Randomized clinical trial of lovastatin in HIV-infected, HAART naïve patients (NCT00721305)

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Accepted 10 October 2012
Available online 17 October 2012

KEYWORDS
HIV infection; Anti-HIV agents; Statin; Lovastatin; Randomized controlled trial

Summary Background: Evidence suggests that statins may modify the immune response against HIV. The aim was to evaluate the antiretroviral and immunomodulatory effects of lovastatin in HIV-infected patients, naïve for antiretroviral therapy.

Methods: Randomized, double-blinded, placebo-controlled, phase-II clinical trial. Primary outcomes were plasma viral load and circulating CD4+ T cell count, after 6 and 12 months of treatment; secondary outcomes were CD8+ T cell count, expression of activation markers (CD38 and HLA-DR) on T cells, and clinical outcomes. With a power of 90% to detect both a decrease of 0.3 log10 in plasma HIV-1 RNA copies and an increase of 20% in the CD4+ T cell count, we estimated a required sample size of 110 HIV-infected patients (55 per group). The results were analyzed by a model of repeated measurements using Generalized Estimating Equations.

Results: Patients were randomized to receive either lovastatin (n = 55) or placebo (n = 57). During the 12-month follow-up, there was no effect of lovastatin either on viral load (estimated average change = 0.157 copies/mL; CI 95% = −0.099 to 0.414), or on the CD4+ T cell
Introduction

Infection by human immunodeficiency virus (HIV) is characterized by progressive quantitative and functional alterations of several immune cells, mainly CD4+ T cells, as well as uncontrolled chronic immune activation that leads to severe immunosuppression, and ultimately to death. Highly active antiretroviral therapy (HAART) significantly decreases HIV replication and plasma viral load, allowing a partial immune restoration associated with better clinical outcomes. However, the well-known adverse effects that lead to lack of adherence, and finally to the development of resistance, as well as the pathogenic persistent immune activation even in patients with controlled viral load by HAART, have encouraged the development of new or complementary therapeutic approaches.

Statins are widely used to prevent atherosclerotic diseases based on their ability to decrease cholesterol biosynthesis, by inhibiting the 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase. Additional benefits of these compounds, that have suggested their use in other clinical disorders, are associated with their immunomodulatory activity and include the regulation of the traffic and function of different leukocyte subpopulations, and the reduction in the production of proinflammatory mediators. These immunomodulatory effects could be different in magnitude for the different statins, due to distinct chemical and biological properties of natural, semi-synthetic, and synthetic statins.

Several in vitro studies have demonstrated the anti-HIV activity of statins, through multiple mechanisms such as alterations in cellular and viral cholesterol, abnormal formation of membrane lipid rafts, inhibition of isoprenoid production and prenylation of small GTP-binding proteins, blockage of LFA-1/ICAM-1 interaction, and regulation in the expression of the HIV co-receptor CCR5 and its ligand CCL5 (RANTES, Regulated Upon Activation, Normally T-cell Expressed and Secreted). The in vivo inhibition of HIV infection mediated by statins is still a matter of debate, due to the contradictory results derived from investigations evaluating the activity of these compounds in HIV-infected subjects. So far, most of the studies have been performed in patients under effective HAART, while those performed in patients without HAART enrolled a reduced number of patients and did not include an evaluation of cellular immune activation markers and clinical outcomes. In addition, most of the in vivo studies were the outcome of observations; only two small randomized trials addressed the role of statins during HIV infection in vivo, with a follow-up not longer than 16 weeks. Due to the fact that lovastatin is one of the statins with demonstrated and consistent in vitro anti-HIV activity, our investigation was designed to explore, in asymptomatic HAART-naïve, HIV-infected patients the effect of the long-term use of daily lovastatin in reducing plasma viral load and improving both peripheral blood CD4+ T cell count and immune activation status.

Methods

Study population

Asymptomatic HIV-infected adults who were HAART naïve, with a peripheral blood CD4+ T cell count ≥350 cells/μL and detectable viral load yet lower than 100,000 copies/mL, were eligible to participate in this study. The main exclusion criteria included: pregnancy and breastfeeding; low adherence profile assessed by the Morisky–Green test; dyslipidemia with indication of using lipid-lowering drugs; history of intolerance or allergy to statins; requirement for long-term use of medications with clinically relevant interactions with lovastatin (i.e., macrolides); chronic active viral hepatitis (B or C); increase of hepatic aminotransferases more than twice the upper limit of reference values; serum creatinine ≥2 mg/dL; increase of creatine phosphokinase (CPK) more than five times the upper limit of reference values, and active substance-related disorders.

All participants were recruited from the outpatient services at two of the most important centers of health care insurance in the city of Medellin, Colombia. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Institutional Ethical Review Board of the University of Antioquia. All participants provided signed informed consent, prepared according to the Colombian legislation (Resolution 008430 of 1993), before participating in the study. The study was registered in Clinical Trials (www.clinicaltrials.gov; ID NCT00721305).

Study design

The randomized, double-blinded, placebo-controlled, phase II clinical trial, was conducted between August 2008 and July 2011. The treatment assignment ratio was 1:1, fixed throughout the study. The allocation sequence was developed by the statistician in the Data Coordinating Center (DCC), using randomly permuted blocks of size 2, 4 and 6 generated by a random number generator (ralloc program, Stataco. 8.2, College Station, TX, USA). Once the sequence was generated, it was matched with sequential numbers between 001 and 150 and given to the manufacturer to label the blisters containing lovastatin or placebo tablets. The allocation sequence remained in a confidential file in the DCC until the end of the study.
Clinical and laboratory follow-up

Before enrollment, and monthly during one year, a physician trained in HIV infection and a pharmacist, both blinded for the type of intervention, evaluated and recorded the following parameters: general physical examination; occurrence of infectious or non-infectious diseases and hospitalization due to diseases related to HIV infection; adherence and tolerance to interventions, and adverse drug events. Blood samples were collected at days 0, 30, 180 and 360 to test for liver enzymes, CPK, creatinine and complete serum lipid profile. The intervention was stopped in the presence of serious adverse drug events, a three-fold increase in serum hepatic aminotransferases or a five-fold increase in CPK. To preserve the blinding, only the first value of serum lipid profile (day 0) was given to the clinical investigators to check the eligibility criteria. At days 30, 180 and 360 of follow-up, a medical safety monitor in the DCC received the lipid report directly from the clinical laboratory.

The serum concentration of creatinine, total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and triglycerides was independently measured by colorimetric enzymatic assays. The concentration of alanine and aspartate aminotransferases was determined by immunoturbidimetry, while the serum levels of CPK were determined by a dry chemical assay. These assays were analyzed in the Cobas 6000 device (Roche, Indianapolis, IN).

Study outcomes

Viral load

The number of plasma HIV-1 RNA copies was determined at times 0, 6 and 12 months using the commercial assay “RT-PCR Cobas Ampliprep-Cobas Amplicor” (Roche, Indianapolis, IN, USA), following the manufacturer’s protocol.

T cell count and phenotypic characterization

The following anti-human monoclonal antibodies were used: anti-CD3 FITC, anti-CD4 APC, anti-CD8 PE-CY5, anti-HLA-DR PE-Cy7, and anti-CD38 PE; all from BD Biosciences (San Diego, CA, USA). Appropriate isotype controls were used for each antibody. The frequency and phenotype of peripheral blood T cells were determined by flow cytometry at 0, 6 and 12 months. Briefly, 130 μL of whole blood were incubated with the specific monoclonal antibodies for 25 min at room temperature in the dark. The erythrocytes were then lysed by incubating for 10 min with 2 mL of BD FACS Lysing Solution 1× (BD Biosciences); the cell suspension was centrifuged for 5 min at 250×g, the supernatant was discarded and the cells were washed twice with 2 mL of cold PBS centrifuging at 250×g for 5 min. Finally, the cells were fixed with 200 μL of 2% paraformaldehyde.

All the stained and fixed cells were stored at 4 °C until acquisition in the cytomter FACS CANTO-II (BD). At least 100,000 events from the lymphocyte region were acquired for each sample. T cell subpopulations were identified as CD3+/CD4+ or CD3+/CD8+, and the co-expression of the surface activation molecules HLA-DR and CD38 was analyzed in each T cell subpopulation. Acquisition analysis was performed using the Cell Quest software. The absolute number of peripheral blood lymphocytes was calculated on the basis of manually determined total and differential blood cell counts.

Data analysis

Sample size

The primary hypothesis was that the use of lovastatin (40 mg/day during one year) compared with placebo could result in a reduction of 50% or more in viral load and an increase of 20% or more in CD4+ T cell count. Based on a pilot cohort of 25 patients collected previously, the baseline values for the outcome measurements were mean viral load = 55,000 copies/mL (SD = 80,000 copies/mL) and mean CD4+ T cell count = 500 cells/mL (SD = 180 cells/mL). Assuming a fixed correlation of 0.8 between the three different measurements of viral load (0, 6 and 12 months), and a time-average difference of 50% between groups (i.e., a decrease of 22,500 copies/mL from the baseline value), with an alpha error of 0.05 and a beta error of 0.2, the sample size required was 55 patients per group. This sample size had more than 90% power to detect an increase of at least 20% over the baseline CD4+ T cell count.

Interim monitoring

An independent Data Safety Monitoring Board (DSMB) comprising three members with expertise in statistics, epidemiology and infectious diseases, was responsible for the interim monitoring process. The statistician at the DCC was the only person with access to the full database who provided the required information for the interim quality assurance and for the DSMB. The first interim monitoring was conducted when the recruitment reached 40% of the estimated sample size and the participants in the study completed at least six months of evaluation. The DSMB and the DCC agreed to no additional interim analysis based on the absence of adverse events and the exploratory profile of the trial. Stopping guidelines for futility were not considered.

Analysis plan

The overall efficiency was established with the intention to treat analysis. The study outcomes, longitudinal data with repeated measurements at 6 and 12 months after the intervention, were analyzed with a Generalized Estimating Equations (GEE) model and using a robust variance estimator (Huber–White) for the standard errors of the estimators. These models have been used in the analysis of some interventions to prevent HIV infection in African–American adolescents, and to evaluate the effect of interventions on outcomes related not only to HIV infection but also to other sexually transmitted diseases.

Results

Patient characteristics

Among 168 HIV-infected patients potentially eligible, 112 were randomly assigned to lovastatin (n = 55) or placebo.
(n = 57); the main reason for exclusion was refusal of 19 patients (34%) to participate. Of the 112 individuals randomized, 104 (93%) completed the 12-month laboratory follow-up (Fig. 1). The median age of the study population was 31 years (interquartile range, IQR = 26–38); 96 (86%) were males; the predominant sexual behavior was male to have sex with males (n = 53, 47%) and diagnosis of HIV infection was mainly by voluntary testing (n = 73, 65%).

The main baseline characteristics of the study groups are shown in Table 1.

**Primary outcomes**

There was no effect of lovastatin on viral load (estimated average change = 0.157 log10 copies/mL; 95% CI = −0.099 to 0.414, Fig. 2A) or on CD4+ T cell count

**Figure 1** Study profile. Diagram showing the flow of the 168 screened HIV-infected patients, with the main causes of refusal and withdrawals, and the final size of the sample with complete laboratory data.

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**Table 1** Baseline characteristics by study group.

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 57)</th>
<th>Lovastatin (n = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, median (IQR)</td>
<td>31 (27–38)</td>
<td>32 (26–39)</td>
</tr>
<tr>
<td>Males</td>
<td>48 (84%)</td>
<td>48 (87%)</td>
</tr>
<tr>
<td>HIV testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical indication</td>
<td>11 (19.3%)</td>
<td>15 (27.3%)</td>
</tr>
<tr>
<td>Blood bank</td>
<td>8 (14%)</td>
<td>5 (9.1%)</td>
</tr>
<tr>
<td>Voluntary</td>
<td>38 (66.7%)</td>
<td>35 (63.6%)</td>
</tr>
<tr>
<td>Sexual behavior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male to have sex with males</td>
<td>45 (79%)</td>
<td>51 (92.7%)</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>12 (21%)</td>
<td>4 (7.3%)</td>
</tr>
<tr>
<td>Viral load (log10 copies/mL), median (IQR)</td>
<td>3.77 (3.37–4.41)</td>
<td>3.98 (3.61–4.39)</td>
</tr>
<tr>
<td>CD3+CD4+ cells/μL, median (IQR)</td>
<td>510 (408–700)</td>
<td>514 (411–635)</td>
</tr>
<tr>
<td>CD3+CD8+ cells/μL, median (IQR)</td>
<td>1169 (846–1473)</td>
<td>1071 (905–1462)</td>
</tr>
<tr>
<td>Percentage CD4+/CD8+/HLA-DR+ cells, median (IQR)</td>
<td>5.2 (3.4–9.6)</td>
<td>5.3 (3.1–10.6)</td>
</tr>
<tr>
<td>Percentage CD8+/CD38+/HLA-DR+ cells, median (IQR)</td>
<td>13.0 (6.4–25.8)</td>
<td>11.0 (7.2–21.8)</td>
</tr>
<tr>
<td>Cholesterol (mg/dL), median (IQR)</td>
<td>162 (147–184)</td>
<td>167 (144–194)</td>
</tr>
<tr>
<td>HDL Cholesterol (mg/dL), median (IQR)</td>
<td>37 (31–42)</td>
<td>35 (31–42)</td>
</tr>
<tr>
<td>LDL Cholesterol (mg/dL), median (IQR)</td>
<td>98 (89–120)</td>
<td>102 (85–127)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL), median (IQR)</td>
<td>111 (85–158)</td>
<td>130 (90–173)</td>
</tr>
<tr>
<td>CPK (mg/dL)</td>
<td>73 (50–102)</td>
<td>72 (46–103)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.93 (0.85–0.99)</td>
<td>0.93 (0.85–1.04)</td>
</tr>
<tr>
<td>Aminotransferase ALT (mg/dL)</td>
<td>24 (18–35)</td>
<td>25 (20–41)</td>
</tr>
<tr>
<td>Aminotransferase AST (mg/dL)</td>
<td>24 (19–29)</td>
<td>25 (20–34)</td>
</tr>
</tbody>
</table>

IQR: interquartile range; HDL: high-density lipoprotein; LDL: low-density lipoprotein; CPK: creatine phosphokinase.
(estimated average change = \(-26.1\) cells/\(\mu\)L; 95% CI = \(-89.8\) to 37.6, Fig. 2B) through the intervention period of 12 months. Instead, there was a significant decrease in serum total cholesterol (estimated average change = \(-19\) mg/dL; 95% CI = \(-29\) to \(-9\), Fig. 3A) and LDL cholesterol (estimated average change = \(-18\) mg/dL; 95% CI = \(-27\) to \(-10\), Fig. 3B) in patients who received lovastatin. There were no significant differences in serum HDL cholesterol and triglycerides between lovastatin and placebo groups (data not shown).

**Other outcomes**

Neither the blood CD8\(^{+}\) T cell count (estimated average change = \(-41.5\) cells/\(\mu\)L; 95% CI = \(-219.8\) to 136.7, data not shown) nor the expression of activation markers CD38 and HLA-DR on CD4\(^{+}\) and CD8\(^{+}\) T cells (estimated average change = 0.62%; 95% CI = \(-1.4\%\) to 2.66%, Fig. 4A, and \(-1.47\%\); 95% CI = \(-4.8\%\) to 1.8%, Fig. 4B, respectively) exhibited any statistically significant change in patients treated with lovastatin. In no study group were there cases of AIDS’ defining diseases, hospitalization for AIDS’ related causes, or deaths.

**Safety and secondary side effects**

In general, the interventions were safe and well tolerated. Only two patients suspended the medication due to effects related to lovastatin: one due to an erythematous maculopapular rash during the first week, and the second one due to the serum aminotransferase concentration higher than those allowed by the study protocol.\(^{25}\) In both cases,

![Figure 2](image-url)
the clinical and laboratory abnormalities improved once the medication was interrupted. During the follow-up, no abnormal values in serum creatinine were found. In three patients, an increase in serum CPK, associated with extreme physical activity the day before the test, was documented; a new evaluation performed 15 days later demonstrated normal values of CPK in these patients (data not shown). Finally, the adherence to intervention (evaluated every month by the Simplified Medication Adherence Questionnaire – SMAQ) was higher than 85%, and similar in both groups of patients (data not shown).

**Discussion**

In this randomized clinical trial with a one-year follow-up, we explored the long-term efficiency of therapeutic doses of lovastatin in HIV-infected individuals, naive for antiretroviral medications. We found no antiviral or immunomodulatory effect of lovastatin, with similar progression patterns in HIV-1 RNA plasma load, CD4+ T cell count, and expression of immune activation markers on T cells in either placebo or lovastatin groups. As biological control, the serum total and LDL cholesterol concentrations showed a significant decrease in lovastatin treated patients, which was visible as of the first month of administration and stable for one year (Fig. 3).

In several *in vitro* studies, the anti-HIV activity of lovastatin was consistently demonstrated, and a small observational study also suggested the *in vivo* potential of this statin in inhibiting HIV replication and transiently improving the CD4+ T cell count. The *in vitro* activity of statins against HIV infection has been evaluated and demonstrated both in cell lines and human mononuclear cells.
cells, and it has been postulated that this inhibition could be mediated by cholesterol-dependent and independent mechanisms.\textsuperscript{30,31} From this \textit{in vitro} evidence, the use of statins in HIV-infected patients was proposed as an alternative to control HIV replication and the immunopathological phenomena observed during this infection.\textsuperscript{32} Some \textit{in vivo} studies aimed at defining the actual anti-HIV effect of statins have been performed using different approaches and methods: observational designs,\textsuperscript{20,21} retrospective evaluations,\textsuperscript{16,19} crossover follow-up\textsuperscript{14} and small randomized trials.\textsuperscript{23,24} Furthermore, different statins and patients in different clinical status have been analyzed: HAART naïve chronically infected,\textsuperscript{20} patients with suppressive HAART,\textsuperscript{14,16–19} or patients who suspended HAART before starting the statins.\textsuperscript{23} Such heterogeneity in designs and study populations may explain discrepancies in the results obtained; they also hamper adequate interpretation and comparison. The impact of stable HAART on inhibiting HIV replication and allowing the partial restoration of the CD4$^+$ T cell pool, could mask the positive activity of statins in patients receiving HAART; in addition, the fact that HIV-infected patients with dyslipidemia were enrolled in some of these investigations could constitute a research bias, because of the well-known effect of abnormal lipids in increasing inflammation and potentiating the pathological activity of HIV.\textsuperscript{33}

Only two randomized controlled trials have evaluated the role of statins during HIV infection. Negredo et al.\textsuperscript{23} enrolled 41 HIV-infected patients, but 16 individuals (39\%) discontinued the study; the patients received atorvastatin (40 or 80 mg/day), initiated at the time of HAART interruption, without any effect on the rate or magnitude of rebound HIV viremia and on CD4$^+$ T cell count at weeks 4 and 12. Ganesan et al.\textsuperscript{24} in a randomized cross-over trial with 22 HIV-1 infected patients (9 individuals were not HAART naïve), found that the short-term use of atorvastatin (8 weeks) neither decreased the viral load nor increased the CD4$^+$ T cell count; regarding the effect of atorvastatin on immune activation, the co-expression of CD38 and HLA-DR was only slightly decreased on CD8$^+$ T cells. When they analyzed the expression of only one of these markers, they found a significant reduction in the frequency of CD4$^+$ and

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure4.png}
\caption{Percentage of CD4$^+$ and CD8$^+$ T cells co-expressing CD38 and HLA-DR molecules by study group before starting interventions and at months 6 and 12 of follow-up. The expression of immune activation markers (both CD38 and HLA-DR) on peripheral blood CD4$^+$ (A) and CD8$^+$ (B) T cells was determined by multicolor flow cytometry; estimated average change by a GEE model $= 0.62\%$; 95\% CI $= -1.4\%$ to 2.66\% and $= -1.47\%$; 95\% CI $= -4.8\%$ to 1.8\%, respectively.}
\end{figure}
CD8+ T cells expressing HLA-DR, but not in the frequency of T cells expressing CD38, the most reliable independent marker so far described to assess immune activation.34 Also, the basal level of immune activation was higher in Ganesan’s patients when compared to our HIV-infected individuals (their basal co-expression of CD38 and HLA-DR was 8% and 44% on CD4+ and CD8+ T cells, respectively, versus 5% and 13% in our patients, Table 1). Moreover, this study was not able to determine if the effect of atorvastatin on chronic immune activation in HIV-infected patients was stable over time. However, it was a cross-over trial with the patient being compared to himself, avoiding the variability in results from one patient to the other.

To overcome those limitations in the evaluation of the anti-HIV activity of statins in vivo, we designed a larger, randomized, double-blinded, placebo-controlled clinical trial with a longer follow-up period, including chronic HIV-infected individuals who were asymptomatic, without dyslipidemia and naive for antiretroviral therapy. This investigation allowed us to conclude that there is no anti-HIV effect of lovastatin at the doses tested, in patients infected by HIV. In addition, this study had no effect on the absolute count of peripheral blood T cell subsets or on the activation status of the immune system.

Several explanations might account for the contradictory data between the in vivo and in vitro anti-HIV activity of statins. Considering that the main sites of HIV replication and immune alterations are the secondary lymphoid organs, pharmacokinetic limitations could hamper the effective biological activity of statins. In particular, if the bioavailability of statins in lymphoid tissues is deficient, then the anti-HIV and immunomodulatory activities of these compounds will be limited. As proposed by Gao et al.,35 statins with better pharmacokinetic profiles or in presentations for parenteral administration will be more suitable to achieve the effects observed in vitro, where direct administration of statins to cells in culture overcomes the potential limitations derived from oral administration. It is also possible that long-term administration of higher doses of lovastatin might be associated with better anti-HIV effects, but the risks of adverse events and intolerance also increase, questioning the beneficial balance of the administration of lovastatin to asymptomatic chronically HIV-infected individuals.

The limited capability of HAART to control chronic immune activation and to reconstitute the function of the immune system, have encouraged the evaluation of anti-inflammatory and immunomodulatory agents as complementary therapies during HIV infection.3 Anti-proliferative and anti-inflammatory agents such as cyclosporine A,36 glucocorticoids,37 and hydroxyurea,38 were considered potential therapeutic options. However, the poor results obtained and the well-known cytotoxicity and other deleterious side effects associated with these compounds, ruled out their systematic use despite their potential benefits. More recently, other immunomodulatory agents such as antioxidants, chloroquine and statins have been proposed.2,32 Moore et al.39 reported, based on a prospective observational study, that the use of statins could impact on the mortality of HIV-infected patients who were effectively treated with HAART, which was independent of viral load, CD4 T cell count and the effect of the statins on lipids. Furthermore, it was recently reported from a randomized trial performed with HAART naïve HIV-infected patients, that the use of hydroxychloroquine did not reduce T cell activation but had a detrimental effect on viral replication and CD4+ T cell count.40 This finding highlights the importance of randomized controlled trials to corroborate in vivo the well defined anti-HIV effects observed in vitro with several chemical substances, and points that the strong pathogenic activity of HIV is not easily surmounted by the immunomodulatory activity of these apparently promising medications.

Advantages of statins rely on their safety and low cost; however, to date, the benefit of orally administered statins during HIV infection is limited, so as to control the increased cardiovascular risk associated directly to this infection, or as secondary effect of antiretroviral drugs.4,33 The potential benefit of the antiviral and immunomodulatory effects mediated by statins during HIV infection await the development of more potent statins based on better profiles of bioavailability.41

Role of funding sources

This work was supported by: Instituto Colombiano para el Desarrollo de la Ciencia y la Tecnología “Francisco José de Caldas” (COLCIENCIAS, Bogotá, Colombia, grant number: 1115-40-820508); Universidad de Antioquia (Medellín, Colombia); Laboratorio Clínico Congregacion Mariana (Medellín, Colombia); Humax Pharmaceutical (Medellin, Colombia); Laboratorios Laproff (Medellin, Colombia). The role of funding sources were: SE, coordination of laboratory evaluation of biochemical parameters from patients at different times of follow-up, periodical supervision of research evolution and review of the manuscript; FJG and NAG, coordination of pharmacotherapeutic evaluation of patients at different times of follow-up, periodical supervision of research evolution and review of the manuscript; MJ, coordination of intervention production (lovastatin and placebo) and quality control, periodical supervision of research evolution and review of the manuscript; CPV, coordination of patients’ enrollment, collection of clinical and epidemiological antecedents of patients, periodical supervision of research evolution and review of the manuscript.

Conflict of interest statement

EAH received a doctoral scholarship from Colciencias; SE is the head of the Laboratorio Clínico Congregacion Mariana; FJG and NAG are employees of Humax Pharmaceutical, which provided the pharmacotherapy follow-up to the patients enrolled in this study. MJ is the head of Laproff Laboratories, which provided the tablets of lovastatin and placebo. CPV is the head of the Program for the control of HIV infection, from EPS SURA in Medellin-Colombia. The other authors declare that they have no competing interest.

Acknowledgments

The authors acknowledge the excellent assistance of Kelly Betancur in coordinating the laboratory and follow-up
appointments, and Erica Henao, Mauricio Monsalve, Diego Lopez and Elizabeth Mazo in performing the pharmacotherapeutical evaluations and follow-up during the study. Finally, the authors thank the participants and the outpatient programs for HIV infection control from EPS SURA and Union HAART, for helping in detection of potential candidates to be enrolled in this investigation.

References