Long-term effects of an intensive intervention in HIV-infected patients with moderate–high atherosclerotic cardiovascular risk

Mar Masía1*, Enrique Bernal1, Catalina Robledano1, Sergio Padilla1, Natividad López2, Esteban Martínez3 and Félix Gutiérrez1

1Infectious Diseases Unit, Hospital General Universitario de Elche, Clinical Medicine Department, Universidad Miguel Hernández, Alicante, Spain; 2Biochemistry Section, Hospital General Universitario de Elche, Elche, Alicante, Spain; 3Infectious Diseases Service, Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain

*Corresponding author. Tel: +34-96-667-91-54; Fax: +34-96-667-91-56; E-mail: marmasiac@gmail.com

Received 20 March 2014; returned 3 May 2014; revised 16 June 2014; accepted 20 June 2014

Objectives: To evaluate the 5 year effects of an intensive intervention versus the standard-of-care intervention on cardiovascular risk factors in HIV-infected patients on antiretroviral therapy (ART).

Methods: This was a longitudinal study including virologically suppressed patients with at least two cardiovascular risk factors or a Framingham risk score ≥10%. Intensive and standard-of-care interventions aimed for low-density lipoprotein cholesterol (LDL-C) 100 and 130 mg/dL, respectively, by using lipid-lowering drugs. In the intensive group, switching ART when needed to achieve the LDL-C target and low-dose aspirin were used. Achievement of LDL-C targets and changes in carotid intima-media thickness (cIMT) and cardiovascular biomarkers were compared between groups at different timepoints through a 5 year period.

Results: Twenty-two and 25 patients in the intensive and standard intervention groups, respectively, were followed up. At 5 years, pre-specified LDL-C targets were achieved in 82% (intensive) and 81% (standard of care) of patients. The median (IQR) change in LDL-C in the intensive and standard intervention groups was 278 (296/239.7) and 249 (272/23), respectively (P = 0.04), and in the Framingham score was 24% (28%/21%) and 0% (24%/6.5%), respectively (P = 0.01). There were no significant intra- or between-group changes in cIMT measurements. A significant decrease was observed in the intensive and standard groups in interleukin6 (P = 0.001 and P = 0.002, respectively) and in tumour necrosis factor (P = 0.023 and P = 0.052, respectively). Asymptomatic creatine phosphokinase elevations were observed in two patients assigned to the standard intervention group.

Conclusions: An intensive intervention on cardiovascular risk factors in HIV-infected patients on ART was feasible, safe and capable of achieving LDL-C targets in the long term. Both intensive and standard interventions were accompanied by antiatherosclerotic changes in inflammatory cytokines and lack of cIMT progression.

Keywords: cardiovascular diseases, LDL cholesterol, carotid intima-media thickness, cIMT, inflammation biomarkers, lipid-lowering therapy, statins

Introduction

HIV-infected persons are at increased risk of cardiovascular disease (CVD).1–3 Their prolonged life expectancy might contribute to intensify the magnitude of the problem, which will likely become more prevalent during the next decades as patients become older. Interventions aimed at reducing cardiovascular risk are therefore imperative in the HIV population.

The intensity of efforts to prevent CVD should be adjusted to individual risk.4,5 Dyslipidaemia, one of the major cardiovascular risk factors (CVRFs) involved in atherogenesis, is frequent among HIV-infected people.6 Because HIV itself and antiretroviral therapy (ART) are considered additional independent risk factors for coronary heart disease, a more aggressive management of lipids has been advocated in the HIV-infected population.7–9 In contrast to the general population, there is no evidence of the benefits of lipid-lowering interventions on the natural history of atherosclerosis in HIV patients. Moreover, the long-term effectiveness and safety of lipid-lowering therapy in these patients remain unknown.8,10,17

We carried out a randomized study to evaluate intensive versus standard-of-care pharmacological management of CVRFs among HIV patients with moderate–high cardiovascular risk. Our hypothesis was that the intensive intervention should be accompanied by lower atherosclerosis progression measured...
with the carotid intima-media thickness (cIMT) and with several biomarkers implicated in the pathophysiology of CVD. Results at 1 year follow-up have been reported previously. We hereby report the 5 year safety and efficacy of both interventions on low-density lipoprotein cholesterol (LDL-C) targets, the cIMT and several biomarkers implicated in the pathogenesis of CVD.

Methods

Patient selection

Inclusion and exclusion criteria have been described elsewhere. Briefly, patients with moderate–high cardiovascular risk, i.e. with at least two CVRFs or a Framingham risk score ≥10%, were asked to participate in the study. CVRFs were those defined by the National Cholesterol Educational Program (NCEP). After the first year of follow-up, patients were invited to continue in the study for a 5 year period. Patients who declined invitation and patients without virological suppression were excluded from this extension follow-up period. Patient recruitment had begun on August 2006 and the last assessments were carried out in September 2012. The study was approved by the local Ethics Committee and all patients signed a new informed consent. Registration number: S.P.0083/2005 (DOGV 5,161).

Intervention

The study design, protocol and sample size calculation have been provided previously. For patients assigned to the intensive intervention, lipids were managed following the recommendations of the Third Report of the NCEP for patients included in the highest risk category of primary prevention or in secondary prevention. The therapeutic goal for LDL-C was <100 mg/dL. Atorvastatin was the lipid-lowering drug of choice at the beginning of the study. If the therapeutic goal was not achieved, ezetimibe was added. By the fourth year of the intervention, rosuvastatin replaced atorvastatin in patients who had not achieved the therapeutic goal. Management of hypertriglyceridaemia, hypertension, diabetes and smoking were the same in both groups.

Strategies for smoking cessation consisted of intense patient counselling, use of nicotine substitution where appropriate and referral to specialized smoking cessation clinics when they became available in our health authority. Daily aspirin at a dose of 100 mg/day was prescribed to patients undergoing intensive therapy, unless contraindicated; in such cases, clopidogrel was the antiplatelet drug prescribed. Finally, patients receiving ritonavir-boosted protease inhibitor (PI)-containing regimens had the PI component switched to atazanavir. For patients assigned to the standard-of-care intervention group, the therapeutic goal for LDL-C was <130 mg/dL. In this group, no antiplatelet therapy was initiated and the antiretroviral regimen was not changed.

Patients were followed up every 3 months during the first year and then annually. Blood samples were collected at each visit.

Measurement of biomarkers

At baseline and years 1, 3 and 5, an additional sample was collected and kept frozen at −70°C. High-sensitivity C-reactive protein (hsCRP), interleukin 6 (IL-6) and tumour necrosis factor α (TNF-α) were measured in defrosted plasma samples after study completion as previously described.

cIMT measurements

Carotid measurements were performed at the baseline visit and at years 1, 3 and 5 of follow-up. For determination of the cIMT, B-mode high-resolution ultrasound was used following a standard procedure described previously. All measurements were performed by the same investigator, who was blinded to the group to which the patients belonged.

Statistical analyses

To compare the study groups, we used the Mann–Whitney U-test and the χ² test where appropriate. The non-parametric Friedman test for repeated measures was used to compare intragroup differences. The Wilcoxon signed-rank test was used to compare differences in the pre-treatment and last on-treatment measures. Significance levels were placed at P < 0.05.

Results

Patient disposition

The flow chart of the patients is shown in Figure 1. There were no significant differences between patients excluded from the study for any reason and those who remained in the study in the levels of LDL-C, high-density lipoprotein cholesterol or total cholesterol. The levels of triglycerides were lower in patients excluded (108 versus 166 mg/dL, P = 0.03).

Nine (41%) patients in the intensive group were receiving PIs; of them, four (18%) changed to atazanavir + ritonavir. In the standard-of-care group, five (20%) received lopinavir/ritonavir, three (12%) received atazanavir + ritonavir and one (4%) received saquinavir. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) included efavirenz in seven (31.8%) and eight (32%) patients in the intensive and standard-of-care groups, respectively, and nevirapine in six patients in each group (27.2% and 24%, respectively). Ten (45.5%) and 9 (36%) patients in the intensive and standard-of-care groups, respectively, received abacavir.

Details on the lipid-lowering drugs used and statin doses are provided in Table 1. Antiplatelet therapy with aspirin was prescribed to all patients in the intensive intervention group, except two (9%) patients who received clopidogrel and one patient receiving oral anticoagulant therapy.

Efficacy on blood lipid levels and other CVRFs

The median (IQR) change in LDL-C at 5 years was −78 (−96/−39.7) mg/dL in the intensive group and −49 (−72/−3) mg/dL in the standard-of-care group (P = 0.04). Fourteen out of 17 (82.4%) patients in the intensive group had reached an LDL-C <100 mg/dL at year 5. The median LDL-C levels throughout the study period are shown in Figure S1 (available as Supplementary data at JAC Online). Notably, the majority of patients in the standard-of-care group achieved the LDL-C goal <130 mg/dL early and, at 5 years, 17 out of 21 (81%) patients had an LDL-C <130 mg/dL.

There was a reduction in the number of smokers in both groups (Table 2). The median (IQR) reduction of the 10 year risk of coronary disease (Framingham score) was higher in the intensive intervention group (P = 0.01).

No discontinuation of statins due to adverse events occurred during the study. There was a slight and non-clinically relevant increase in alanine aminotransferase (ALT) levels in patients included in the intensive group (data not shown). In two patients included in the standard-of-care group, high creatine phosphokinase (CPK) levels without concurrent muscular symptoms were observed during the study; one of them had a CPK of 2417 U/L at year 3 and the other had a CPK of 1120 U/L at year 5. Both results could not be confirmed subsequently and the patients acknowledged intense physical exercise immediately before the blood tests. Glucose and glycated haemoglobin did not change.
significantly during the 5 year follow-up. There was a significant increase in CD4 cell counts in both groups during follow-up (Table 2).

**cIMT**

There were no significant changes in cIMT measurements intragroup or between the intensive and the standard-of-care groups during the 5 year study period. Median values of cIMT obtained at baseline and at years 1, 3 and 5 in each group are shown in Table S1 (available as Supplementary data at JAC Online).

**Changes in blood biomarkers**

Median (IQR) values of blood biomarkers at baseline and at years 1, 3 and 5 are shown in Table S1. Compared with baseline, there was a significant decrease in both groups in the levels of IL-6 and TNF-α. No significant changes were observed in hsCRP.

**Discussion**

Our study confirms that long-term lipid-lowering therapy with a strict goal of <100 mg/mL for LDL-C is safe and the therapeutic target can be achieved and maintained over time in HIV-infected patients.
patients receiving ART. This intervention was accompanied by an antiatherosclerotic change in the inflammation cytokines IL-6 and TNF-α and absence of progression in subclinical atherosclerosis measured with the cIMT during the 5 year follow-up.

There is wide experience with intensive lipid-lowering therapy in the general population, where it has shown to be a useful and safe intervention. However, studies dealing with statin therapy in the HIV-infected population have frequently employed low doses and short follow-up periods. Moreover, a difficulty in achieving the lipid targets has been described in HIV-infected patients compared with HIV-uninfected subjects. In contrast, most patients in our study achieved the planned therapeutic LDL-C goals, which were maintained throughout the study period. High doses of atorvastatin and rosuvastatin were used for a long time with good tolerance and lack of significant adverse effects.

The number of smokers decreased during the study, to a higher degree in the intensive group, although the difference in the change between the groups did not reach statistical significance. However, a significant proportion of patients did not quit smoking. Likewise, blood pressure was not as well controlled as LDL-C levels were. Since there was a substantial cardiovascular mortality in this moderate- to high-risk population sample, a more aggressive control of all CVRFs should have been warranted to reduce event occurrence.

We did not find regression of the cIMT in any intervention group. However, in contrast to other longitudinal studies in HIV-infected patients, we did not find progression of subclinical atherosclerosis, despite the inclusion of patients with a high-risk cardiovascular profile and a long follow-up duration. On the other hand, the low number of patients in each group, many of them already receiving lipid-lowering therapy at inclusion, and the high number of individuals treated with statins and with good LDL-C control in both groups might have contributed to attenuation of intra- or intergroup differences.

Actually, if patients had been managed according to the 2013 American College of Cardiology/American Heart Association guidelines for cholesterol treatment, 76.2% of patients in the standard-of-care group would have been appropriately treated. The analysis of our data after excluding patients on lipid-lowering therapy at baseline provided similar results (data not shown).

Table 1. Characteristics of the patients at baseline and lipid-lowering drugs prescribed at inclusion

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intensive intervention (n = 22)</th>
<th>Standard intervention (n = 25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (IQR)</td>
<td>50.04 (43.76–58.17)</td>
<td>48.17 (43.85–58.66)</td>
<td>1</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>20 (90.9)</td>
<td>21 (84.0)</td>
<td>0.67</td>
</tr>
<tr>
<td>Body mass index (kg/m²), median (IQR)</td>
<td>26.4 (21.5–27.9)</td>
<td>24.5 (21.9–26.3)</td>
<td>0.37</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm³), median (IQR)</td>
<td>335 (270–535)</td>
<td>550 (355–735)</td>
<td>0.047</td>
</tr>
<tr>
<td>PI-based ART, n (%)</td>
<td>9 (40.9)</td>
<td>9 (36.0)</td>
<td>0.77</td>
</tr>
<tr>
<td>NNRTI-based ART, n (%)</td>
<td>13 (59.1)</td>
<td>14 (56.0)</td>
<td>1</td>
</tr>
<tr>
<td>Duration of ART (years), median (IQR)</td>
<td>8.0 (5.50–11.25)</td>
<td>10 (7.50–12.50)</td>
<td>0.14</td>
</tr>
<tr>
<td>Dyslipidaemia, n (%)</td>
<td>15 (68.2)</td>
<td>17 (68)</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>5 (22.7)</td>
<td>11 (44)</td>
<td>0.22</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>15 (68.2)</td>
<td>16 (64)</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>2 (9.1)</td>
<td>8 (32)</td>
<td>0.08</td>
</tr>
<tr>
<td>Metabolic syndrome, n (%)</td>
<td>6 (27.3)</td>
<td>9 (36)</td>
<td>1</td>
</tr>
<tr>
<td>10 year risk of coronary heart disease (Framingham), median (IQR)</td>
<td>16 (10–20)</td>
<td>15 (9.5–20)</td>
<td>0.71</td>
</tr>
<tr>
<td>Lipodystrophy, n (%)</td>
<td>10 (45.5)</td>
<td>16 (64)</td>
<td>0.25</td>
</tr>
<tr>
<td>Family history of ischaemic heart disease, n (%)</td>
<td>4 (18.2)</td>
<td>7 (28.0)</td>
<td>0.51</td>
</tr>
<tr>
<td>Peripheral vascular disease, n (%)</td>
<td>2 (8.1)</td>
<td>1 (4.0)</td>
<td>0.60</td>
</tr>
<tr>
<td>Carotid plaques, n (%)</td>
<td>10 (45.5)</td>
<td>14 (56)</td>
<td>0.56</td>
</tr>
<tr>
<td>LDL-C (mg/dL), median (IQR)</td>
<td>145 (124–170)</td>
<td>129 (110–145)</td>
<td>0.04</td>
</tr>
<tr>
<td>Glycated haemoglobin (%), median (IQR)</td>
<td>5.4 (5.0–5.8)</td>
<td>5.3 (4.7–6.1)</td>
<td>0.91</td>
</tr>
<tr>
<td>CPK (U/L), median (IQR)</td>
<td>100 (75–142)</td>
<td>166 (88–200)</td>
<td>0.09</td>
</tr>
<tr>
<td>History of lipid-lowering therapy, n (%)</td>
<td>6 (27.3)</td>
<td>11 (44)</td>
<td>0.23</td>
</tr>
<tr>
<td>statin use</td>
<td>5 (22.7)</td>
<td>8 (32)</td>
<td>0.53</td>
</tr>
<tr>
<td>Lipid-lowering drugs at inclusion, n (%)</td>
<td>22 (100)</td>
<td>12 (48)</td>
<td>0.001</td>
</tr>
<tr>
<td>atorvastatin</td>
<td>22 (100)</td>
<td>9 (36)</td>
<td></td>
</tr>
<tr>
<td>dose (mg), median (IQR)</td>
<td>20 (10–40)</td>
<td>20 (10–40)</td>
<td></td>
</tr>
<tr>
<td>rosuvastatin</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>ezetimibe</td>
<td>7 (31.8)</td>
<td>11 (44)</td>
<td></td>
</tr>
<tr>
<td>fibrates</td>
<td>2 (0.9)</td>
<td>7 (3.5)</td>
<td></td>
</tr>
</tbody>
</table>

Dyslipidaemia, diabetes and hypertension were defined according to the NCEP criteria (hypertension, repeated blood pressure ≥140/90 mm Hg; high total cholesterol, ≥240 mg/dL; diabetes, plasma glucose value ≥126 mg/dL), by a previous diagnosis or by a current prescription of pharmacological therapy for any of such risk factors.

Carotid plaque was defined as an intima-media thickness >1.5 mm.
third comparison group with no intervention might have helped clarify the benefits of the strategies assessed in the study. Some previous cohorts where the benefits of statin therapy were demonstrated included a control group free from lipid-lowering therapy.15,16 Finally, the lower CD4 cell count of patients included in the intensive intervention group might have contributed to ameliorate the differences in the cIMT changes between groups, since lower CD4 cell count and nadir have been associated with progression of atherosclerosis.23,25,27

There was a decrease in the pro-inflammatory cytokines IL-6 and TNF-α. Apart from the effects on LDL-C, statins possess well-known anti-inflammatory properties independent of lipid lowering, with a reduction in inflammation markers under statin therapy being reported in the general population 28,29 and in HIV-infected patients.16,18,30 So far, data evaluating the relationship of inflammation biomarkers with the cIMT in HIV-infected patients have been mostly restricted to cross-sectional studies.31,32

As previously stated, the main limitations of the study are the low number of patients reaching the 5 year follow-up and the absence of a control group with no intervention. Therefore, the study might have been underpowered to detect differences in atherosclerosis progression between the groups. While we focused on LDL-C, a more stringent intervention on smoking and blood pressure might have helped delay atherosclerotic disease progression, consequently improving surrogate atherosclerosis markers. The strengths of the study are the novelty of such an intervention in HIV-infected patients and the prolonged follow-up with serial measurements of lipids and different biomarkers implicated in the pathogenesis of atherosclerosis.

In conclusion, our study supports the long-term efficacy and safety of an intensive intervention on CVRFs in HIV-infected patients on ART. Besides attaining the lipid targets, this intervention was associated with antiatherosclerotic changes in inflammation cytokines and with the absence of atherosclerosis progression measured with the cIMT, which need to be verified in larger studies.

Funding
This work was partially funded by the RD12/0017/0023 project as part of the Plan Nacional R + D + I, and cofinanced by ISCIII- Subdirección General de Evaluación y el Fondo Europeo de Desarrollo Regional (FEDER), FIBELX10/11, FIBELX10/12 and Instituto de Salud Carlos III-FIS (PI081893, PI13/002256).

Transparency declarations
None to declare.

Supplementary data
Figure S1 and Table S1 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References


22 Johns KW, Bennett MT, Bonda GP. Are HIV positive patients resistant to statin therapy? Lipids Health Dis 2007; 6: 27.


32 Longenecker CT, Funderburg NT, Jiang Y et al. Markers of inflammation and CD8 T-cell activation, but not monocyte activation, are associated with subclinical carotid artery disease in HIV-infected individuals. HIV Med 2013; 14: 385–90.