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Published in: The Journal of Infectious Diseases

DOI: 10.1086/597475

Citation for published version (APA):

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Increase in Carotid Artery Intima-Media Thickness and Arterial Stiffness but Improvement in Several Markers of Endothelial Function after Initiation of Antiretroviral Therapy

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Background. The risk of cardiovascular disease in human immunodeficiency virus (HIV)–infected patients is an increasing concern. We studied the changes in vascular properties after the initiation of combination antiretroviral therapy (cART) as well as the contribution of different drug classes.

Methods. cART-naive men were randomized to receive either lopinavir/ritonavir (LPV/r) plus zidovudine/lamivudine (ZDV/3TC) (n = 19) or LPV/r plus nevirapine (NVP) (n = 18). Carotid artery intima-media thickness (C-IMT), arterial stiffness (distensibility coefficients [DCs] and compliance coefficients [CCs] of the carotid, femoral, and brachial arteries; carotid elastic modulus; and augmentation index), and markers of endothelial function (soluble vascular cell adhesion molecule [sVCAM]–1, intercellular adhesion molecule [sICAM]–1, plasma von Willebrand factor (vWF) antigen, and plasminogen activator inhibitor–1 antigen) and inflammation (high-sensitivity C-reactive protein) were measured before the initiation of cART and after 3, 12, and 24 months of cART.

Results. C-IMT increased by 0.061 ± 0.016 mm (P < .001) in the ZDV/3TC/LPV/r arm and by 0.044 ± 0.018 mm (P = .012) in the NVP/LPV/r arm (data are estimated means ± SEs). Femoral artery DC (−1.66 ± 0.78 × 10−3/kPa [P = .035]) and CC (−0.11 ± 0.053 mm²/kPa [P = .043]) decreased in the ZDV/3TC/LPV/r arm and femoral DC decreased in the NVP/LPV/r arm (−1.72 ± 0.85 × 10−3/kPa [P = .046]), with no significant difference in C-IMT or arterial stiffness between arms. sVCAM-1, sICAM-1, and vWF levels decreased significantly in both groups.

Conclusion. C-IMT and femoral artery stiffness increased after the initiation of cART, whereas several markers of endothelial function improved, regardless of the composition of cART.

Trial registration. ClinicalTrials.gov identifier: NCT00122226.

The risk of cardiovascular disease in HIV-infected patients is an increasing concern. Although the findings of retrospective cohort studies addressing the risk contributed by the use of combination antiretroviral therapy (cART) and HIV protease inhibitors (PIs) in particular have been equivocal [1–6], a large prospective study found a significant association between cumulative exposure to PI-containing (but not to nonnucleoside reverse-transcriptase inhibitor–containing) cART and the risk of myocardial infarction [7]. Recently, the same
METHODS

Subjects and study design. We studied a subgroup of participants in the Metabolic Effects of Different Classes of Antiretrovirals (MEDICLAS) trial, a multicenter, multinational, single-blinded, randomized trial of 36 months’ duration conducted in previously antiretroviral-naive male patients 18–70 years old with an indication to initiate cART. The trial compared an NRTI-containing regimen of LPV/r (400/100 mg twice daily) plus ZDV/3TC (300/150 mg twice daily) with an NRTI-sparing regimen of LPV/r (533/133 mg twice daily) plus NVP (200 mg twice daily). The main objective of the trial was to assess and compare the impact of both treatments on body fat distribution and metabolic complications. Subjects with severe obesity (defined as a body mass index [BMI] >35; BMI was calculated as the weight in kilograms divided by the square of height in meters), a history of hyperlipidemia, or diabetes mellitus were excluded. For the purpose of the substudy, patients taking medication that could influence vascular measurements were also excluded.

Patients were recruited into the substudy if they were recruited at the VU University Medical Center, Amsterdam, the Netherlands, or were referred from other participating centers. The study was approved by the ethics committees of all participating centers. Written informed consent was obtained from all participants before study entry. We report here the results after 24 months of follow-up.

Randomization. At the central study coordinating center, a treatment allocation sequence (1:1 for ZDV/3TC/LPV/r and NVP/LPV/r) was generated using the minimization variable BMI (<25 vs. >25).

Procedures. C-IMT, arterial stiffness, and markers of endothelial function and inflammation were measured at baseline and at 3, 12, and 24 months after the initiation of treatment. At the same time points, body fat distribution, fasting lipid profile, and glucose metabolism markers were assessed as described elsewhere [15]. Limb and trunk fat were quantified by dual energy X-ray absorptiometry (Hologic QDR-4500W; whole body; software version 8.26A.5). A standardized single-slice abdominal computed tomography scan was performed, from which the area of visceral, subcutaneous, and total adipose tissue was determined. Lipid levels included measurements of total, high-density lipoprotein (HDL), and (calculated) low-density lipoprotein (LDL) cholesterol and triglycerides. Insulin sensitivity was estimated by homeostasis model assessment of insulin resistance (HOMA), calculated as [fasting insulin (μU/mL) × fasting glucose (mmol/L)]/22.5.

Arterial properties. All C-IMT and arterial stiffness measurements were performed by a single investigator in a blinded fashion. Arterial properties for the estimation of arterial stiffness were assessed according to guidelines for user procedures and with the use of reproducible and valid methods and devices [17]. All measurements were done after an 8-h fast. Participants abstained from smoking on the study day and rested in a supine position for 15 min in a quiet, temperature-controlled room before measurements were taken. Properties of the right common carotid and common femoral and brachial arteries were obtained using an ultrasound scanner equipped with a 7.5-MHz linear array probe (Pie Medical Imaging). This scanner was connected to a computer equipped with an acquisition system and a vessel wall movement detector software system (Wall Track System 2; Pie Medical Imaging). This device enables measurements of arterial diameter, distension, and C-IMT, as described elsewhere [17]. The mean values for diameter, distension, and
C-IMT from 3 consecutive measurements were used in the analyses. The carotid artery was measured ∼10 mm proximal to the beginning of the bulb, the femoral artery was measured 20 mm proximal to the flow divider, and the brachial artery was measured 20 mm above the antecubital fossa. C-IMT was measured in a region free of plaque (defined as C-IMT > 1.5 mm).

Throughout the period of ultrasonography, blood pressure and heart rate were assessed at 5-min intervals by means of an oscillometric device (model BP-8800; Colin Press-Mate). Brachial artery pulse pressure was defined as systolic minus diastolic blood pressure, and pulse pressure at the carotid and femoral arteries was calculated according to the calibration method first described by Kelly and Fitchett [18], using distension waveforms as adapted by van Bortel et al. [19].

The mean diameter, distension, and local pulse pressure were used to estimate the distensibility coefficient (DC) and compliance coefficient (CC), as described elsewhere [17]. Distensibility reflects the elastic properties of the artery, and compliance reflects its buffering capacity. DC and CC are indices of elasticity and, therefore, are inversely related to arterial stiffness. From C-IMT, diameter, and DC, we calculated carotid Young elastic modulus (YEM) [17], an estimate of the intrinsic elastic properties of the vessel wall.

Radial applanation tonometry was used to obtain the aortic augmentation index and was performed with a Millar piezoresistive pressure transducer connected to an arterial waveform analysis device (Sphygmocor; Atcor Medical). The aortic augmentation index was calculated as augmented pressure divided by (tonometrically derived) central pulse pressure.

Reproducibility for arterial property measurements was assessed in 10 healthy subjects (5 men and 5 women; mean ± SE age, 30.3 ± 8.5 years) who were examined by the same observer twice, 1 week apart. The median intraobserver intersession coefficients of variation were as follows: for C-IMT, 2.4%; for diameter, 1.0% (carotid), 0.3% (femoral), and 1.1% (brachial); for distension, 1.9% (carotid), 1.4% (femoral), and 2.4% (brachial); for DCs, 4.2% (carotid), 5.6% (femoral), and 2.2% (brachial); for CCs, 4.0% (carotid), 3.3% (femoral), and 3.3% (brachial); for YEM, 5.4%; and for the augmentation index, 19.6%.

Markers of endothelial function and inflammation. Plasma von Willebrand factor (vWF) antigen was quantified by sandwich ELISA, using rabbit anti–vWF antigen IgG as catching antibody and peroxidase-conjugated rabbit anti–vWF antigen as detecting antibody (Dako). o-Phenylenediamine (Sigma Chemical) was used as substrate. vWF levels were expressed as the percentage of antigen levels in normal pooled plasma, defined as 100%. The intra- and interassay coefficients of variation were 2.0% and 8.2%.

Soluble vascular cell adhesion molecule (sVCAM)–1 and soluble intercellular adhesion molecule (sICAM)–1 were measured in duplicate by means of commercially available ELISA kits (Diaclone). The intra- and interassay coefficients of variation were 4.4% and 4.6% for sVCAM–1 and 4.0% and 7.3% for sICAM–1, respectively.

Human plasminogen activator inhibitor (PAI)–1 antigen was measured by sandwich ELISA (Elitest; Hyphen BioMed), with intra- and interassay coefficients of variation of 2.7% and 9.8%. High–sensitivity C-reactive protein (hs-CRP) was measured by a highly sensitive in-house sandwich ELISA, using rabbit anti–human CRP immunoglobulin and peroxidase-conjugated rabbit anti–human CRP immunoglobulin as catching and detecting antibody, respectively (Dako), and o-phenylenediamine (Sigma Chemical) as substrate. Intra- and interassay coefficients of variation were 3.9% and 6.8%, respectively [20].

Statistical analysis. Analyses were done on an intent-to-treat basis. Within-group changes and between-group differences for the overall course of the study and at study visits were analyzed by mixed-model repeated-measures analysis, with adjustment for baseline values. Differences for which \( P < .05 \) were considered statistically significant. Data are presented as estimated means ± SEs. SAS statistical software (version 9.2) was used.

RESULTS

Patient characteristics. Fifty patients were included in the MEDICLAS study, of whom 37 were enrolled in this substudy. Nineteen were randomized to receive ZDV/3TC/LPV/r, and 18 were randomized to receive NVP/LPV/r. Baseline characteristics are shown in table 1. Two patients in each arm used antihypertensive medication (in the ZDV/3TC/LPV/r arm, 1 patient used nifedipine and lisinopril, and 1 used metoprolol; in the NVP/LPV/r arm, 1 patient used hydrochlorothiazide with atenolol added just before 24 months, and 1 used metoprolol and hydrochlorothiazide with losartan added after 12 months). None of the patients used lipid-lowering drugs at baseline, but 1 patient randomized to receive ZDV/3TC/LPV/r started taking fish oil capsules after 3 months with fenofibrate added after 19 months, and 3 patients randomized to receive NVP/LPV/r started taking pravastatin after 8, 20, and 23 months, respectively.

ART was modified for 6 patients. In the ZDV/3TC/LPV/r arm, 1 patient switched from ZDV to tenofovir after 3 months for anemia, 1 switched to tenofovir/3TC/efavirenz after 4 months for anemia and hypercholesterolemia, and 1 switched from LPV/r to NVP after 17 months for hypercholesterolemia. In the NVP/LPV/r arm, 2 patients switched to ZDV/3TC/NVP, 1 after 3 months for diarrhea and 1 after 24 months at the patient’s request. For 1 patient, NVP was replaced with efavirenz after 2 months for hepatotoxicity and rash. One patient in the NVP/LPV/r arm died at home, presumably of an acute myocardial infarction, after 14 months.

Body composition, lipid profile, and insulin sensitivity. Patients randomized to receive ZDV/3TC/LPV/r had a progressive decline in limb fat after the first 3 months, whereas limb fat increased in patients randomized to receive NVP/LPV/r (table 2). Trunk fat increased in
both groups, but visceral adipose tissue increased only in patients receiving ZDV/3TC/LPV/r. Total and HDL cholesterol levels increased in both arms, but after 24 months patients randomized to receive NVP/LPV/r had higher total and HDL cholesterol levels than did those randomized to receive ZDV/3TC/LPV/r. LDL cholesterol level increased only in the NVP/LPV/r arm. HOMA results did not change in either of the arms. However, in a subgroup of patients in whom glucose metabolism was studied in more detail by means of the hyperinsulinemic-euglycemic clamp technique, peripheral insulin sensitivity was shown to decrease after 3 months only in the ZDV/3TC/LPV/r arm [16]. Changes in body composition and lipid profile in substudy participants were comparable to those in patients in the main study, except that in the main study the between-group difference in HDL cholesterol level was not significant [15].

Virology and immunology. Patients in both arms had similar immunologic and virologic responses to cART (table 2). The median (interquartile range) increase in CD4 cell count over 24 months was 280 (205–455) and 310 (210–370) 10^6 cells/L in the ZDV/3TC/LPV/r and NVP/LPV/r arms, respectively. At 24 months, 17 (89%) of 19 of patients randomized to receive ZDV/3TC/LPV/r and 15 (83%) of 18 randomized to receive NVP/LPV/r had a plasma HIV RNA level <50 copies/ml.

C-IMT. C-IMT increased significantly over 24 months—by 0.061 ± 0.016 mm (P < .001) in the ZDV/3TC/LPV/r arm and by 0.044 ± 0.018 (P = .12) in the NVP/LPV/r arm—with no significant difference between groups (table 3).

Stiffness of the carotid, brachial, and femoral arteries and augmentation index. There was no change in carotid DC or CC over 24 months in either of the groups (table 3). Carotid artery YEM decreased by −0.08 ± 0.03 × 10^{-3} kPa (P < .001) in the ZDV/3TC/LPV/r arm and by −0.05 ± 0.03 × 10^{-3} kPa (P = .07) in the NVP/LPV/r arm, with no overall difference between groups. Brachial artery stiffness (DC and CC) did not change in either of the study arms.

In the ZDV/3TC/LPV/r arm, femoral artery DC and CC decreased over 24 months (−1.66 ± 0.78 × 10^{-3} kPa [P = .035] and −0.11 ± 0.053 mm²/kPa [P = .043] for DC and CC, respectively), mainly because of a decrease in distention. In the NVP/LPV/r arm, femoral artery DC decreased over time (−1.72 ± 0.85 × 10^{-3} kPa [P = .046]), mainly because of an increase in diameter, but femoral artery CC did not change (−0.041 ± 0.059 mm²/kPa [P = .48]). There was no overall difference in femoral artery stiffness between groups.

The augmentation index did not change in either of the arms.

Markers of endothelial function and inflammation. Levels of sICAM-1, sVCAM-1, and vWF decreased significantly after the initiation of cART in both study arms (table 3). After 24 months, levels of sVCAM-1 were higher in patients in the ZDV/3TC/LPV/r arm than in patients in the NVP/LPV/r arm (difference, 178 ± 87 ng/mL; P = .043), whereas there was no difference in sICAM-1 and vWF levels between study arms. PAI-1 levels increased by 61 ± 26 ng/mL (P = .024) in the NVP/LPV/r arm but remained unchanged in the ZDV/3TC/LPV/r arm, leading to a difference of 57 ± 27 ng/mL (P = .034) between study arms after 24 months.

Although hsCRP levels did not change significantly over 24 months in either of the study arms, there was a significant difference overall between arms due to higher levels in the NVP/LPV/r arm after 3 and 12 months.

All analyses were repeated after exclusion of patients taking antihypertensive and lipid-lowering drugs and after exclusion of patients who changed antiretroviral medication. Also, analyses were repeated with adjustment for baseline differences in age and smoking. Results for these analyses were essentially identical to the results reported above (same effect sizes with slight loss of significance levels to .05 < P < .08 for some parameters).

**DISCUSSION**

The main findings of the present study were that patients initiating cART experienced a deterioration in several arterial wall properties—that is, increases in C-IMT and in femoral artery stiffness and decreases in carotid and femoral artery YEM.
Table 2. Body composition, lipid profile, insulin sensitivity, virology, and immunology.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ZDV/3TC/LPV/r (n = 19)</th>
<th>NVP/LPV/r (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Month 0</td>
<td>Month 3</td>
</tr>
<tr>
<td>BMI</td>
<td>23.0 ± 0.2</td>
<td>23.0 ± 0.2</td>
</tr>
<tr>
<td>CT/DEXA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limb fat, g†</td>
<td>5966 ± 215</td>
<td>6267 ± 224</td>
</tr>
<tr>
<td>Trunk fat, g</td>
<td>6790 ± 236</td>
<td>6754 ± 247</td>
</tr>
<tr>
<td>Total fat, g</td>
<td>12,752 ± 386</td>
<td>13,016 ± 406</td>
</tr>
<tr>
<td>VAT, cm²</td>
<td>105.1 ± 6.9</td>
<td>97.1 ± 7.1</td>
</tr>
<tr>
<td>SAT, cm²</td>
<td>110.7 ± 4.7</td>
<td>108.4 ± 4.8</td>
</tr>
<tr>
<td>Lipid profile (fasting), mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol†</td>
<td>4.2 ± 0.2</td>
<td>5.2 ± 0.2</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>1.10 ± 0.05</td>
<td>1.23 ± 0.05‡</td>
</tr>
<tr>
<td>LDL cholesterol†</td>
<td>2.5 ± 0.1</td>
<td>2.7 ± 0.1</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.3 ± 0.4</td>
<td>2.8 ± 0.4</td>
</tr>
<tr>
<td>Insulin sensitivity (fasting)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOMA values</td>
<td>1.8 ± 0.2</td>
<td>1.5 ± 0.2</td>
</tr>
<tr>
<td>Virology/immunology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 cell count, median (IQR), 1 x 10^6 cells/L</td>
<td>220 (170-264)</td>
<td>344 (250–450)</td>
</tr>
<tr>
<td>HIV RNA level &lt;50 copies/mL, no. (%)</td>
<td>0 (0)</td>
<td>11 (58)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are estimated means ± SEs, unless otherwise indicated. Statistical significance (P < .05) is indicated for within-group differences between 0 and 24 months (*), for between-group differences for the overall course of the study from 0 to 24 months (**), and for between-group differences at the indicated study time point (†). BMI, body mass index (calculated as the weight in kilograms divided by the square of height in meters); CT, computed tomography; DEXA, dual energy X-ray absorptiometry; HDL, high-density lipoprotein; HOMA, homeostasis model assessment of insulin resistance; IQR, interquartile range; LDL, low-density lipoprotein; NVP/LPV/r, nevirapine/lopinavir/ritonavir; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; ZDV/3TC/LPV/r, zidovudine/amprenovir/lopinavir/ritonavir.
Table 3. Carotid artery intima-media thickness (C-IMT), arterial stiffness estimates, and biochemical markers of endothelial function and inflammation.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ZDV/3TC/LPV/r (n = 19)</th>
<th>NVP/LPV/r (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Month 0</td>
<td>Month 3</td>
</tr>
<tr>
<td><strong>Carotid artery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-IMT, mm</td>
<td>0.62 ± 0.01</td>
<td>0.62 ± 0.01</td>
</tr>
<tr>
<td>DC, 10⁻³kPa</td>
<td>23.8 ± 0.8</td>
<td>25.9 ± 0.8‡</td>
</tr>
<tr>
<td>CC, mm²/kPa</td>
<td>0.99 ± 0.03</td>
<td>1.05 ± 0.03</td>
</tr>
<tr>
<td>Elastic modulus, 10⁻¹ kPa</td>
<td>0.57 ± 0.02</td>
<td>0.51 ± 0.02</td>
</tr>
<tr>
<td><strong>Brachial artery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DC, 10⁻³kPa</td>
<td>12.7 ± 1.0</td>
<td>13.5 ± 1.0</td>
</tr>
<tr>
<td>CC, mm²/kPa</td>
<td>0.19 ± 0.01</td>
<td>0.21 ± 0.01</td>
</tr>
<tr>
<td><strong>Femoral artery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DC, 10⁻³kPa</td>
<td>12.1 ± 0.6</td>
<td>11.6 ± 0.7</td>
</tr>
<tr>
<td>CC, mm²/kPa</td>
<td>0.88 ± 0.05</td>
<td>0.83 ± 0.05</td>
</tr>
<tr>
<td>Augmentation index</td>
<td>12.1 ± 1.6</td>
<td>13.8 ± 1.6</td>
</tr>
<tr>
<td>sICAM-1 level, ng/mL</td>
<td>880 ± 37</td>
<td>775 ± 38</td>
</tr>
<tr>
<td>sVCAM-1 level, ng/mL</td>
<td>1566 ± 55</td>
<td>1257 ± 56</td>
</tr>
<tr>
<td>WVF level, %</td>
<td>219 ± 9</td>
<td>179 ± 9</td>
</tr>
<tr>
<td>PAI-1 level, ng/mL</td>
<td>111 ± 17</td>
<td>103 ± 17</td>
</tr>
<tr>
<td>hsCRP level, mg/L†</td>
<td>2.5 ± 0.8</td>
<td>1.9 ± 0.8‡</td>
</tr>
</tbody>
</table>

**NOTE.** Data are estimated means ± SEs. Statistical significance (P < .05) is indicated for within-group differences between 0 and 24 months (*), for between-group differences for the overall course of the study from 0 to 24 months (†), and for between-group differences at the indicated study time point (‡). CC, compliance coefficient; DC, distensibility coefficient; hsCRP, high-sensitivity C-reactive protein; NVP/LPV/r, nevirapine/lopinavir/ritonavir; PAI-1, plasminogen activator inhibitor–1 antigen; sICAM, soluble intercellular adhesion molecule; sVCAM, soluble vascular cell adhesion molecule; vWF, plasma von Willebrand factor antigen; ZDV/3TC/LPV/r, zidovudine/ stavudine/lopinavir/ritonavir.

stiffness—that appeared regardless of allocated treatment. In contrast, levels of vWF, an endothelial cell molecule involved in coagulation, and of the endothelial adhesion molecules sICAM-1 and sVCAM-1 significantly decreased in both groups, indicating an improvement in endothelial function after the initiation of cART. Levels of PAI-1, a marker of antifibrinolytic activity, increased only in the NVP/LPV/r arm.

C-IMT increased progressively in both study arms after the initiation of cART, with no difference between groups despite their different metabolic profiles. This may be due to our limited sample size resulting in lack of power to reveal differences between regimens; alternatively, differences in effects on the vascular wall may become apparent only after longer exposure. The C-IMT progression rate observed over 24 months (0.061 ± 0.016 mm in the ZDV/3TC/LPV/r arm [P < .001] and 0.044 ± 0.018 in the NVP/LPV/r arm [P = .012]) appears to suggest a higher progression rate than the ~0.01 mm/year reported in HIV-negative subjects [21, 22].

Previous longitudinal studies analyzing C-IMT in HIV-infected patients have had conflicting results, which is possibly partially explained by differences in the selection of participants. Progression rates in 2 studies including both cART-naive and cART-experienced patients were 0.02 (95% confidence interval, 0.012–0.029) and 0.074 ± 0.13 mm/year [23, 24]. Another study found no significant difference in the C-IMT progression rate between patients taking a PI, those without prior PI exposure, and matched HIV-negative control subjects (median progression rates of 0.0096, 0.0058, and 0.0085 mm/year, respectively) [25]. None of these studies investigated C-IMT progression in patients initiating cART for the first time. In this setting, a number of factors besides the direct or indirect effects of antiretroviral drugs may simultaneously play a role, such as suppression of viral replication and restoration of immunity. The extent to which such factors contribute to changes in the risk of vascular disease remains to be established.

The increase in arterial stiffness after the initiation of cART was observed only in the femoral artery. Different cardiovascular risk factors are known to have diverse effects on different arterial segments. The effects of fat accumulation and distribution as well as of impaired glucose tolerance and metabolic syndrome are most pronounced in the muscular femoral artery [26, 27], suggesting that this artery is particularly susceptible to metabolic changes. Stiffness of the elastic carotid artery, on the other hand, is mainly associated with aging and hypertension [28]. It is therefore not surprising that, in patients experiencing metabolic complications of cART, the most pronounced changes in arterial stiffness occurred in the femoral artery. These findings are also consistent with those of another cross-sectional study, in which we found an independent association between the use of ART and femoral artery stiffness [29]. Given that most treatment-related risk factors developed in the ZDV/3TC/LPV/r arm, including decreased insulin sensitivity, central fat accumulation, and limb fat loss, one might have expected a greater deterioration in arterial stiffness in this group than in the NVP/LPV/r arm.
arm. Although only femoral artery DC decreased in the NVP/LPV/r arm, in contrast to decreases in both DC and CC in the ZDV/3TC/LPV/r arm, differences between groups were not significant. Again, sample size may have been insufficient to detect smaller differences. On the other hand, it may be speculated that the negative effects that the increased LDL cholesterol level had on arterial stiffness in the NVP/LPV/r arm overshadowed any beneficial effects provided by the increased HDL cholesterol level and the absence of insulin resistance.

We found no change in the augmentation index, a measure of systemic arterial stiffness. This is in agreement with the findings of another study, in which no difference was found in this parameter between cART-treated patients with clinical lipodystrophy and those without [30]. In that study, duration of treatment with and cumulative exposure to antiretroviral drugs were independent predictors of the augmentation index. Given that cumulative exposure to cART was relatively short in our study, we cannot rule out the possibility that any effects that cART has on the augmentation index may take longer to appear. The coefficient of variation for augmentation index measurements was relatively high but was comparable to those of previous studies [31, 32]. This is a known limitation of the measurement technique, which, in combination with the limited sample size, could have played a role in our not finding any significant changes.

In contrast to the deterioration in arterial wall thickness and stiffness, we observed an improvement in several endothelial markers after the initiation of cART. During the pre-HAART era, HIV-infected patients were shown to have increased levels of sICAM-1, sVCAM-1, vWF, and PAI-1 [33–35]. Most studies also reported an association between levels of endothelial markers and progression of HIV infection. Endothelium may be activated directly by HIV or HIV-associated proteins or indirectly through an inflammatory cascade triggered by HIV [36]. ART may therefore reduce endothelial activation by suppressing HIV. Studies showing decreases in levels of adhesion molecules and vWF after the initiation of cART support this theory [37–39]. However, not all markers of endothelial function improve with antiretroviral treatment. Elevated PAI-1 levels have been found in patients receiving PI-containing cART [40, 41] and, in one longitudinal study [42], to not improve after the initiation of cART, similar to our present observations. Antiretroviral drugs, by virtue of their metabolic side effects, may therefore also contribute to endothelial dysfunction, and the balance between the beneficial effects of the suppression of HIV and the potentially deleterious effects of cART complications may differ between antiretroviral drug classes and individual drugs.

In HIV-infected patients, PAI-1 level has been associated with hyperlipidemia, insulin resistance, visceral and subcutaneous fat accumulation, and lipodystrophy [41, 43, 44]. Therefore, it seems surprising that, in our study, PAI-1 levels increased only in the NVP/LPV/r arm and not in the ZDV/3TC/LPV/r arm, in which lipodystrophy and insulin resistance developed. The higher lipid levels in the NVP/LPV/r arm may have affected the between-group difference in hs-CRP levels. The observed differences in markers of inflammation and coagulation activation between groups, despite their comparable effects on viral suppression, might suggest a greater degree of residual immune activation in those receiving NVP/LPV/r early on.

The disconnect between the observed changes in arterial stiffness and endothelial function is interesting. These findings may suggest that the microcirculation and large vessels respond differently in this setting. Another potential explanation may be that the increase in arterial stiffness is mediated by nonendothelial mechanisms, including changes in extracellular matrix properties, vascular smooth muscle function, or advanced glycation end products, as has been shown in patients with diabetes mellitus [45–47].

Our study had several limitations. Because the study was limited to men, findings may not be applicable to women. Also, given that recent data suggest that differences exist in cardiovascular risk and inflammatory markers among different NRTIs [8, 48], the changes observed for ZDV/3TC may not apply to all NRTIs. Furthermore, there appeared to be differences in age and smoking status between groups, both to the disadvantage of the NVP/LPV/r arm. Analyses were therefore corrected for these potential confounders.

Because of the relatively small sample size, our study had limited power to detect between-group differences in arterial properties. However, our findings are highly consistent with those of studies conducted in non–HIV-infected patients and also with the scarce cross-sectional data available on HIV-infected patients, as outlined above. Therefore, although we cannot draw definite conclusions concerning differences between groups, our results support further prospective exploration in comparative trials of different antiretroviral regimens concerning their effects on metabolism and the vasculature. We suggest that such studies also account for changes in immune activation, inflammation, and coagulation.

Acknowledgments

We are indebted to Ingrid Knufman for her assistance in planning all study days. We also gratefully acknowledge the contributions of the following investigators and research nurses, who coordinated the study at their respective sites: K. Brinkman, A. Carroll, F. A.P. Claessen, O. Debnam, W. Dorama, A. van Eeden, L. Elsborg, P. H. J. Friesen, S. E. Geerlings, L. Gelinck, L. Hegeman, N. Hulschoff, R. W. ten Kate, A. Kriitos, F. P. Kroon, S. Lowe, R. M. Perenboom, M. Ristola, M. Schoemaker, W. E. M. Schouten, L. Schrijnders, J. Stadwijk, J. Sutinen, J. Tesselaar, H. Wiggers, and M. Youle.

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