Genetic polymorphisms in estrogen receptors and sexual dimorphism in fat redistribution in HIV-infected patients on HAART

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Objective: To investigate genetic single nucleotide polymorphisms (SNPs) in estrogen receptor-α (ERα) (*ESR1*, rs2234693, rs1801132, rs7757956 and rs2813544) and ERβ (*ESR2*, rs3020450, rs7154455 and rs4986938) genes and relate them to the adverse effects lipodystrophy, dyslipidemia and metabolic syndrome as well as to differences in their prevalence between sexes in HIV-infected individuals on HAART.

Design: Cross-sectional study.

Methods: Blood samples and anthropometric measurements were collected from 614 patients at reference services in the cities of Porto Alegre, Pelotas and Rio Grande in Brazil. The SNPs were genotyped by real-time PCR.

Results: The lipodystrophy subtype frequencies in patients of different sexes showed statistically significant differences; the atrophic pattern was more prevalent in men, and the hypertrophic pattern was more prevalent in women. Furthermore, metabolic syndrome prevalence was higher in women than in men. The *ESR1* rs2813544 G-allele was associated with higher measurements of several anthropometric variables in women: BMI, total subcutaneous fat and subcutaneous fat of limbs. Additionally, patients who were AA homozygous for *ESR2* rs3020450 presented an increased risk for developing lipoatrophy (prevalence ratio 1.37, 95% confidence interval 1.09–1.73, $P = 0.007$).

Conclusion: Significant differences in lipodystrophy and metabolic syndrome prevalence were detected between sexes. Moreover, the *ESR1* gene (rs2813544) presented significant sex-specific associations with anthropometric variables, and the *ESR2* gene (rs3020450) was associated with an increased risk of developing lipoatrophy. Our results suggest that these genes are in part responsible for the sexual dimorphism in fat tissue redistribution and patterns of lipodystrophy.

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Introduction

Since the introduction of HAART, an improvement in the survival of HIV-infected patients and a dramatic decrease in the incidence of many opportunistic infections have been observed [1]. However, the development of adverse effects in patients may interfere with patient adherence to HAART and may be the most significant factor determining regimen failures [2]. Therefore, metabolic abnormalities that include abnormal body fat redistribution (lipodystrophy) and metabolic syndrome might compromise treatment outcomes [3].

Not all patients who take a particular antiretroviral medication develop an adverse effect that has been attributed to that drug. This observation suggests that genetic predispositions play an important role in the development of such adverse effects [4]. In addition, an important difference in the development of fat redistribution has been observed between sexes. A large HIV cross-sectional study showed that women have a higher risk of developing adipose tissue abnormalities than men [5]. Moreover, female patients had lower high-density lipoprotein (HDL)–cholesterol (HDL-C) values and a higher prevalence of metabolic syndrome and abdominal obesity than males [6]. Such sex-specific genetic architecture suggests new models of susceptibility for common diseases and sheds light on potential mechanisms of sexual dimorphism [7].

Estrogens play a critical role in adipose cell differentiation and fat distribution by acting through their receptors [8]. Therefore, genes encoding estrogen receptors (ERs) are plausible candidates that may be responsible for the observed sexual dimorphism of fat redistribution patterns in people with HIV and AIDS. The *ESR* gene family consists of two specific genes: *ESR1* on chromosome 6q25.1 encoding the ERα and *ESR2* on chromosome 14q23.2 encoding the ERβ [9]. Previous studies associated single nucleotide polymorphisms (SNPs) in both genes in a sex-specific manner with variations in the BMI, waist circumference [10,11] and lipid profile [12] of individuals who were not infected with HIV. Furthermore, differences in ERβ expression were found in HIV-infected individuals with lipodystrophy [13]. However, SNPs in these genes were not evaluated for association with lipodystrophy and its complications in these individuals.

Therefore, the aim of this study was to investigate the frequencies of selected SNPs in *ESR1* (rs2234693, rs1801132, rs7757956 and rs2813544) and *ESR2* (rs3020450, rs7154455 and rs4986938) genes and relate them to differences in the prevalence of fat redistribution, dyslipidemia and metabolic syndrome of HIV-infected patients on HAART between sexes. The SNP selection was based on previous data relating these SNPs with variables of interest in populations that were not infected with HIV and their locations in different haplotype blocks within the candidate genes.

Methods

Study population

This cross-sectional study included 614 patients consecutively recruited from government-supported HIV reference treatment services in three cities from the Brazilian southernmost state: Porto Alegre, Pelotas and Rio Grande. The evaluation routine consists in visits every 4 months in each center with evaluation by their attending physicians, and laboratory evaluations that include CD4 cell counts, viral load, fasting glucose and lipid levels. The patients were invited to participate of the study and had their information and blood sample for DNA extraction collected once in one of these visits.

The inclusion criteria for the study were that patients were older than 18 years of age, had confirmed HIV infection, were receiving HAART for at least 1 year and had a viral load below the limit of detection (50 copies/ml) of the test. This last parameter was used to verify adherence to HAART. The exclusion criteria for the study were pregnancy and/or the inability to understand the study and answer the questionnaires.

Procedures

An interview was performed at enrollment to obtain demographic and lifestyle information. Details of HIV infection (time from diagnosis, current and prior antiretroviral medications), lipid-lowering intervention and relevant clinical variables were obtained from medical records. The patients' ethnicities were phenotypically defined by the interviewer because there might be a strong cultural tendency to claim European ancestry in Brazil [14]. Patients were classified as Euro or Afro-descendants because in the Brazilian South Region the Amerindian contribution is very low [15].

Anthropometric analysis

At the moment of inclusion in the study, a complete physical examination of each patient was performed by trained researchers that included measurements of weight (kilograms), height (meters), waist circumference (centimeters) and seven skinfolds (millimeters). Biceps, triceps and calf folds were grouped into a single categorical measurement named limbs subcutaneous fat (LSF). Subscapular, axillary, suprailiac and abdominal folds were grouped into a single categorical measurement called central subcutaneous fat (CSF). Total subcutaneous fat (TSF) was the total sum of LSF and CSF. The use of these subdivisions to assess subcutaneous fat in HIV patients was validated by Florindo *et al.* [16]. BMI was calculated using the following formula: BMI = weight in kilograms/(height in meters)^2.

Fat redistribution diagnosis was performed by the same physician at each center. Lipoatrophy was identified by the loss of fat in the face and/or members; lipohypertrophy was identified by the accumulation of fat in the abdominal and/or dorsocervical region. Patients who had both types of adipose tissue redistribution were classified as having a mixed pattern [17]. Additionally, metabolic syndrome was defined following the International Diabetes Federation (IDF) guidelines [18]. On the basis of this definition, three or more of the following criteria needed to be met for defining metabolic syndrome: fasting serum triglycerides more than 150 mg/dl or drug treatment for elevated triglycerides; HDL-C less than 40 mg/dl in a man or less than 50 mg/dl in a woman (or drug treatment for reduced HDL-C); SBP of at least 130 mmHg and/or DBP of at least 85 mmHg indicative of hypertension and/or use of an antihypertensive drug; fasting blood glucose of at least 100 mg/dl or treatment for elevated glucose; and waist perimeter at least 94 cm in men or at least 80 cm in women indicative of an abnormal waist circumference.

The National Cholesterol Education Program Adult Treatment Panel III (NCEP, 2001) report was also used for the definition of metabolic syndrome [19]. Both guidelines used the same components and cut-off points, except the NCEP cut-offs were more than 102 cm in men or more than 88 cm in women for waist circumference and at least 110 mg/dl for fasting blood glucose.

Dyslipidemia was defined by total cholesterol values of at least 200 mg/dl, low-density lipoprotein values (LDL–cholesterol) of at least 130 mg/dl, HDL-C of 40 mg/dl or less (men) and 50 mg/dl or less (women) and/or triglycerides values of at least 150 mg/dl [19].

Laboratorial analysis

Fasting blood samples were collected and sent to the Molecular Biology Laboratory for DNA extraction. Simultaneously, lipid profile (total cholesterol, HDL-C and triglycerides), glucose levels and viral load were measured in each participating center. In individuals with triglyceride levels less than 400 mg/dl, LDL–cholesterol levels were estimated using the Friedewald equation [20]. All data were stored in a database using the Microsoft Excel program (Microsoft Corporation, Redmond, Washington, USA).

Genomic DNA was obtained from peripheral leukocytes by a standard salting out technique [21]. The SNPs were genotyped by real-time PCR using the TaqMan methodology. The SNPs were chosen based on previous data of significant SNP associations with one or more of the following variables: adipose mass, BMI, anthropometric and biochemical parameters related to HAART adverse effects or to sex. The selected SNPs are in different haplotype blocks of both genes [22] (Table 1).

Table 1. Genotyped single nucleotide polymorphisms in *ESR1* and *ESR2* genes.

SNPs	Position	Change
ESR1 gene		
rs2234693	Intron 1	C>T
rs1801132	Exon 4	C>G
rs7757956	Intron 4	T>A
rs2813544	3′-UTR	A>G
ESR2 gene		
rs3020450	5′-UTR	G>A
rs7154455	Intron 3	G>C
rs4986938	3′-UTR	G>A

SNP, single nucleotide polymorphism; UTR, untranslated region.

Ethical considerations

All participants were informed about the study and signed a free and informed consent form. This study was approved by the Research Ethics Committee in each participating center (protocol numbers: 05/295, 718/08 and 154/07).

Statistical analysis

Demographic and clinical variables were compared among the three centers and between sexes. Categorical variables were contrasted with the χ^2-test or Fisher's exact test. Anthropometric and biochemical parameter means were compared between genotypes using a Student's *t*-test for independent samples, a Mann–Whitney *U*-test and an analysis of variance (ANOVA) or a Kruskal–Wallis test. Differences between groups were compared with the Tukey test when appropriate. Asymmetrically distributed data (triglycerides levels and LSF) were transformed using the natural logarithm and then used for statistical analysis.

Poisson regression models with robust variance were used to estimate the contribution of each variable to the phenotypes of lipoatrophy, lipohypertrophy and metabolic syndrome. Poisson regression was used because it provides more accurate estimates than logistic regression and is considered to be the best statistical method for analysis of cross-sectional studies with binary outcomes [23]. All data were analyzed using the SPSS 16.0 program (SPSS Inc., Chicago, Illinois, USA). All tests were two sided, and the level of significance was predefined at less than 0.05.

Results

Of the 614 patients, 55.5% were male, 56.8% were characterized as Euro-descendants and their mean age was 42.6 ± 9.5 years. The total patient population was stratified by sex, and its main features are shown in Table 2.

The overall prevalence of lipodystrophy was not different between sexes. Nevertheless, when only patients who had lipodystrophy were compared, lipodystrophy subtypes

Table 2. Main features of 614 HIV-infected patients stratified by sex.

Features	Women ($n=237$)	Men ($n=341$)	P value
Demographic			
Age (years)	41.3 ± 9.8	43.6 ± 9.2	0.003[b]
Ethnicity (%)			
Euro-descendants	60.8	53.7	0.090[a]
Afro-descendants	39.2	46.3	
Clinical			
Therapy time (months), median (quartiles)	59.5 (27.3–99.8)	59.0 (33.0–102.5)	0.344[c]
Use of protease inhibitor (%)	51.6	47.5	0.348[a]
BMI (kg/m^2)	25.7 ± 5.3	24.6 ± 3.7	0.003[b]
Waist circumference (cm)	90.2 ± 21.3	88.6 ± 10.5	0.224[b]
TSF (mm)	135.6 ± 52.0	86.8 ± 39.0	<0.001[b]
LSF (mm)	43.2 ± 23.2	22.1 ± 14.3	<0.001[d]
CSF (mm)	92.4 ± 35.5	64.8 ± 29.8	<0.001[b]
Adverse effects (%)			
Lipodystrophy	54.8	48.5	0.145[e]
Atrophy	26.8[f]	52.7[g]	<0.001[h]
Hypertrophy	35.6[i]	18.2[j]	
Mixed pattern	37.6	29.1	
Metabolic syndrome (%)			
IDF	37.4	27.6	0.012[a]
NCEP	23.4	16.1	0.030[a]
Dyslipidemia	75.6	74.9	0.933[a]

Data presented as mean ± SD, percentage or median (quartiles). CSF, central subcutaneous fat; IDF, the International Diabetes Federation; LSF, limbs subcutaneous fat; NCEP, the National Cholesterol Education Program Adult; TSF, total subcutaneous fat.
[a]χ^2-Test with Yates correction.
[b]Student's t-test for independent samples.
[c]Mann–Whitney U-test.
[d]Student's t-test for independent samples with $\log_n$-transformed variable.
[e]χ^2-Test between sexes
[f]Adjusted residual = −4.67, P < 0.05.
[g]Adjusted residual = +4.67, $P < 0.05$.
[h]χ^2-Test between individuals with lipodystrophy only.
[i]Adjusted residual = +3.49, $P < 0.05$.
[j]Adjusted residual = −3.49, $P < 0.05$.

frequencies showed heterogeneity between sexes ($\chi^2 = 23.629$, $P < 0.001$); the atrophic pattern was more prevalent in lipodystrophic men (52.7%), and the hypertrophic pattern was more prevalent in lipodystrophic women (35.6%, Table 2). In our study, metabolic syndrome was more frequent in women than in men by both IDF and NCEP definition criteria. Metabolic syndrome was present in 37.4% of women vs. 27.6% of men ($\chi^2 = 6.253$, $P = 0.012$) using the IDF criteria and in 23.4% of women vs. 16.1% of men using the NCEP criteria ($\chi^2 = 4.734$, $P = 0.030$, Table 2). The prevalence of dyslipidemia was not significantly different between sexes (Table 2).

Genotype and allele frequencies of the SNPs analyzed are shown in Table 3. Genotype frequencies for all SNPs were in agreement with those expected under Hardy–Weinberg equilibrium. All SNP frequencies were compared between ethnic groups, and only rs4986938 in the *ESR2* gene showed a statistically significant difference in frequency ($\chi^2 = 7.744$, $P = 0.021$). Nonetheless, ethnicity was tested as a covariate in all statistical analyses and was included when significant.

The means of anthropometric and metabolic variables were compared among the different genotypes in the study and in each sex separately. For the *ESR1* gene, the rs2813544 G-allele was associated with higher anthropometric measurements exclusively in women: BMI (ANOVA, $P = 0.008$), TSF (ANOVA, $P = 0.003$) and LSF (ANOVA, $P = 0.004$, Table 4). Other variables were not found to be different among genotypes for the other SNPs in the *ESR1* and *ESR2* genes (data not shown), with the exception of triglycerides levels. Triglycerides levels were different among *ESR1* rs7757956 genotypes in the patient population (ANOVA, $P = 0.016$). Carriers of the T/T, T/A and A/A genotype showed a mean and a SD of 202.5 ± 164.4, 178.9 ± 195.2 and 137.5 ± 83.6 mg/dl, respectively (Tukey test, T/T vs. A/A, $P = 0.045$).

Poisson regression analyses were used to determine whether any of the SNPs analyzed was a significant predictor of the categorical phenotypes investigated (e.g. lipoatrophy, lipohypertrophy and metabolic syndrome). In Table 5, we present the best Poisson regression model for lipoatrophy. Patients who were AA homozygotes for *ESR2* rs3020450 presented an increased risk of developing lipoatrophy (prevalence ratio 1.36, $P = 0.008$). Other significant predictors of lipoatrophy were age (prevalence ratio 1.02, $P < 0.001$), European ancestry (prevalence ratio 1.30, $P = 0.009$) and protease inhibitor

Table 3. Genotypic and allelic frequencies of *ESR1* and *ESR2* polymorphisms.

Polymorphisms	Genotypic frequency	Allelic frequency	
*ESR*1 rs2234693		T	C
T/T	209 (34.7%)	0.60	0.40
T/C	298 (49.4%)		
C/C	96 (15.9%)		
Total	603		
*ESR*1 rs1801132		C	G
C/C	380 (62.0%)	0.79	0.21
C/G	206 (33.6%)		
G/G	27 (4.4%)		
Total	613		
ESR1 rs7757956		T	A
T/T	444 (72.4%)	0.85	0.15
T/A	155 (25.3%)		
A/A	14 (2.3%)		
Total	613		
ESR1 rs2813544		A	G
A/A	366 (59.8%)	0.77	0.23
A/G	208 (34.0%)		
G/G	38 (6.2%)		
Total	612		
ESR2 rs3020450		G	A
G/G	275 (44.9%)	0.67	0.33
G/A	272 (44.4%)		
A/A	66 (10.7%)		
Total	613		
ESR2 rs7154455		G	C
G/G	274 (44.7%)	0.67	0.33
G/C	270 (44.0%)		
C/C	69 (11.3%)		
Total	613		
ESR2 rs4986938		G	A
G/G	280 (45.7%)	0.66	0.34
G/A	256 (41.8%)		
A/A	77 (12.5%)		
Total	613		

The difference in the number of individuals among single nucleotide polymorphisms (SNPs) is due to failure in genotyping some SNPs in the whole sample.

use (prevalence ratio 1.24, $P = 0.028$, Table 5). Protease inhibitor users have longer treatment duration because this class of drug is used when the first-line drug therapy fails. Thus, treatment time is being represented by this variable in the best regression model. Apart from protease inhibitor use, zidovudine (ZDV) use was also shown to be a protective factor (prevalence ratio 0.72, $P = 0.001$). Sex did not show significance in the regression model. The other SNPs studied were not predictors for the adverse effects of HAART (data not shown).

Discussion

Up to 83% of HIV-infected patients on HAART develop changes in fat tissue distribution (lipodystrophy) and related metabolic complications that differ between sexes [6,24]. These features are worrisome because they can stigmatize the patient, which might affect the patient's quality of life and lead to treatment discontinuation [25].

In our study, the lipohypertrophy pattern was more common in women, and the lipoatrophy pattern was more common in men. This sex-specific difference in the prevalence of lipodystrophy subtypes was also reported in a study of HIV-positive Brazilians [26]. Although not all studies report this difference between sexes [5], the percentage of women and racial/ethnic minorities participating was small in many initial, randomized clinical trials of HAART [27]. Furthermore, female patients had a higher prevalence of metabolic syndrome than males using IDF and NCEP definitions (Table 2). This finding is supported by a similar result reported for a cohort of Latin American HIV-infected patients [6]. In addition, higher BMI means in women were also found in an adult HIV-infected patient cohort [28]. These data suggest that the sex differences in the prevalence of these

Table 4. Comparison of anthropometric variables between *ESR1* rs2813544 genotypes in both sexes.

	BMI (kg/m^2)				TSF (mm)				CSF (mm)				LSF (mm)[a]			
Genotype	*n*	Mean	SD	*P* value	*n*	Mean	SD	*P* value	*n*	Mean	SD	*P* value	*n*	Mean	SD	*P* value
Women																
A/A	163	25.3	4.8	0.008[b]	148	128.4	49.8	0.003[c]	148	89.0	34.9	0.055	149	39.4	19.7	0.004[d]
A/G	92	25.9	5.4		88	142.6	54.0		88	95.3	35.9		91	46.8	25.6	
G/G	17	29.2	8.2		15	165.5	49.7		15	108.1	36.5		16	58.2	31.0	
Total	272	25.7	5.3		251	135.6	52.1		251	92.4	35.6		256	43.2	23.3	
Men																
A/A	201	24.5	3.9	0.548	192	86.0	40.4	0.901	192	64.7	32.5	0.993	193	21.4	12.9	0.504
A/G	116	24.9	3.4		110	88.6	38.2		110	65.0	26.0		110	23.6	17.1	
G/G	21	24.0	3.2		19	84.4	30.5		19	63.7	24.8		19	20.6	8.2	
Total	338	24.6	3.7		321	86.8	39.0		321	64.8	29.9		322	22.1	14.3	

Data obtained by ANOVA with variables adjusted by multiple linear regression. BMI: adjusted by exercise and smoking; TSF and CSF: adjusted by age, exercise and smoking; and LSF: adjusted by age and exercise. CSF, central subcutaneous fat; LSF, limbs subcutaneous fat; TSF, total subcutaneous fat.

[a]Tests performed with natural logarithm transformed variable.

[b]Tukey test, A/A vs. G/G, $P = 0.006$; A/G vs. G/G, $P = 0.041$.

[c]Tukey test, A/A vs. G/G, $P = 0.010$.

[d]Tukey test, A/A vs. A/G, $P = 0.042$; A/A vs. G/G, $P = 0.020$.

Table 5. Poisson regression model and predictive variables for atrophy development in HIV-positive patients on HAART.

Outcome	Variable	PR	95% CI	*P* value
Lipoatrophy	Age	1.02	1.01–1.03	<0.001
	Ethnic group (Euro-descendent)	1.30	1.07–1.58	0.009
	PI use	1.24	1.02–1.50	0.028
	ZDV use	0.72	0.59–0.87	0.001
	rs3020450 AA genotype	1.36	1.08–1.72	0.008

95% CI, 95% confidence interval; PI, protease inhibitor; PR, prevalence ratio; ZDV, zidovudine.

adverse effects among HIV-infected patients are consistent.

As far as we know, this is the first report of an *ESR1* rs2813544 G-allele sex-specific association with higher anthropometric measurements in HIV-infected individuals. Nilsson *et al.* [29] reported an association of this SNP with obesity in a cohort of Swedish whites who were not infected with HIV. However, the GG genotype showed a protector effect in women and in the whole population when this genotype was compared with the AA genotype. We believe that their cohort is not comparable to that of our study in many aspects. Association studies of genetics polymorphisms may show contradictory results in different samples because different variants act with the true genetic variant, causing changes in the expression or structure of the ERs that may be in partial linkage disequilibrium with the variant studied. The rs2813544 polymorphism is a noncoding A-to-G transition located in the 3′-untranslated region (UTR) of the *ESR1* gene. Polymorphisms at 3′-UTRs could affect the processing and/or stability of the transcript, thereby altering the effectiveness of the template [30]. The functional importance of the SNP could also be related to the fact it might be located in the 3′-UTR-binding target region of microRNAs, which are predicted to regulate almost a third of the human genome [31,32]. This polymorphism might be altering gene expression by creating or abolishing a microRNA target site, or by changing secondary structure of the *ESR1* transcript that alters the accessibility of microRNA [33].

Additionally, the association of the *ESR1* rs7757956 T-homozygote genotype with higher triglyceride levels is a novel finding. In a cross-sectional study of children, the rare allele (A) of this SNP was associated with a reduction in BMI and the risk of being overweight [34]. Unfortunately, lipid profile was not assessed in that study. Our finding might be related to the fact that sex steroids, for which biologic activity is mediated through ERs, modulate the risk of cardiovascular disease by impacting lipids [35]. Although this SNP is an intronic polymorphism, potential functional mechanisms include modification of *ESR1* expression or affinity of the receptor for estrogen [12].

In our analysis of the *ESR2* gene, rs3020450 AA homozygous patients were observed to have a higher risk for developing lipoatrophy. To our knowledge, this SNP was previously associated with obesity, and the G allele was considered to be a protective element in the same noninfected Swedish cohort studied by Nilsson *et al.* [29]. As previously discussed, we believe that their results are hardly comparable with ours and probably reflect different linkage disequilibrium patterns in both populations. Estrogen signaling is implicated in both central, which is regulation of food intake, and peripheral pathways protecting against adiposity [29]. The 5′-flanking UTR of the *ERβ* gene is large and contains various regulatory elements [36]. One important role of 5′-untranslated regulatory regions of a gene is to control the amount of primary transcript in the basal state or in response to stimuli through the binding of transfactors to cognate responsive elements [30]. This suggests a versatile utilization of regulatory signals and tissue-specific expression [37,38]. Therefore, any alteration in this promoter region might be functionally important and may alter the expression of the *ESR2* transcript.

Lichtenstein [39] reviewed a series of large epidemiological studies using multivariate analysis and showed that the most common statistically significant risk factors for lipoatrophy were the use of specific nucleoside analogues (d4T), increasing age, the presence of markers of disease severity, the duration of therapy and being of white ethnicity. We believe that this argues for a role of genetic factors influencing this phenotype because different studies have shown that ethnicity (white, European, etc.) is a risk factor for adipose tissue redistribution in different countries or environments.

Regarding the role of nucleoside analogues in the cause of lipoatrophy, d4T was not a significant contributor to this phenotype, but ZDV was a significant protective factor against the development of lipoatrophy. Notably, only 24 individuals in our study currently use d4T, which may explain why we did not find association of d4T with lipoatrophy. On the contrary, 488 individuals in our study were on ZDV-containing regimens. McComsey *et al.* [40] and several other authors have shown that if patients develop lipoatrophy while receiving d4T, then it is prudent to switch them to either abacavir or ZDV as soon as possible because there is a subsequent improvement in HAART-associated lipoatrophy. It is logical that the group who uses ZDV seems to be protected from the development of lipoatrophy when compared with

those who use d4T because in our study, all individuals used nucleoside reverse transcriptase inhibitors. Poma *et al.* [41] investigated different candidate genes that influence the onset of atrophy and fat accumulation in HIV-related lipodystrophy. In agreement with our findings, these authors concluded that different factors are related to different manifestations of lipodystrophy syndrome and that genetic predisposition plays an important role in addition to other previously identified factors such as sex, age and the type of drug.

Despite the limitations of our study (e.g. cross-sectional design, heterogeneity in patient treatment and the possibility that the cause of the alterations reported is linkage disequilibrium of the identified SNPs), our findings about the sex-specific prevalence of adverse effects are similar to those of larger studies among HIV-patients from Latin America; this provides further support for the relevance of the information reported herein. In addition, our study is the first to our knowledge to analyze SNPs in ERs and sex-specific HAART adverse effects (lipodystrophy, dyslipidemia and metabolic syndrome). The abundance of estrogen responsive elements in the genome and the wide anatomical distribution of ERs indicate that most physiological actions of these hormones in several systems involve ERs. Therefore, much of the sexual dimorphism observed in different sex-specific characteristics might be mediated by these receptors due to differences in hormone concentrations in men and women.

In conclusion, sexual dimorphism was observed to be associated with an *ESR1* genetic variant (rs2813544), and this was restricted to the female sex. Regarding fat tissue redistribution, the rs3020450 SNP in the *ESR2* gene was related to the risk of developing atrophy. Therefore, these genes might play important roles in metabolic pathways involved in the development of body alterations in patients exposed to HAART. Obviously, these results need to be confirmed in different samples and in functional studies. However, it is important to account for these differences in the patterns of adverse effects between sexes because it might help physicians prevent patients under HAART from leaving the therapy and provide them with a better lifelong treatment.

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Conflicts of interest

There are no conflicts of interest.

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