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Dyslipidemia and Fasting Glucose Impairment among HIV-Infected Patients 48-Weeks after the First Antiretroviral Regimen

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Abstract

Background: People infected with human immunodeficiency virus (HIV) develop lipid and glucose metabolic alterations, which predisposes them to cardiovascular disease. The aim of this study was to evaluate the cumulative incidence of dyslipidemia and fasting glucose impairment after 48 weeks of initiating the first antiretroviral (ART) regimen and the association with the type of ART regimen.

Method: Retrospective cohort of HIV-1 infected patients attending in the AIDS clinic of five centers of the country, between February 2009 and March 2013. Lipids (total cholesterol and triglycerides) and fasting glucose, were collected prior and 48 weeks after starting ART. We assessed risk factors for dyslipidemia and fasting glucose. To adjust for the effects of potential confounders of metabolic alterations we used logistic regression model.

Results: During the study, 223 patients on ART were evaluated. Median age was 34 years [interquartile range (IQR): 28-43]. Of the total patients, 201 (90%) were men. Most common OBR regimens were tenofovir/emtricitabine (TDF/FTC), and efavirenz (EFV) in 42%, abacavir/lamivudine (ABC/3TC) +EFV in 16.6% and TDF/FTC+nevirapine (NVP) in 11.7% patients. Cumulative incidence per 1,000 patients/year of glucose ≥ 100 mg/dL was 233.1, total cholesterol >200 mg/dL was 273.5 and tryglicerides >200 mg/dL was 372.2.

The proportion of patients with hypertriglyceridemia (>200 mg/dL) at 48 weeks of ART initiation was 37.2% (95% CI: 31.1-43.7%), hypercholesterolemia (>200 mg/dL) 32.3% (95% CI: 26.5-38.6%) and impairment of fasting glucose (IFG) (>100 mg/dL) 23.3% (95% CI: 18.2-29.2%), After adjustment in a logistic regression model for IFG, EFV-containing regimen OR 2.9 (95%CI 1.12-7.45); p=0.027; for hypertriglyceridemia, age >40 years old OR=1.9 (95% CI: 1.01-3.63); p=0.044, ABC/LAM-containing regimen OR=2.69 (95% CI: 1.42-5.09); p=0.002 and LPV/r-containing regimen OR=5.04 (95% CI 2.32-10.92); p=0.001 were significant; finally, for hypercholesterolemia age >40 years old OR=2.4 (95% CI: 1.15-4.9); p=0.004 and ABC/3TC-containing regimen OR=1.87 (95% CI: 1.01-3.49); p=0.05 remain significant.

Conclusion: These data show high risk of cumulative incidence of IFG and dyslipidemia after initiation of ART. Age >40 years old, ABC/3TC and LPV/r-containing regimens were independent factors to develop dyslipidemia and EFV-containing regimen for IFG in this cohort.

Keywords: Dyslipidemia; Impaired fasting glucose; Antiretroviral therapy; HIV

Background

With the increased survival of HIV-infected patients, there have emerged a number of unexpected consequences of chronic illness and drugs adverse events, especially in the form of metabolic disease [1].

Available data suggest the presence of an accelerated process of coronary atherosclerosis in this population due to multiple factors, including a higher prevalence (compared with non–HIV-infected patients) of conventional risk factors, emerging risk factors (chronic inflammation, immune activation, and senescence related to HIV infection itself), and the role of antiretroviral therapy (ART), regarding metabolic syndrome as one of the major problems [2]. Some studies have showed that the prevalence of metabolic syndrome was higher among HIV-infected patients on ART than among non-HIV-infected healthy controls (15.8 vs. 3.2%) [3]. A high incidence of diabetes mellitus (DM) and impaired fasting glucose (IFG) has been detected in HIV-infected patients receiving ART [4,5]. Another studies have found relationship between some classes of antiretroviral (ARV) drugs such as protease inhibitors (PIs) and nucleos(t)ide retrotranscriptase inhibitors (NRTIs) with a higher frequency of new-onset DM and IFG [6].

Dyslipidemia is particularly frequent and is mostly characterized by hypertriglyceridemia and low HDL-cholesterol concentrations.

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Although this is observed in treatment-naïve HIV-infected patients, suggesting that HIV infection itself has a metabolically deleterious effect, this phenomenon has been attributed, principally, to the use of PIs (i.e., ritonavir- boosted treatments), and some NRTIs (i.e., zidovudine or abacavir) [7,8].

Dyslipidemia is a significant risk factor for cardiovascular disease. People infected with HIV have alterations in lipids and glucose metabolism, which predisposes to cardiovascular disease. ART may contribute to these changes.

The objective of this study was to evaluate the cumulative incidence of dyslipidemia and IFG 48 weeks after initiating an antiretroviral regimen, and the association with the type of antiretroviral used in a cohort of naïve HIV-infected patients.

Method

Design

We conducted a retrospective cohort from 1 June 2014 to 30 December 2014 of HIV-1 treatment naïve-infected adults who started therapy for the first time. Dyslipidemia (total cholesterol and triglycerides) and fasting plasma glucose, before and 48 weeks after starting ART were collected.

Patients

The hospital institutional review board and ethics committee reviewed and approved this study (reference number R-2015-3502-70).

Patients who had indication for HIV treatment, were recruited from 4 referral centers in 4 different States of Mexico. Patients were >16 years of age with confirmed HIV-1 infection by Enzyme-Linked ImmunoSorbent Assay and Western blot. Patients had baseline levels of glucose <100 mg/dL, tryglicerides (TG) and total cholesterol (TC) <200 mg/dL. They were stratified according to age ≥ 40 years old. The ARV regimen started was selected according to the availability in the HIV clinics and to the decision of the treating physician; the backbone was abacavir/lamivudine (ABC/3TC) or tenofovir/emtricitabine (TDF/FTC), and the third drug was among efavirenz (EFV), nevirapine (NVP), atazanavir/ritonavir (ATV/r) or lopinavir/ritonavir (LPV/r).

Exclusion criteria were baseline values of alanine or aspartate aminotransferase ≥ 200 mg/dL (5 times the upper normal limit), creatinine ≥ 2.6 mg/dL (2 times the upper normal limit), IFG ≥ 100 mg/dL, DM or by the use of anti-diabetic agents, obesity defined as a body mass index ≥ 30 kg/m^2, TC or TG ≥ 200 mg/dL, use of drugs known to affect lipid or glucose metabolism within 1 month prior to inclusion, any AIDS-defining event requiring parenteral therapy, change of a drug in the regimen, patient on virological failure, and pregnancy or lactation at the inclusion or during the first 48 weeks of study. Patients with missing data were not included in the cohort.

Measurements

Clinical history regarding CD4+ cells count, HIV-1 RNA viral load, and serum laboratory parameters were recorded at each site at the beginning of the therapy and after 48 weeks, with similar methods of performance. Fasting plasma glucose, TG and TC were collected and measured using commercial enzymatic kits. We were not able to measure HDL in all of our HIV clinics; therefore, we excluded it in the analysis. Newonset diabetes was defined if fasting plasma glucose >126 mg/dL was measured on two consecutive occasions, fasting glucose impairment if fasting plasma glucose ≥ 100 mg/dL was measured on two consecutive occasions. Finally, hy- percholesterolemia and dyslipidemia were defined as total cholesterol 200 mg/dL or greater, tryglierides 200 mg/dL or greater, or receiving cholesterol-lowering medication.

Statistical analysis

Baseline characteristics were summarized using medians and interquartile ranges (IQR) for continuous variables, and proportions for categorical variables. Descriptive statistics were used to evaluate changes in TG, TC, CD4+ cells count and HIV-1 RNA viral load from baseline. For categorical variables, number of values in each category and percentage of the values with regard of the number of patients in the study population were calculated. Explorative statistical methods were used considering the efficacy endpoints and changes in safety-relevant laboratory parameters. Significance changes from baseline of TC and TG were tested using the Wilcoxon signed-rank test.

Cumulative incidence was calculated with number of events per 1,000 people/years.

For those patients with hypertriglyceridemia and hypercholesterolemia, we analyzed the potential causes, including the antiretroviral regimen in a bivariate analysis, which included crude odds ratios (OR) by Fisher's exact test and Chi-squared. Independent risk factors associated with hypertriglyceridemia and hypercholesterolemia at week 24 and 48 were identified in the multivariate logistic regression analysis that included variables from bivariate analysis with a *P* value ≤ 0.1. All analyses were performed using SPSS software (Version 19.0. Armonk, NY: IBM Corp.).

Results

During the study, 223 patients on ART were evaluated. Median age was 34 years (IQR: 28-43); 34.1% of patients (76) were ≥ 40 years old. Of the total patients, 201 (90.1%) were men. Median baseline glucose was 88 mg/dL (IQR 82-94), TC 145 mg/dL (IQR 119-167) and TG 133 mg/dL (IQR 101-159) (Table 1).

Characteristic	*Value* [a]
Male, n (%)	201 (90.1%)
Age, years	34 (28–43)
Age ≥ 40 years	76 (34.1%)
BMI [b] (kg/m^2)	23 (21–25)
Baseline CD4$^+$ cell count (cells/μL)	209 (92–316)
Baseline CD4$^+$ cell count <200 cells/μL, n (%)	107 (48.0%)
Baseline HIV-1 RNA viral load, $\log_{10}$ copies/mL	4.97 (4.54–5.42)
Baseline HIV-1 RNA viral load >100,000 copies/mL, n (%)	108 (48.4%)
TDF/FTC [c] in regimen, n (%)	109 (66.5%)
ABC/LMV [d] in regimen, n (%)	71 (31.8%)
EFV [e] in regimen, n (%)	131 (58.7%)
NVP [f] in regimen, n (%)	36 (16.1%)
LPV/r [g] in regimen, n (%)	45 (20.2%)
ATV/r [h] in regimen, n (%)	11 (4.9%)
Glucose (mg/dL)	88 (82–94)
TC [i] (mg/dL)	145 (119–167)
TG [j] (mg/dL)	133 (101–159)

a Values are presented as number (percentage) or as median (IQR). b BMI: Body mass index. c TDF/FTC: Tenofovir/emtricitabina.
d ABC/3TC: Abacavir/lamivudina. e EFV: Efavirenz, f NVP: Nevirapine, g LPV/r: Lopinavir/ritonavir, h ATV/r: Atazanavir/ritonavir, i TC: Total cholesterol, j TG: Trygliderides

Table 1: Baseline characteristics, n=223.

Characteristic	*No. of patients (%)*	*Incidence***
Glucose ≥ 126 mg/dL* (type 2 DM)	3 (1.3%)	3/223=13.4
Glucose ≥ 100 mg/dL (IFG)	52 (23.3%)	52/223=233.1
Total cholesterol ≥ 200 mg/dL	61 (27.4%)	61/223=273.5
Triglycerides ≥ 200 mg/dL	83 (37.2%)	83/223=372.2

* Glucose>126 md/dL on two occasions
** per 1000 person/years
Table 2: Cumulative incidence of metabolic alterations 48 weeks after initiation of art.

Baseline CD4+ cells count was 209 cells/μL (IQR 92-316), 107 patients (48%) had CD4+ cells count <200 cells/μL; median RNA HIV-1 viral load was 94.700 copies/mL (IQR 35,435-266,520), 108 (48%) started with VL>100,000 copies/mL.

Most common regimens were TDF/FTC+EFV in 42% patients, ABC/3TC+EFV in 16.6% patients and TDF/FTC+NVP in 11.7% patients. The two PIs included were LPV/r and ATV/r (Table 1).

After 48 weeks of treatment, DM2 was found in 3 patients (1.3%), IFG (≥ 100 mg/dL) in 52 patients (23.3%), hypercholesterolemia (≥ 200 mg/dL) in 72 patients (32.3%) and hypertriglyceridemia (≥ 200 mg/dL) in 83 patients (37.2%) (Table 2).

Regarding the antiretroviral regimen, cumulative incidence of IFG was associated with ABC/3TC+EFV in 324.3 per 1000 people/year; cumulative incidence of hypercholesterolemia was associated with TDF/FTC+LPV/r in 619.0 per 1000 people/year; finally, higher cumulative incidence of hypertriglyceridemia was found with ABC/3TC+LPV/r in 791.6 per 1000 people/year (Table 3).

After adjustment in a logistic regression model for IFG, EFV-containing regimen OR 2.90 (95% CI 1.12-7.45); p=0.027, for hypertriglyceridemia, age 40 years old 1.9 (95% CI: 1.01-3.63); p=0.044, ABC/3TC-containing regimen OR=2.69 (95% CI: 1.42-5.09); p=0.002 and LPV/r-containing regimen OR=5.04 (95% CI 2.32-10.92); p=0.001 were significant,and for hypercholesterolemia age ≥ 40 years old 2.4 (95% CI: 1.15-4.9); p=0.004, and ABC/3TC-containing regimen OR=1.87 (95% CI: 1.01-3.49); p=0.05 remain significant (Table 4).

Discussion

In this study, a high frequency of metabolic alterations after one year of antiretroviral treatment was found. The most frequent alteration was hypertriglyceridemia (37.2%), followed by hypercholesterolemia (27.4), IFG (23.3%), and finally 3 patients (1.3%) developed DM2 during the study period. Regarding the antiretroviral regimen, the

Regimen	*TDF/FTC+EFV*	*TDF/FTC+NVP*	*ABC/3TC+LPV/r*	*ABC/3TC+EFV*	*ABC/3TC+NVP*	*TDF/FTC+LPV/r*	*TDF/FTC+ATV/r*	*p value*
Glucose ≥ 126 mg/dL* (type 2 DM)	10.6	38.4	41.6	0	0	0	0	0.704
Glucose ≥ 100 mg/dL (IFG)	180.8	230.7	83.3	324.3	100	95.2	90.9	0.170
TC ≥ 200 mg/dL	212.7	153.8	416.6	513.5	200	619.0	571.4	**0.001**
TG ≥ 200 mg/dL	255.3	115.3	791.6	459.4	400	666.6	181.8	**0.001**

Table 3: Cumulative incidence of metabolic alterations by regimen at 48 weeks.

4a. Bivariate and multivariate analysis of risk factors associated with IFG.						
	Bivariate			Multivariate		
Risk factor	OR unadjusted	95% CI	p value	OR adjusted	95% CI	p value
Male gender	0.742	(0.25–2.14)	0.580			
Age ≥ 40 years	2.143	(1.07–4.26)	0.028	1.81	(0.92–3.55)	0.083
Baseline HIV-1 RNA ≥ 100,000 copies/mL	1.057	(0.53–2.09)	0.874			
Baseline CD4⁺ cells count <200 cells/μL	0.671	(0.33–1.32)	0.250			
ABC/LMV-containing regimen [a]	1.298	(0.63–2.63)	0.470			
LPV/r-containing regimen [b]	0.372	(0.12–3.09)	0.066	1.50	(0.47–4.70)	0.487
EFV-containing regimen [c]	1.938	(0.93–4.03)	0.074	2.90	(1.12–7.45)	0.027
4b. Bivariate and multivariate analysis of risk factors associated with hypercholesterolemia.						
Risk factor	*OR unadjusted*	*95% CI*	p *value*	*OR adjusted*	*95% CI*	p *value*
Male gender	1.02	(0.39–2.63)	0.960			
Age ≥ 40 years	2.77	(1.54–4.98)	0.001	2.462	(1.33–4.54)	0.004
Baseline HIV-1 RNA ≥ 100,000 copies/mL	0.799	(0.45–1.40)	0.437			
Baseline CD4⁺ cells count <200 cells/μL	1.34	(0.76–2.35)	0.309			
ABC/LMV-containing regimen [a]	2.09	(1.16–3.78)	0.013	1.870	(1.01–3.49)	0.05
LPV/r-containing regimen [b]	2.75	(1.40–5.38)	0.003	2.411	(0.94–6.16)	0.066
EFV-containing regimen [c]	0.717	(0.40–1.26)	0.248			
4c. Bivariate and multivariate analysis of risk factors associated with hypertrigliceridemia.						
Risk factor	OR unadjusted	95% CI	p value	OR adjusted	95% CI	p value
Male gender	0.684	(0.28–1.66)	0.400			
Age ≥ 40 years	2.467	(1.39–4.37)	0.002	1.924	(1.01–3.63)	0.044
Baseline HIV-1 RNA ≥ 100,000 copies/mL	0.944	(0.57–1.71)	0.984			
Baseline CD4⁺ cells count <200 cells/μL	0.725	(0.42–1.25)	0.247			
ABC/LMV-containing regimen [a]	3.271	(1.81–5.88)	0.001	2.695	(1.42–5.09)	0.002
LPV/r-containing regimen [b]	7.040	(3.36–14.71)	0.001	5.044	(2.32–10.92)	0.001
EFV-containing regimen [c]	0.559	(0.32–0.97)	0.038	1.972	(0.85–4.55)	0.112

a ABC/3TC: Abacavir/Lamivudina, b LPV/r: Lopinavir/Ritonavir, c EFV: Efavirenz,

Table 4: Bivariate and multivariate analysis of risk factors associated with IFG and dyslipidemia.

highest cumulative incidence of dyslipidemia was associated with ABC/3TC and LPV/r containing regimens.

Some independent risk factors were found to be associated with metabolic alterations; regarding IFG, EFV-containing regimens was the only factor that remained significant; other studies have associated EFV as an independent risk factor for increase glucose [9,10].

Some factors were common risk factors for dyslipidemia, such as age ≥ 40 years; in other studies, metabolic alterations has been found to be associated with older age, and in patients over 40 years old a higher rate of dyslipidemia, diabetes and metabolic syndrome has been described [11,12].

Our data is similar to those of Desfaye, who found that more than 25% of patients developed dyslipidemia; in addition, an increase in lipids and glucose levels was reported after starting ART [13].

These findings are similar to those reported by Pinto Neto, who found 22.3% of dyslipidemia after 3 years of treatment; in this study, LPV/r was reported as an associated risk factor [14]. Another study, ACTG5142, showed a high increase in TC and TG associated with LPV/r, similar to ours observed in this cohort [15].

In this cohort, one of the independent risk factor associated with dyslipidemia was ABC/3TC-containing regimen confirming previous reported results. The association of ABC with dyslipidemia has been reported in some studies; in the HEAT trial, ABC/3TC was associated with an increase in TC and TG at 96 weeks; however, glucose had no modification related to this backbone [16]. Another study, ACTG5202, found a higher frequency of dyslipidemia with ABC/3TC either with ATV/r or with EFV [17]. Finally, the ASSERT trial, found a statistically significant increase in TC and TG with ABC/LMV regimens compared with TDF/FTC in treatment-naïve infected patients [18].

The present study has some limitations; it includes a retrospective method, few numbers of patients in some groups such as ATV/r and the absence of patients with RAL-containing regimens due to it is not approved for initial therapy in our country. Another limitation is that we did not have the possibility to measure HDL and LDL in our HIV Clinics; these lipoproteins have a strong correlation with cardiovascular risk. Finally because the retrospective method, we were not able to evaluate lifestyle and its impact on lipid levels.

On the other hand, this is the first study developed in Mexico, which analyzed lipids and glucose levels after the first year of ART in treatment-naïve infected patients. These results allow us to have a panoramic vision about how many patients might develop dyslipidemia and that will require interventions, concerning modifications in lifestyle and the use of drugs that decrease lipids, such as statins and hypoglycemic drugs for example metformin; in addition, we confirmed that ABC/3TC and LPV/r are drugs associated with dyslipidemia in this population.

It is necessary to conduct a prospective cohort study including a higher number of patients to confirm these findings being representative of our country.

Conclusion

In conclusion, in Mexico there is a high incidence of metabolic alterations in HIV infected patients during the first year of ART initiation, even if they are young patients, especially when their ART regimen contains ABC/LMV and/or LPV/r.

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