Impact of highly active antiretroviral therapy on blood pressure in HIV-infected patients. A prospective study in a cohort of naive patients

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Objectives
To assess the impact of highly active antiretroviral therapy (HAART) on the blood pressure (BP) of naive patients after 1 year of treatment.

Methods
A prospective, observational study of 95 HIV-positive patients in our Unit starting HAART between January 2001 and October 2002 and maintaining the same regimen for 48 weeks of follow-up was carried out. Data on blood pressure (BP) and demographic, epidemiological, clinical, immunovirological and therapeutic characteristics related to HIV infection were collected prior to HAART and at week 48. High blood pressure (HBP) [systolic BP (SBP) ≥ 140 mm Hg and/or diastolic BP (DBP) ≥ 90 mm Hg] was defined according to international criteria.

Results
Of the 95 patients, 78 were men, 44% had AIDS and 68% were smokers, and their mean age was 40 years. At week 48 the prevalence of HBP was 26% and SBP, DBP and pulse pressure (PP) increased (121.8 versus 116.6 mm Hg, P = 0.0001; 76.3 versus 69.7 mm Hg, P = 0.004; 46.9 versus 43.8 mm Hg, P = 0.001, respectively). Univariate analysis showed that HBP was associated with older age, higher body mass index (BMI), higher baseline lipids, and higher baseline BP. A linear regression model adjusting for age and sex suggested a significant impact of older age, higher baseline SBP, higher baseline hypercholesterolaemia and lower baseline CD4-cell count on SBP increase.

Conclusions
Blood pressure increased after 48 weeks of HAART, leading to an important prevalence of hypertension. The increase in SBP depended on age and baseline lipid profile and immunological status. BP should be periodically measured and treated when necessary in HIV-infected patients on HAART.

Keywords: cardiovascular risk, HAART, hypertension, pulse pressure

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Introduction
Highly active antiretroviral therapy (HAART) has led to a marked reduction in morbidity and mortality in patients with HIV infection [1,2]. However, it has also resulted in the appearance of important short- and long-term adverse effects [3,4]. An increased cardiovascular risk is currently the complication of HAART arousing most interest and concern [5–8]. The association between HAART and the development of dyslipidaemia and insulin resistance has been widely studied and validated [9–11]. Although HAART has also been associated with hypertension, the data available are still controversial and none of the previous studies was longitudinal [12–21]. The aim of our study was to assess the impact of HAART on the blood pressure (BP) of treatment-naive patients after 1 year of treatment.

Patients and methods
We undertook a prospective, observational study of HIV-infected patients attending our Unit who started HAART between January 2001 and October 2002 and who followed the same regimen for 48 weeks. HAART was composed of
two nucleoside reverse transcriptase inhibitors (NRTIs) plus a nonnucleoside reverse transcriptase inhibitor (NNRTI) or at least one protease inhibitor (PI). The indications for HAART and HAAART regimen were assessed by the patient’s physician. Patients were excluded if they were pregnant, were breastfeeding, or were current alcohol or illegal drug abusers. Patients who stopped HAART or switched from a PI to a NNRTI or vice versa during the study period were also excluded.

Clinical, anthropometrical and laboratory data were recorded at the start of the study and after 48 weeks of HAART. Smokers were considered to be those who smoked one or more cigarettes a day. BP, measured with a mercury sphygmomanometer, was taken with the patient sitting in a relaxed, upright position and remaining silent. Patients had been resting for at least 5 min before BP was measured. Two measurements were made at 30 s intervals and the mean BP was calculated. High blood pressure (HBP) [systolic BP (SBP) ≥140 mm Hg and/or diastolic BP (DBP) ≥ 90 mm Hg] was defined according to international criteria [22] and a high pulse pressure (HPP) was defined as a pulse pressure (PP) > 50 mm Hg [23]. Blood was drawn after a 12-h fast for the measurement of plasma lipids. Diagnosis of dyslipidaemia was based on cholesterol levels ≥ 0.5200 mg/dL (1.89 mmol/L) and triglyceride levels ≥ 0.5150 mg/dL (1.69 mmol/L) [24]. A body mass index (BMI) above 25 kg/m² was considered to be high [25]. Lipodystrophy syndrome was defined according to the modified criteria of Carr et al. [26]. Fat accumulation or loss was scored for the neck, abdomen, parotid glands, breasts, legs, arms, face and buttocks on a scale of 0–3 according to severity (0, absent; 1, mild; 2, moderate; 3, severe). The final score was the sum of the individual scores for each body region and this was used to define the degree of lipodystrophy: 1–8, mild; 9–16, moderate; 17–24, severe [26].

Patient data were collected in a computerized database for later statistical analysis with SPSS®, version 11.0 for Windows (SPSS Inc., Chicago, IL, USA). Categorical variables were analysed with the χ² test and Yates’ correction or Fisher’s exact test when necessary. Comparison of quantitative variables prior to starting HAART and at week 48 was performed with the paired Student’s t-test or the Mann–Whitney U-test for variables that did not follow a normal distribution. Quantitative variables for hypertensive and normotensive patients were compared with Student’s t-test or the Mann–Whitney U-test for variables that did not follow a normal distribution. The change in SBP compared with baseline was defined as the outcome variable. Pearson correlation coefficients between this variable and continuous variables were determined, and a linear regression model adjusting for age and gender, with the variables correlated with the change in SBP, was used to investigate which variables better explained the increase in SBP.

**Results**

During the study period, HAART was started in 128 patients, of whom 116 fulfilled the inclusion criteria. Of these, 21 patients were excluded from the final analysis: five patients were excluded as a result of a change in their antiretroviral regimen due to intolerance or failure and 16 were lost to follow-up. The analysis includes the 95 patients who completed the follow-up. Their baseline characteristics (Table 1) showed that 44% had AIDS and most had acquired their infection sexually. Hypertension was detected in seven patients (7%) before starting HAART. Those patients with AIDS had a lower BP than those without criteria for AIDS (SBP 111.6 vs 121.8; P < 0.005; DBP 69.7 vs 76.3 mmHg; P < 0.005). At week 48 the prevalence of HBP was 26%. The mean increase in SBP was 7.9 mm Hg, that in DBP was 4.9 mm Hg (Figs 1 and 2) and that in PP was 3.0 mm Hg. High SBP was present in 26% and high DBP in 18% of patients. Increases in SBP and DBP

Table 1 Clinical and epidemiological characteristics of the 95 patients and study parameters before antiretroviral therapy

| Variable | n (%)
|----------|----------
| Sex | 78 (82%)
| | Male | 78 (82%)
| | Female | 17 (18%)
| Age (years) | 40 ± 10.1
| Smokers | 64 (68%)
| HIV risk | 37 (39%)
| | Homosexual | 37 (39%)
| | Parenteral drug abuser | 29 (31%)
| | Heterosexual | 28 (30%)
| | AIDS | 42 (44%)
| | HCV infection | 35 (37%)
| | ARV | 48 (48%)
| | PI | 49 (52%)
| | NNRTI | 49 (52%)
| | Body mass index (kg/m²) | 23.0 ± 3.9
| | Systolic blood pressure (mm Hg) | 117.4 ± 17.8
| | Diastolic blood pressure (mm Hg) | 73.4 ± 11.5
| | High blood pressure [n (%)] | 7 (7.3%)
| | Total cholesterol (mg/dL) | 167.3 ± 57.8
| | LDL cholesterol (mg/dL) | 105.5 ± 49.3
| | HDL cholesterol (mg/dL) | 33.8 ± 13.3
| | Triglycerides (mg/dL) | 165.2 ± 87.5
| | CD4 count (cells/μL) | 164.2 ± 125.3
| | HIV viral load (log₁₀ copies/mL) | 5.17 ± 0.78

Quantitative variables are expressed as the mean ± standard deviation (SD), HCV, hepatitis C virus; ARV, antiretroviral therapy; PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitors; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
were higher in patients with AIDS than in those without AIDS [increase (Δ)SBP 13.1 vs 3.8 mm Hg; P < 0.01; ΔDBP 8.6 vs 1.9 mm Hg; P < 0.01]. There were no differences between the patients on PIs and the patients on NNRTIs (ΔSBP 10.1 vs 5.7 mm Hg; P = 0.29; ΔDBP 6.5 vs 3.2 mm Hg; P = 0.25). Antihypertensive therapy was initiated in five patients during the follow-up period. These patients were included as hypertensive patients at 48 weeks, and we used their BP at the moment they initiated treatment with antihypertensive drugs to calculate SBP changes. More than 40% of our patients presented lipodystrophy at 48 weeks. Univariate analysis showed that older age, higher BMI, higher baseline lipids, and higher baseline BP were associated with HBP (Table 2). Age was positively correlated with SBP increase (P = 0.03), baseline BMI (P = 0.033), baseline SBP (P < 0.0001) and baseline CD4-cell count (P = 0.033) were negatively correlated with it. Entering these variables one by one, a multivariate regression analysis was performed in order to estimate and better explain the variability of the change in SBP, showing that each 10 additional years of age at baseline were associated with a 4.7 mm Hg greater increase in SBP at 48 weeks and that each additional mm Hg of baseline SBP and each additional 100 CD4-cell counts at baseline were, respectively, associated with a 0.53 mm Hg and a 2 mm Hg lower increase in SBP at 48 weeks (Table 3).

**Discussion**

As far as we are aware, this is the first prospective study to analyse the influence of HAART on BP. The study cohort was mainly composed of immunosuppressed men around 40 years of age, with a high prevalence of AIDS patients. PI and NNRTI formed the basis of antiretroviral therapy in a similar number of patients. After 48 weeks on HAART the BP increased, with a high prevalence of hypertension.

The linear regression model that best explained the increase in SBP included the following factors: age, gender, and baseline SBP, hypercholesterolaemia and CD4-cell count. Several studies have been carried out on hyperten-
Quantitative variables are expressed as the mean ± standard deviation (SD).

HCV, hepatitis C virus; PI, protease inhibitors; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; Δ, increase; BMI, body mass index; overweight, BMI > 30 kg/m²; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Table 3 Multivariate analysis (linear regression model) with change in systolic blood pressure (SBP) as the dependent variable

<table>
<thead>
<tr>
<th>Variables entered (model)</th>
<th>β coefficient (increase in SBP)</th>
<th>95% confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.7</td>
<td>0.1, 0.8</td>
<td>0.010</td>
</tr>
<tr>
<td>Gender</td>
<td>-6.5</td>
<td>-15.9, 2.8</td>
<td>0.170</td>
</tr>
<tr>
<td>Baseline SBP</td>
<td>-0.5</td>
<td>-3.7, 0.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Baseline HCT</td>
<td>12.6</td>
<td>4.1, 12.6</td>
<td>0.004</td>
</tr>
<tr>
<td>Baseline CD4</td>
<td>-2</td>
<td>-0.5, 0.0</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Age, for each 10 additional years of age; gender, female; baseline SBP, for each additional mm Hg of baseline SBP; baseline HCT, hypercholesterolemia; baseline CD4, for each additional 100 cells/L.

Like most other studies, we found no correlation between hypertension and the prevalence of AIDS, duration of HIV infection, HIV RNA level, CD4-cell count or PI use [14,17,19]. Our results suggest that the increase in BP in HIV-infected patients on HAART was partly attributable to the HAART-induced improvement in the general state of health of these patients, and that is the reason why patients with more advanced HIV disease (AIDS...
cases, lower baseline CD4 counts and lower total cholesterol levels) and with lower baseline SBP had a greater SBP increase.

Although we do not yet know what influence PP may have on cardiovascular risk in HIV-infected patients, it should be considered an added risk factor, as has been reported in the general population [23]. In addition to the increase in SBP, our study showed an increase in PP after 48 weeks on HAART.

In summary, BP in HIV-infected patients increased after 48 weeks on HAART, leading to a high prevalence of hypertension. Longer follow-up of patients on HAART and case-control studies will reveal more information about the true role of HAART and its metabolic consequences for high BP. Larger studies with a longer follow-up periods are also required in other populations to determine the true scope of the problem. Whatever the case, hypertension is a cardiovascular risk factor, which in HIV-infected patients is additional to the risk factors of metabolic disorders related to HAART [3–6,9–11], so should be monitored periodically and treated when necessary.

References


