Fasting blood glucose and insulin sensitivity are unaffected by HAART duration in Cameroonian receiving first-line antiretroviral treatment

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Résumé

La glycémie à jeun et la sensibilité à l’insuline ne sont pas affectées par la durée de la thérapie antirétrovirale chez les camerounais infectés par le VIH.

Objectifs. – Évaluer la relation entre la durée de traitement antirétroviral et les troubles cardio-métaboliques chez des camerounais infectés par le VIH.

Méthodes. – Chez des camerounais VIH positifs âgés de 21 ans ou plus, suivis à l’hôpital central de Yaoundé (centre agréé de traitement du VIH/sida), nous avons évalué l’anthropométrie, la composition corporelle (bio-impédance), la glycémie à jeun, les lipides sanguins et la sensibilité à l’insuline (test court à l’insuline).

Résultats. – Au total, 143 participants (âge moyen 39,5 ± 9,8 ans, 72 % de femmes), avec une durée de traitement antirétroviral variable (naïf de tout traitement [n = 28], 1–13 mois [n = 44], 14–33 mois [n = 35] et 34–86 mois [n = 36]) ont été recrutés. La moitié environ (52 %) était sous
une combinaison thérapeutique incluant la stavudine. Nous avons observé une tendance à une augmentation significative de l’indice de masse corporelle (IMC) et du rapport taille–hanche avec la durée de traitement antirétroviral (P = 0,02 dans les deux cas). Les pressions artérielles systolique (P = 0,04) et diastolique (P = 0,03), le cholestérol sanguin (P = 0,01), la prévalence de l’hypertension artérielle (P = 0,04) et de l’hypercholestérolémie (P = 0,007) étaient significativement augmentés avec la durée du traitement antirétroviral. Les triglycérides, la glycémie à jeun et la sensibilité à l’insuline n’étaient pas modifiés par la durée du traitement antirétroviral. Une accumulation de troubles métaboliques (P = 0,02 pour au moins un facteur de risque, P = 0,09 pour au moins deux facteurs de risque) avec l’augmentation de la durée du traitement antirétroviral a également été observée.

Conclusion. – La durée du traitement antirétroviral est associée à l’IMC, la redistribution de graisses, l’hypertension artérielle, la dyslipidémie chez les sujets camerounais séropositifs pour le VIH. Cependant, elle ne paraît pas avoir d’effet sur le métabolisme glucidique.

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Mots clés : Antirétroviraux ; Virus de l’immunodéficience humaine ; Hyperglycémie ; Sensibilité à l’insuline ; Facteurs de risque cardiovasculaires

1. Introduction

The advent of antiretroviral therapy has considerably reduced human immunodeficiency virus (HIV)-related morbidity and mortality, transforming the condition into a chronic disease [1]. Nevertheless, the benefits of highly active antiretroviral therapy (HAART) can be offset by the development of metabolic abnormalities such as insulin resistance, dyslipidaemia and lipodystrophy [2–4] that, in turn, increase the risk of cardiovascular disease (CVD) in HIV-infected patients.

The pathogenesis of HIV-related metabolic abnormalities has implicated the HIV infection itself as well as protease inhibitors (PIs) and nucleoside analogue reverse transcriptase inhibitors (NRTIs), especially stavudine [5,6]. For this reason, new drugs with less-detrimental metabolic side-effects have been developed [7]. However, in sub-Saharan Africa (SSA), which harbours the highest burden of HIV/acquired immunodeficiency syndrome (AIDS) [8], first-generation NRTIs (such as stavudine and zidovudine) are still widely recommended as first-line therapies in treatment protocols. These drugs have been associated with various adverse metabolic effects [5,6]. Furthermore, with the initiatives by governments to scale-up care for HIV/AIDS, several SSA countries, including Cameroon, now provide antiretroviral drugs free of charge [9,10]. Consequently, patients are increasingly being prescribed lifelong HAART and are therefore at risk of developing related metabolic disorders and premature CVD. These consequences can have negative impacts on treatment compliance and outcomes in an already vulnerable population, especially in settings where healthcare systems are ill-prepared to manage chronic diseases.

Despite the high HIV/AIDS burden and increased access to HAART in SSA, data on HAART-associated and duration-dependent cardiometabolic disorders in African populations are sparse. What studies there are suggest that the metabolic consequences of HAART in Africans may be similar to those observed outside of the continent [11–14]. However, studies have been limited to only a few countries or to certain regions of the continent. Our present study looked at the relationship between the duration of HAART and the cardiometabolic profile of HIV-infected patients attending an outpatient unit in Cameroon.

2. Methods

2.1. Patients

HIV-infected patients with different durations of HAART were recruited consecutively and on a cross-sectional basis at the certified HIV care centre of the Yaoundé Central Hospital. This tertiary care unit specializes in the management of people living with HIV/AIDS in Cameroon. Eligibility criteria included documented HIV infection and an age 21 years or above. Patients were excluded if they were pregnant or taking a drug other than an antiretroviral that can alter glucose or lipid metabolism.

The study had the approval of the National Ethics Committee of Cameroon, and all participants gave their written informed consent before being enrolled.

2.2. Sociodemographic characteristics and medical history

Upon enrolment, a targeted history and physical examination were carried out, allowing the collection of sociodemographic and lifestyle (physical activity, fruit and vegetable intake) data. Patients were asked to come back the following day for anthropometric measurements and collection of blood samples after an overnight fast of at least 8 h. Patients’ clinical records were reviewed, and information extracted regarding antiretroviral regimens, duration of antiretroviral therapy and CD4 counts.

2.3. Anthropometry and body composition

After subjects had removed their shoes, socks and emptied their bladders, weight and height were measured in standing position, using an electronic weighing device (Laica, Vicenza, Italy) and a stadiometer, respectively. Body mass index (BMI) was calculated as the weight (kg) divided by the height in meters squared (m²). Waist and hip circumferences were measured to the nearest 0.1 cm using a D-loop non-stretch fiberglass tape measure with participants wearing light indoor clothing. With the subject erect, waist circumference (WC) was measured at the midpoint between the lower costal margin and the level of the anterosuperior iliac crests during expiration. Hip circumference (HC) was measured with the tape at the level of the greater trochanters. The cut-off points used to define adiposity were BMI scores ≥ 30 kg/m² for obesity and ≥ 25 kg/m² for
overweight, WC > 102 cm in men and > 88 cm in women, and a waist-to-hip ratio (WHR) > 0.90 for men and > 0.85 for women.

Fat-free mass (FFM) was estimated by bioelectrical impedance (BIA) using a Quantum-III 101 Q analyzer (RJL Systems, Clinton Township, MI, USA), and calculated as specified by Chumlea et al. [15].

Systolic and diastolic blood pressures were measured to the nearest 1 mmHg on the right arm at the level of the heart with an electronic sphygmomanometer (HEM-712C, Omron Healthcare Inc., Lake Forest, IL, USA) after 5 min of rest in a sitting position. Three readings were taken and their mean used for the analyses.

2.4. Biochemistry assessments

For measurements of fasting glucose and lipids, a 5-mL sample of whole blood was collected in a vacutainer from a peripheral vein after asepsis and an overnight fast of at least 8 h. The blood was centrifuged at 4000 rpm for 5 min at 4 °C to obtain sera. Blood glucose was measured using a HemoCue Glucose 201+ Analyzer (Angelholm, Sweden). Serum total cholesterol (TC) and triglyceride (TG) levels were measured using a Lisa 380 Plus analyzer (Hycel Diagnostics, Massy, France).

The short insulin tolerance test (SITT) was used to assess insulin sensitivity, as described by Scheen et al. [16]. The SITT consists of intravenously administering a fixed bolus of rapid insulin (0.1 IU/kg body weight), then measuring blood glucose every 3 min over 15 min. The slope of the linear decline in blood glucose concentration (KITT) was derived from the SITT by dividing it by 2 with the plasma glucose half-life (50% from baseline) as follows: KITT (%/min) = 0.693/t1/2 × 100, where t1/2 represents the half-life of the decrease in plasma glucose [17].

Tertiles of KITT values were also calculated, and participants with values in the lower tertile were considered to have insulin resistance (IR), those in the upper tertile were considered to be insulin sensitive (IS) and those in the middle tertile were considered to have an intermediate IR.

2.5. Statistical analyses

Data are presented as percentages for categorical variables and as means (SD), adjusted means (SEM) or medians (interquartile range) for continuous variables. Subjects were grouped into quartiles on the basis of treatment duration. Treatment categories were treatment-naïve, and first (1 to 13 months), second (14 to 33 months) and third (34 to 86 months) quartiles of HAART duration. Comparisons of participants’ characteristics across categories of treatment duration used linear- (for continuous outcomes) and logistic- (for categorical outcomes) regression models that were adjusted for age and gender where necessary. The chi-square test was used to assess trends, and all tests were two-sided. Data analyses were performed using Stata 10 software (StataCorp LP, College Station, TX, USA).

3. Results

3.1. Patients’ characteristics

A total of 143 participants (mean age: 39.5 ± 9.8 years) were enrolled in our study; their characteristics by treatment duration are presented in Table 1. Of these participants, 20% (n = 28) were treatment-naïve and 72% were women; there was no variation in the proportion of women by treatment duration. The mean age of the participants increased with treatment duration (P < 0.001); those not treated were younger than those receiving HAART (mean age: 35.8 vs 40.4 years; P = 0.001). All participants were receiving first-line HAART including an NRTI and none was taking a protease inhibitor (PI). The percentage of subjects prescribed either stavudine or zidovudine increased with the duration of treatment (P = 0.001).

3.2. Anthropometry and body composition measures

The prevalence of BMI-defined overweight (BMI 25–29.9 kg/m²) and obesity (BMI ≥ 30 kg/m²) increased with the duration of HAART (Table 2). After adjusting for age and gender (Table 1), indices of general obesity (BMI) and abdominal obesity (P = 0.02 for WHR) were significant, but...
not for BMI, WC, HC and FFM, which showed a rising trend across quartiles of treatment duration.

### 3.3. Cardiovascular risk factors and insulin sensitivity

Mean systolic and diastolic blood pressures and total cholesterol, as well as the prevalence of hypertension and hypercholesterolaemia, significantly increased with treatment duration (Table 3), whereas TG, blood glucose levels and estimates of insulin sensitivity were not related to HAART duration (Table 3). Also, insulin-resistant patients were younger, with less general (BMI and FFM) and abdominal adiposity (WC, HC), and lower fasting plasma glucose (FPG) than the insulin-sensitive group \((P < 0.05; \text{Table 4})\).

The age- and gender-adjusted proportions of participants with one or more or two or more metabolic abnormalities by duration of treatment are shown on Fig. 1. The proportion of those with at least one metabolic risk factor significantly increased with duration of treatment \((P = 0.02)\), whereas the corresponding proportion with at least two metabolic disorders did not \((P = 0.09)\). The prevalence of metabolic factor clustering in people with a treatment duration of 34 months or above was twice that observed in those with 14–33 months of treatment.

### 4. Discussion

A significantly higher prevalence of BMI-defined overweight and obesity, hypertension and hypercholesterolaemia, as well as abdominal fat deposition (WHR), was found with increasing duration of HAART in adult Cameroonian with HIV. Furthermore, there was a significant clustering of metabolic risk factors with HAART duration. However, TG levels, fasting blood glucose (FBG) and insulin sensitivity were not affected by HAART duration.

#### 4.1. Comparisons with previous studies and explanation of results

Our present blood pressure (BP) findings concurred with those of previous studies showing a higher prevalence of hypertension with increasing HAART duration [18–20]. The observed prevalence of hypertension (27.8%) among those with a minimum HAART duration of 34 months was comparable to...
Table 4
Comparison of characteristics of insulin-resistant and insulin-sensitive subjects.

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Insulin-resistant(lower tertile of KITT)</th>
<th>Insulin-sensitive(upper tertile of KITT)</th>
<th>P valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>37.34 (10.6)</td>
<td>40.24 (10.0)</td>
<td>0.14</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>60.18 (9.5)</td>
<td>69.52 (13.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference, cmf</td>
<td>78.32 (7.90)</td>
<td>84.89 (9.92)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hip circumference, cm</td>
<td>89.26 (7.64)</td>
<td>94.31 (10.50)</td>
<td>0.009</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.88 (0.06)</td>
<td>0.90 (0.05)</td>
<td>0.061</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.57 (3.12)</td>
<td>25.72 (4.62)</td>
<td>0.009</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>43.82 (8.57)</td>
<td>51.93 (12.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total body-fat, %</td>
<td>17.34 (7.04)</td>
<td>20.04 (10.41)</td>
<td>0.15</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>117.41 (23.81)</td>
<td>118.29 (21.27)</td>
<td>0.85</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>74.27 (13.16)</td>
<td>71.90 (13.67)</td>
<td>0.39</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biological characteristics</th>
<th>Total cholesterol, g/L</th>
<th>Triglycerides, g/L</th>
<th>Fasting blood glucose, mg/dL</th>
<th>CD4 count, n/mm³</th>
<th>K insulin tolerance test (KITT), %/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.00 (0.62)</td>
<td>0.80 (0.29)</td>
<td>75.18 (5.23)</td>
<td>284.62 (191.61)</td>
<td>1.56 (0.03)</td>
</tr>
<tr>
<td></td>
<td>1.98 (0.68)</td>
<td>0.76 (0.29)</td>
<td>101.25 (7.53)</td>
<td>249.96 (173.23)</td>
<td>1.75 (0.06)</td>
</tr>
</tbody>
</table>

Data are presented as means (SD); CD4: cluster of differentiation antigen 4; KITT: linear decline in blood glucose as assessed by the short insulin tolerance test (SITT).

a Age- and gender-adjusted comparisons where necessary and also for CD4 counts with KITT.

that found by Palacios et al. [18] (26%) after 48 weeks of HAART in treatment-naïve subjects in a prospective study. In our present population, older age, higher BMI and higher lipid levels were associated with higher BP levels. The trend towards higher BP could therefore be linked to HAART-related changes in these risk factors as well as body-fat distribution, which have been shown to mediate HAART effects on BP [18,20,21]. The observed changes in BMI, WC, FFM and, more importantly, WHR also corroborate previous findings, thereby suggesting that longer treatment leads to mobilization of body-fat stores and the accumulation of more metabolically detrimental intra-abdominal fat. A 6-year nested case-control study, for example, comparing HIV-uninfected men with HIV-positive men found a significant increase in WC with HAART duration, regardless of lipodystrophy status [22]. However, in our present study, HC did not change with treatment duration, indicating that the increase in WC (a surrogate for intra-abdominal fat stores) was mostly responsible for the significant rise in WHR. Fat redistribution may also be explained by the high number of subjects receiving stavudine- or zidovudine-containing HAART regimens, which have been linked to lipodystrophy and especially lipohypertriglyceridaemia [18,20,21]. However, apart from the WC and HC, no further clinical assessments of lipoatrophy were performed.

Our results showed changes in lipid profile that are generally in agreement with the previous findings obtained in other African populations [24–26], some of which have reported increases in blood lipid levels with longer HAART duration [25]. In general, treatment-naïve HIV-infected subjects tend to have hypertriglyceridaemia [4,27,28], with either an increase or no change in total cholesterol and TG after starting HAART [4,11,25], depending on the type of antiretroviral therapy. PI-based regimens are more atherogenic than non-PI-based regimens [4,11], and nevirapine-containing regimens display antiatherogenic effects [4,29]. Lipid fractions [low-density lipoprotein (LDL) or high-density lipoprotein (HDL) cholesterol] were not assessed in the present study and, therefore, no comments can be made on whether or not the observed higher total cholesterol with HAART duration was driven by these fractions.

Glucose metabolism (FBG levels and insulin sensitivity) was not affected by treatment duration in our study, whereas results from other African studies have shown variable findings. Manuthu et al. [12] found no differences in the prevalence of impaired fasting glucose, impaired glucose tolerance or overt diabetes mellitus between untreated and treated HIV-infected patients. On the other hand, Mutimura et al. [13] indicated slight differences in impaired fasting glucose prevalence in lipodystrophic HIV-infected patients, non-lipodystrophic HIV-infected patients and healthy controls, although serum insulin levels...
were similar in all three groups. Dave et al. [14] found no differences in the prevalence of dysglycaemia between HAART-naive and HAART-treated patients, with no differences in β-cell function or insulin sensitivity between dysglycaemic patients with or without HAART. Our present results and those of previous studies suggest that subjects of African descent may be less prone to developing HAART-related abnormalities of glucose metabolism. Nonetheless, our results cannot provide definitive conclusions on glucose metabolism in HIV-positive Cameroonian patients taking HAART, as the role of a residual confounding factor related to our somewhat limited assessment of adiposity cannot be excluded.

4.2. Study strengths and limitations

There is a paucity of data on cardiometabolic disorders in HIV-positive patients in SSA. However, our present study is among the rare Africa-based investigations aiming to comprehensively and rigorously assess body composition (anthropometry and bioimpedance) and glucose metabolism, including insulin sensitivity (using the SITT), in HIV-infected patients, and to relate these parameters to duration of HAART. Most of the published Africa-based studies have used only anthropometry to evaluate body-fat distribution and have seldom evaluated IR appropriately.

Nevertheless, some limitations of our study should be mentioned. First, compliance to treatment was not objectively measured, and it was assumed to be evenly distributed across the various quartiles of treatment duration. Second, the sample size was relatively small, and the cross-sectional design does not permit follow-up of serial changes in the measured parameters, which would help to elucidate the effects of ART over time. Third, longer durations of exposure to HAART might have allowed better characterization of the effects of HAART and, finally, the different body-fat compartments (visceral adipose tissue and subcutaneous adipose tissue) and insulin secretion and, thus, pancreatic β-cell function were not measured. These parameters would have allowed further exploration of HAART effects on body-fat distribution and glucose metabolism, thereby allowing a better explanation of our results. However, despite these limitations, the present study contributes novel findings on the relationship between duration of first-line HAART and metabolic disorders in people of African origin.

5. Conclusion

Duration-dependent HAART-induced key cardiometabolic abnormalities are present in Cameroonian HIV-infected adults, although the duration of HAART does not appear to affect glucose metabolism. These cross-sectional findings help to refine the management of African HIV-positive patients, as having access to new and less toxic antiretroviral agents may take some time and may not happen simultaneously in all countries. In any case, large and sufficiently long prospective studies are needed to better characterize these metabolic abnormalities.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Acknowledgements

We acknowledge the contributions of all the participants to this study. We are also grateful to Ms Sylvie Ngamani, who helped with data collection, and the staff of the Laboratory of Biochemistry of the University Teaching Hospital of Yaoundé, and the National Obesity Centre of the Yaoundé Central Hospital, which undertook various assessments.

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