate

between trabecular and cortical bone. Our findings therefore suggest that cortical bone is mainly affected in the ZDV/3TC/LPV/r group, whereas trabecular bone loss was similar in the two treatment groups. A histomorphometric study of bone biopsies could confirm this hypothesis. Another possible explanation for this discrepancy, underestimation of bone mineral density by DXA scan due to changes in surrounding fat and lean tissue, appears to be unlikely as analyses adjusted for local fat and lean mass did not change the results.

In order to investigate the effect the different cART-associated metabolic complications on the risk for cardiovascular disease, we studied various surrogate markers of atherosclerosis. These include carotid artery intima-media thickness (C-IMT), a valid measure of subclinical atherosclerosis, which has consistently been related to future cardiovascular events in population studies[22] and arterial stiffness, an independent predictor of cardiovascular morbidity and mortality[23-26]. In addition, biochemical markers of endothelial dysfunction, which are commonly employed as biomarkers of early stages of atherosclerosis[27], were studied. The findings of our cross-sectional study suggest that HIV infection itself is independently associated with increased C-IMT and generally increased arterial stiffness. A low degree of inflammation due to HIV may be a potential explanation, as both C-IMT and arterial stiffness have been shown to be elevated in chronic inflammatory conditions. Recent findings of a study in which patients who interrupted cART were shown to have an increase in several markers of inflammation and coagulation, which was independently associated with an increased risk of death[28, 29], appear to support this hypothesis. Theoretically, the use of cART could therefore have both beneficial and detrimental effects on the vascular wall, by suppressing HIV and inflammation and by influencing traditional risk factors such as hyperlipidemia and insulin resistance. Our findings that femoral artery stiffness deteriorated after start of cART, whereas carotid artery stiffness remained unchanged and several markers of endothelial function improved, suggest that both beneficial and detrimental effects of cART exist, and that the balance of these two may differ between arterial segments and in different parts of the arterial wall. Also, our finding that cumulative PI use is associated with femoral artery stiffness, while no such association was found for cumulative NNRTI use, may suggest that effects of ART on arterial stiffness vary between different drug classes. In conclusion, our findings indicate that the effects of HIV and cART on the arterial wall are complex. The net effect of different treatment strategies and interventions on the risk of cardiovascular disease may eventually only be revealed

by large intervention studies with clinical cardiovascular endpoints. It is unlikely however that such trials of sufficient size will ever be feasible in the context of HIV.

Clinical strategies to limit metabolic complications

The TA-NRTI sparing strategy

We found that lipodystrophy and insulin resistance did not occur in patients using a first line regimen of NVP/LPV/r, at least during the first two years after initiation of cART. In addition, the use of this TA-NRTI sparing regimen may limit the extent of bone mineral density loss after start of treatment. However, an important limitation of this regimen is the observed worse lipid profile. Although the total/HDL cholesterol ratio, a powerful predictor of cardiovascular risk, did not increase, the observed LDL cholesterol elevation gives rise to concern. Comparison of the ZDV/3TC containing with the ZDV/3TC sparing regimen with respect to their potential impact on longer- term cardiovascular risk is quite complex. Given our results with respect to the effects on insulin sensitivity and fat distribution, NVP/LPV/r should be expected to be superior to ZDV/3TC/LPV/r in terms of cardiovascular risk, whereas regarding lipid profiles the opposite would be expected to be true. Our study on surrogate markers of atherosclerosis and cardiovascular risk did not clarify this issue, there was no significant difference in deterioration of vascular properties between the two study groups. The absence of abnormalities in fat distribution and insulin sensitivity in the NVP/LPV/r arm may have been counteracted by the more severe dyslipidemia observed in patients using this regimen, although this remains speculative. Another possibility is that negative effects of some of these cardiovascular risk factors on the vascular wall may take longer to develop. Furthermore, due to the small number of patients, the MEDICLAS study had limited power to detect differences between study groups. Smaller differences may therefore have remained undetected.

The atazanavir switch strategy

We clearly demonstrated that the dyslipidemia associated with cART is (partially) reversible after switching to an atazanavir- based regimen, even in patients with reported lipodystrophy. Although it remains preferable to prevent lipid abnormalities from developing by choosing a first line therapy with relatively lipid friendly drugs, no such possibility existed in the past for many patients, especially for those with a longer history of antiretroviral treatment. A potential limitation of this strategy may be an increased risk of virological failure. This risk should always be taken into

account when switching from an effective antiretroviral regimen in a cART-experienced patient with possible resistant virus. In our study, patients switching to atazanavir had a higher rate of virological failure compared to patients in the continued cART group, and this difference remained when the analysis was restricted to patients switching from another PI to atazanavir without changes in their background regimen. Many factors, including higher rates of pretreatment before start of cART (leading to resistance mutations) and use of unboosted atazanavir (leading to lower atazanavir levels and therefore potentially less effective viral suppression), may have played a role. In apparent contrast with our findings, two other studies found comparable or lower rates of virological failure in patients switching to atazanavir compared to patients continuing their PI based regimen[30, 31]. These trials however included patients with a shorter duration of cART, and one of these excluded those with a history of virologic failure while receiving PI-based cART[30], in whom the risk of PI-associated resistance mutations would be expected to be low compared to our more experienced study population. A careful review of antiretroviral treatment history, previous virological failure and, when possible, resistance testing, will always be necessary before considering any switch of antiretroviral treatment, and the beneficial effect on lipid profile after switching to atazanavir should be balanced against a possible higher risk of virological failure.

Implications for current treatment of HIV infection

Our findings support to no longer recommend ZDV/3TC as one of the preferred backbones of first-line antiretroviral therapy. Recent updates of treatment guidelines in Europe and the United States have removed ZDV/3TC from the list of preferred components of initial cART[32-34]. However, worldwide ZDV/3TC is still widely used and both TA-NRTI (stavudine and ZDV) are currently recommended as one of the preferred first line NRTI options in many resource- limited countries for reasons of cost and availability. As antiretroviral treatment availability expands, lipodystrophy and other metabolic abnormalities are increasingly being reported from resource- limited settings. Hopefully, non TA-NRTI will become affordable and available for patients in these countries in the near future.

Despite its beneficial effects on body composition and insulin sensitivity, the NVP/LPV/r regimen does not appear to be the best choice for first-line antiretroviral therapy due to its detrimental effects on lipid profile. With the currently available

drugs, combinations of non-TA-NRTI with an NNRTI or a PI with less effects on lipid profile would seem preferable in order to limit most metabolic abnormalities, although longer term comparisons between these regimens should be performed.

Future perspectives

Many of the metabolic complications of treatment of HIV infection may become more prominent as patients age. Thus, as patients with HIV infection are getting older, prevention of these complications is becoming an even more important issue. Unraveling the underlying mechanisms may eventually aid the development of new drugs and treatment strategies that not only effectively suppress viral replication and restore immunity, but also have the least possible side effects.

Pathogenesis of metabolic complications

Concerning the pathogenesis of metabolic complications of antiretroviral therapy, many questions remain. One of the possibilities to gain more insight into the pathogenesis of the lipodystrophy syndrome is to study molecular effects of cART on adipose tissue. In the MEDICLAS study, adipose tissue biopsies from the abdomen and thigh were performed. This stored material will be used to prospectively analyse changes in mitochondrial DNA content and quality, mitochondrial function, markers of inflammation and expression of a range of genes involved in lipid and glucose metabolism.

Another topic of interest is microvascular function. Microvascular dysfunction (impaired capillary recruitment and microvascular vasodilatation) has been postulated to form a pathophysiological link between obesity, insulin resistance and hypertension[35]. Obesity, especially visceral adiposity, is associated with impaired capillary recruitment [36], which in turn has been postulated to play a causative role in decreased insulin mediated peripheral glucose uptake[35]. Defects in microcirculation have also been observed in patients with hypertension[37, 38]. Although hypertension is not a recognized part of the constellation of metabolic abnormalities in HIV- infected patients treated with cART, it would be interesting to explore whether decreased peripheral insulin sensitivity in patients with lipodystrophy is also associated with disturbances in microcirculation. The prospective measurements of microvascular function (capillary recruitment induced

by post-occlusive reactive hyperemia and endothelium-dependent vasodilatation in response to iontophoresis of acetylcholine) performed in a subgroup of patients in the MEDICLAS study will give us the opportunity to study any changes in microcirculation after initiation of cART and associations between microvascular function, objectively determined insulin sensitivity and (visceral) fat accumulation.

Novel strategies to limit metabolic complications of treatment for HIV infection

As new antiretroviral drugs are being developed and become available, alternative TA-NRTI sparing regimens are becoming feasible, which may have less detrimental effects on lipids than the TA-NRTI sparing regimen of NVP/LPV/r used in the MEDICLAS study, while maintaining the beneficial effects on body composition and insulin sensitivity. These include regimens with non TA-NRTI such as abacavir or tenofovir in combination with lamivudine or emtricitabine. In two studies, the TA-NRTI sparing regimen of tenofovir/lamivudine with efavirenz was associated with significantly less lipoatrophy and smaller increases in total cholesterol and triglycerides after 144 weeks than the TA-NRTI containing regimens of ZDV/3TC and efavirenz [39] and stavudine/lamivudine/efavirenz[40]. Other potential regimens include PI – NNRTI combinations with other PI than LPV/r, but also NRTI class sparing regimens incorporating the latest antiretroviral drug classes such as CCR5 inhibitors and HIV integrase inhibitors. Long term prospective evaluation of such alternative treatment strategies incorporating assessments of both body composition and metabolic effects may eventually identify first line regimens which lack detrimental effects on both body composition and lipid and glucose metabolism. These evaluations should also include bone density measurements, especially when using tenofovir- containing regimens, as some concern has risen that this frequently used non TA-NRTI may lead to more bone loss.

Similarly, as more antiretroviral drugs with less unfavorable effects on lipid profile are becoming available, switching to drugs other than atazanavir may become a valuable strategy to ameliorate cART-associated dyslipidemia in cART-experienced patients.

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