Short Communication

African ethnicity can influence immunological responses to highly active antiretroviral therapy and immunological success at 48 months: a retrospective pilot study

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Objective: To assess whether African ethnicity is independently associated with a poorer CD4 reconstitution with highly active antiretroviral therapy (HAART) compared to Caucasian ethnicity.

Methods: We conducted a retrospective epidemiological study among 575 HIV-1-positive patients at our center and defined immunological success as the presence of blood CD4 lymphocyte counts >500 cells/mm³ in more than 50% of the values collected from 6 to 48 months after beginning HAART. Patients displaying an HIV-1 viral load >200 copies/ml or more than one HIV-1 viral load between 20 and 200 copies/ml during follow-up, were excluded. Patients with baseline blood CD4 counts >500 cells/mm³ were also excluded.

Results: Two hundred and eighty patients met the inclusion criteria and no exclusion criteria. After 48 months of HAART, blood CD4 lymphocyte counts were lower in Africans than in Caucasians: 449 (65–975) vs. 569 (131–1698) cells/mm³ (p = 0.02). Immunological success was present in 142/220 (64.5%) Caucasians vs. 29/60 (48.3%) Africans (p = 0.02). African ethnicity was independently associated with the absence of immunological success (odds ratio 2.22, 95% confidence interval 1.097–4.504; p = 0.02) despite similar baseline blood CD4 counts (219 vs. 204 cells/mm³, p = 0.72).

Conclusion: Our findings suggest that African ethnicity is independently associated with a poorer CD4 reconstitution during HAART than Caucasian ethnicity.

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1. Introduction

Patients of African origin still bear the heaviest burden of the HIV pandemic.1 These patients have absolute peripheral blood CD4 lymphocyte counts similar to those of Caucasian patients2, but significant immunological discrepancies have been seen in patients of African origin.3

During the natural course of HIV infection, the CD4+ count decreases more slowly in patients of African origin than in Caucasian patients.4 Previous studies have found the CD4+ count increase with highly active antiretroviral therapy (HAART) not to be significantly different between HIV-infected patients of African origin and HIV-infected Caucasian patients.5 Only one investigation has reported evidence of a greater CD4+ count increase in Caucasian patients compared to patients of African origin during the first months of HAART.6 Discrepancies between these studies could be linked to the low number of patients of African origin compared to the Caucasian patients, to the various geographic origins of patients of African origin, and to the time delay between the diagnosis of HIV infection and the initiation of HAART, as well as the potential impact of HIV−1 subtypes.7

The effect of ethnicity on the CD4 immune reconstitution during HAART remains an unsolved question, the answer to which could be of major interest. We conducted a retrospective epidemiological investigation to assess whether African ethnicity is independently associated with a poorer CD4 reconstitution during HAART.

2. Patients and methods

Five hundred and seventy-five HIV-1-infected adult patients under HAART on December 31, 2011, at the Reims University
hospital center (France), who gave informed consent for the digitization of their medical records using Nadis software, were included.

Socio-demographic, clinical, and immunovirological data (HIV-1 subtype, CD4+ count, and HIV-1 viral loads at baseline and during follow-up at 6, 9, 12, 18, 24, 36, and 48 months after beginning HAART) were extracted from Nadis. This database has been declared to the Commission Nationale Informatique et Liberté (number 1585477).

The baseline CD4+ count was defined as the lowest absolute value before HAART. Immunological success (IS) was defined as the presence of a CD4+ count >500 cells/mm³ in more than 50% of the values collected during follow-up.8

Age, US Centers for Disease Control and Prevention (CDC) classification category B or C, and HIV-1 viral load at baseline were those extracted before the first line of HAART in patients with multiple lines of therapy. The last line was considered for immunovirological data collection during follow-up, except when a previous line had lasted more than 48 months without any significant HIV-1 viral load variations (see exclusion criteria described below).

In accordance with the ANRS (Agence Nationale de Recherche sur le SIDA et les Hépatites Virales) algorithm, HIV-1 subtype was defined as non-B in the presence of mutations at positions 35, 36, 61, 69, and 89 during routine pol gene sequencing.

The following patients were excluded: those displaying an HIV-1 viral load >20 copies/ml (TaqMan, Roche) 6 months after beginning HAART and those displaying an HIV-1 viral load >200 copies/ml, or more than one HIV-1 viral load between 20 and 200 copies/ml, from 9 to 48 months after beginning HAART. Patients lost to follow-up, with a duration of follow-up less than 9 months, and patients with a baseline CD4+ count >500 cells/mm³ were also excluded.

### 2.1. Statistical analysis

Quantitative variables were compared using the Mann-Whitney U-test and qualitative variables were compared using Fisher’s exact test or Pearson’s Chi-square test, as appropriate. A p-value of <0.05 was considered significant. All variables with a p-value of <0.20 were entered into a multiple logistic regression model. Statistical analyses were performed using StatView 5.0 software (SAS Institute, Cary, NC, USA).

### 3. Results

Two hundred and twenty (78.6%) Caucasian patients and 60 (21.4%) patients of African origin met the inclusion criteria and none of the exclusion criteria (Table 1). Study patients of African origin came mainly from West Africa (92%). Excluded patients were Caucasian in 80.7% of cases and patients of African origin in 19.3% of cases. HIV-1 viral loads decreased after initiation of first-line HAART in both groups (see Supplementary Material, Figure S1).

At 36 and 48 months after initiation of HAART, CD4+ counts were different between patients of African origin (n = 38 and 31) and Caucasian patients (n = 167 and 148): 409 (93–677) vs. 528 (45–1383) at 36 months (p = 0.03), and 449 (65–975) vs. 569 (131–1698) cells/mm³ at 48 months (p = 0.02). CD4+ count reconstitution

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**Figure 1.** (A) Blood CD4 lymphocyte count evolution at baseline and at 48 months (n=48) after beginning HAART in HIV-1-infected Caucasian patients (Caucasian) and HIV-1-infected patients of African origin (African). Median CD4 lymphocyte count absolute values at 48 months were 574 (range 131–1698) vs. 449 (range 65–975) cells/mm³ in Caucasian and African patients, respectively (p = 0.02). **(B) Variables significantly associated with the absence of immunological success. Immunological success was defined as the presence of blood CD4 cell count absolute values >500 cells/mm³ in more than 50% of the values collected during follow-up at 6, 9, 12, 18, 24, 36, and 48 months after beginning HAART. MD, missing data; OR, odds ratio; 95% CI, 95% confidence interval. “p-Value univariate analysis.” “p-Value multivariate analysis.” Fisher’s exact test. Hosmer and Lemeshow goodness-of-fit gives p = 0.163. HIV-1 subtype non-B and ‘opportunistic infection’ were not included in the model because of collinearity with variables ‘African origin’ and ‘CDC classification category B or C’, respectively (Table 1).**
Table 1
Characteristics of Caucasian patients and patients of African origin included in the study.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>African origin n = 60 (100%)</th>
<th>Caucasian n = 220 (100%)</th>
<th>Missing data</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>40.1</td>
<td>50.3</td>
<td>0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age &gt;50 years at the beginning of HAART, n (%)</td>
<td>3 (5.0%)</td>
<td>61 (27.7%)</td>
<td>0</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>15 (25.0%)</td>
<td>174 (79.1%)</td>
<td>0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sexual transmission, n (%)</td>
<td>54 (90.0%)</td>
<td>192 (87.2%)</td>
<td>15</td>
<td>0.14</td>
</tr>
<tr>
<td>Chronic B or C viral hepatitis, n (%)</td>
<td>10 (16.6%)</td>
<td>32 (14.5%)</td>
<td>0</td>
<td>0.68</td>
</tr>
<tr>
<td>Median number of years since diagnosis of HIV-1 seropositivity (min–max)</td>
<td>7 (2–20)</td>
<td>14 (2–28)</td>
<td>0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CDC classification category B or C at the beginning of HAART, n (%)</td>
<td>18 (30.0%)</td>
<td>103 (46.9%)</td>
<td>0</td>
<td>0.02</td>
</tr>
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<td>Opportunistic infection, n (%)</td>
<td>17 (28.3%)</td>
<td>101 (45.9%)</td>
<td>0</td>
<td>0.01</td>
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<tr>
<td>Tuberculosis, n (%)</td>
<td>4 (6.6%)</td>
<td>3 (1.3%)</td>
<td>0</td>
<td>0.04</td>
</tr>
<tr>
<td>Median baseline blood CD4 cell count absolute value, cells/mm³ (min–max)</td>
<td>219 (3–415)</td>
<td>204 (1–479)</td>
<td>9</td>
<td>0.72</td>
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<tr>
<td>Patients with HIV-1 viral load &gt;5 log₁₀ copies/ml at baseline, n (%)</td>
<td>18 (30.0%)</td>
<td>70 (31.8%)</td>
<td>19</td>
<td>0.96</td>
</tr>
<tr>
<td>Median baseline HIV-1 viral load, copies/ml (min–max)</td>
<td>47 414 (20–3 191 780)</td>
<td>44 781 (39–10 000 000)</td>
<td>19</td>
<td>0.77</td>
</tr>
<tr>
<td>HAART regimen including protease inhibitor, n (%)</td>
<td>45 (75.0%)</td>
<td>183 (83.1%)</td>
<td>0</td>
<td>0.14</td>
</tr>
<tr>
<td>HIV-1 subtype non-B, n (%)</td>
<td>32 (53.3%)</td>
<td>6 (2.7%)</td>
<td>89</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

HAART, highly active antiretroviral therapy; CDC, US Centers for Disease Control and Prevention.

* Fisher’s exact test.

Discussion

In the present study, CD4+ counts were found to be significantly lower in patients of African origin than in Caucasian patients at 36 and 48 months after the initiation of HAART. Rates of patients with CD4+ counts >500 cells/mm³ at 48 months were also significantly lower in patients of African origin than in Caucasian patients, whereas baseline CD4+ counts were not significantly different between the two patient groups. Both the use of drastic exclusion criteria designed to rule out lack of adherence to HAART and our patients of African origin group mainly originating from West Africa and accounting for 20% of study patients, allowed us to properly assess the dynamics of CD4+ count recovery according to ethnicity. However our results could be linked to the small number of patients of African origin at 48 months and to an insufficient duration of follow-up. In our study, follow-up was stopped at 48 months because this time was considered as the time of steady-state for CD4+ count recovery.10

Because we observed that patients of African origin have a lesser propensity to reach CD4+ counts >500 cells/mm³ and because that threshold value is known to be correlated with a life-expectancy similar to that of the general population,11 we assessed whether our immunological success criteria were independently associated with African ethnicity. Using our criteria, African ethnicity was the only factor independently associated with the absence of immunological success, except the baselineCD4+ count, which has been described previously.5,11 The effect of HIV-1 subtype non-B could not be excluded because of collinearity. In any case, taking all these results together, we could ask ourselves whether patients of African origin should not be treated earlier in order to definitely obtain a CD4+ count >500 cells/mm³. Such early treatment could be justified only if we have first demonstrated that survival of patients of African origin is the same as in the general population, after adjustment for confounding factors such as HIV-1 subtype non-B, which has been associated once with a better immunological outcome in a different study setting.7 Compared to this previous study, which was designed to focus on the modelization of the CD4+ increase slope of non-B HIV-1 HAART-treated patients at the primary infection stage, our retrospective investigation was designed to focus on the propensity of HAART-treated African patients to restore their CD4+ count >500 cells/mm³ during the 48 months following the beginning of HAART. Such design discrepancies could explain the differences in results obtained in the previous study and ours.

In conclusion, our findings suggest that African ethnicity is independently associated with a poorer CD4 reconstitution during HAART than Caucasian ethnicity. Further prospective studies with larger numbers of patients of African origin and a follow-up longer than 48 months would be of major interest.

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Conflict of interest: No conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2013.08.001.
References


