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Metabolic Profile of People Living with HIV in a Treatment Hub in Manila, Philippines: A Pre- and Post-Antiretroviral Analysis*

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Abstract

Objectives. People living with HIV (PLHIV) are susceptible to develop dyslipidemia and hyperglycemia. This study aims to determine the prevalence of these metabolic derangements among Filipino PLHIV.

Methodology. We reviewed 635 medical records in a treatment hub in Manila, Philippines from January 2004 to July 2016. Logistic regression analysis was done to determine factors associated with dyslipidemia and hyperglycemia pre- and post-ART.

Results. Among 635 PLHIV, 97.3% were males with mean age of 30 years and median CD4 count of 207 cells/mm^3. Pre-ART, prevalence of dyslipidemia was 65.4% and hyperglycemia was 10.4%. Risk factors for dyslipidemia include hyperglycemia (AOR 3.8, *p* 0.001) and >320 days delay in ART initiation from HIV confirmation (AOR 1.5, *p* 0.032), while dyslipidemia was associated with hyperglycemia (AOR 3.1, *p* 0.001). Post-ART, prevalence of dyslipidemia was 48.6% and hyperglycemia was 15.6%. Risk factors for post-ART dyslipidemia include being WHO stage 4 (AOR 2.1, *p* 0.021), hyperglycemia (AOR 16.1, *p*<0.001), >36 months ART duration (AOR 8.7, *p*<0.001) and efavirenz-based ART (AOR 2.8, *p*<0.001). Low CD4 count post-ART had a negative correlation with dyslipidemia (AOR 0.5, *p* 0.005). Post-ART hyperglycemia was associated with age >30 years (AOR 2.1, *p* 0.004), being overweight (AOR 1.8, *p* 0.023), dyslipidemia (AOR 17.8, *p*<0.001) and zidovudine-based ART (AOR 1.4, *p* 0.051).

Conclusion. Dyslipidemia and hyperglycemia prevalence was high in Filipino PLHIV. Traditional, HIV and treatment related factors contributed to its development. Intensive monitoring and initiation of appropriate treatment is recommended.

Key words: HIV, AIDS, dyslipidemia, hyperglycemia, antiretroviral therapy

INTRODUCTION

Antiretroviral therapy (ART) improves survival and has made Human Immunodeficiency Virus (HIV) infection a chronic, controllable disease.[1] As such, there is increasing interest among experts on the long-term complications of HIV and ART use.

HIV infection induces immune activation making patients susceptible to metabolic abnormalities.[2] In addition, prolonged ART use is linked to the increasing prevalence of dyslipidemia and hyperglycemia.[1,3] Like the non-HIV infected population, traditional risk factors (e.g., smoking, obesity) also contribute to its development.[4]

Multi-center, cross-sectional studies from both developed and resource limited settings reported an alarming rate of dyslipidemia between 54-81%,[5,6] while hyperglycemia was present in 32% of PLHIV.[7] A 2013 study investigated the role of ethnicity in the development of dyslipidemia and hyperglycemia. African Americans with cluster of differentiation 4 (CD4) <300 cells/mm^3 and Hispanics with CD4 >300 cells/mm^3 were at risk to develop these metabolic abnormalities,[8] however Asians were not represented in

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this study. On the other hand, a Malaysian cross-sectional study reported dyslipidemia rate at 82.3% (1318/1583 subjects) among ART experienced PLHIV.[9]

In the Philippines, ART previously consisted of nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) with or without protease inhibitors (PIs).[10] Until recently, integrase strand transfer inhibitors (INSTIs) were included as part of the first line ART regimen as recommended by World Health Organization.[11] PIs have been identified as a risk factor for dyslipidemia and hyperglycemia.[3,9-12] However, recent studies have demonstrated an increased risk in developing dyslipidemia and hyperglycemia even on NRTI/NNRTI combinations.[5] The NRTI stavudine (d4T) and zidovudine (AZT), and the NNRTI efavirenz (EFV) has been linked to dyslipidemia[12,13] which often occurs after prolonged use.[14] On the other hand, INSTIs are less likely to produce lipid derangements.[11,15]

Insulin resistance (IR) and type 2 diabetes mellitus (T2DM) are increasingly recognized in PLHIV, particularly among those on ART.[16,17] IR is said to precede weight loss and is implicated in the pathogenesis of T2DM in PLHIV.[18] Glucose abnormalities were seen after 66 months of ART use.[19]

These HIV and ART induced metabolic derangements overlap with the components of metabolic syndrome, making PLHIV at high risk for cardiovascular diseases (CVD).[20,21] Various multicenter studies have shown that metabolic syndrome is present in 1.8% among ART naïve and 14-45.4% among ART experienced patients.[22]

Despite the HIV epidemic, these metabolic consequences have not been reported in the Philippine setting. We conducted a retrospective cohort study to determine the prevalence and risk factors for dyslipidemia and hyperglycemia pre- and post-ART exposure.

METHODOLOGY

Study Design and Setting

This is a retrospective cohort study conducted at a government-run treatment hub in the University of the Philippines-Philippine General Hospital (UP-PGH). The study was approved by the Research Ethics Board of the University of the Philippines Manila. The Research Ethics Board waived the need for patient's informed consent since the study will only involve analysis of existing database, has minimal risk, and the risk and welfare of the participants are not adversely affected.

Study population and patient selection

We reviewed all patient records from January 2004 to July 2016. All adult patients confirmed to have HIV infection were included in the study. Patients who died and those who were lost to follow up during the study period were excluded. Patients without any serum lipid profile or fasting blood glucose determination from the time of clinic enrollment and subsequent follow up were also excluded from the study (Figure 1). A total of 635 PLHIV were included in the study.

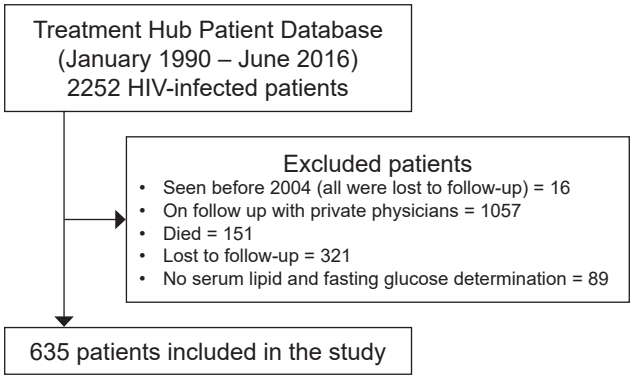

Figure 1. Schematic diagram of patient inclusion and exclusion in the study.

Sample size computation

The sample size requirement for each study objective pre- and post-ART was computed. Estimating the prevalence of dyslipidemia and hyperglycemia required the largest sample size. Consequently, a minimum sample size of 382 PLHIV was needed to estimate the prevalence of dyslipidemia and 334 PLHIV to estimate prevalence of hyperglycemia among Filipino PLHIV in a treatment hub in Manila, Philippines. The formula for sample size for estimating the population proportion was used in this computation. The information used in the computation were: 1) Expected prevalence of dyslipidemia is 54%[5] and for hyperglycemia is 32%,[7] 2) Margin of error set at 5%, and 3) Confidence interval set at 95%. A logistic regression of a binary response (dyslipidemia) on a binary independent variable (ART) with a sample size of 215 PLHIV achieves 80% power at a 0.05 significance level. Appropriate adjustment was done since an R^2 of 0.03 was obtained in the multiple regression of independent variable on other variables in the final logistic regression model. Power Analysis & Sample Size (PASS-NCSS) software was used in the sample size computation.

Definition of terms

Dyslipidemia is defined by the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) as presence of one of the following: Total cholesterol (TC) >5.2 mmol/L, triglyceride (TG) >1.7 mmol/L, low density lipoprotein cholesterol (LDL-C) >2.6 mmol/L, high density lipoprotein cholesterol (HDL-C) <1.0 mmol/L. Hyperglycemia is defined by the American Diabetes Association (ADA) as presence of Type 2 Diabetes Mellitus (T2DM) and/or Impaired Fasting Glucose (IFG). Type 2 Diabetes Mellitus is defined as fasting blood glucose

(FBG) level ≥7.0 mmol/L. Impaired Fasting Glucose (IFG) is defined as FBG 5.6-6.9 mmol/L. Metabolic syndrome is defined as per NCEP-ATP III as having met any three of the five criteria: waist circumference 40 inches in men / 35 inches in women; FBG ≥5.6 mmol/L or on medications; TG >1.7 mmol/L, HDL-C<1.0 mmol/L or on medications; and blood pressure of >130 mmHg systolic or >85 mmHg diastolic or on medications for hypertension.

Data collection

The clinic database was reviewed for relevant clinical and laboratory data from the date of enrollment until last follow up. To determine factors associated with dyslipidemia and hyperglycemia pre- and post-ART, the following variables were obtained from the records: age, sex, baseline, nadir and subsequent CD4 counts, baseline and subsequent height and weight, co-morbidities, smoking history, alcohol intake, type and duration of ART and intake of other medications. Serum lipid parameters and fasting blood glucose levels were determined using the Vitros DT60 II (Vitros 5.1) chemistry analyzer (Ortho Clinical Diagnostics, New Jersey, United States of America).

Statistical analysis

Descriptive statistics were used to present patient demographics. Quantitative data were reported using means and medians for normally distributed and non-normally distributed data, respectively. Qualitative variables were reported using frequencies and percentages. Point and 95% confidence interval estimates of the prevalence of dyslipidemia and hyperglycemia were computed. Chi-square test was used to compare categorical variables. Continuous variables with normal and non-normal distribution were compared using T-test and Mann Whitney U test, respectively. To determine the factors associated with dyslipidemia and hyperglycemia, univariate and stepwise multivariate logistic regression analysis was done. Variables found to be significant (p<0.25) in the univariate logistic regression analysis and other variables of known clinical relevance to the outcomes were included in the multivariate logistic regression model for dyslipidemia and hyperglycemia. The final model of the stepwise logistic regression analysis performed was used to identify factors that are significantly associated with dyslipidemia and hyperglycemia. Significance level was set at α=0.05. Data was analyzed using STATA version 13 (Stata Corp, College Station, Texas, USA).

RESULTS

We reviewed and included 635 medical charts in this study. Majority of the participants were males (618/635, 97.3%) with a mean age of 30 years (SD 7.5). Median baseline CD4 count is at 213 cells/mm^3 (SD 195.9) and a BMI of 21.5 (SD 3.8). Demographic and clinical characteristics of participants are summarized in Tables 1 and 2.

Metabolic abnormalities pre-ART exposure

Prior to the initiation of ART, the initial mean lipid profile was as follows: TC of 4.5 mmol/L (SD 1.2), TG of 1.63 mmol/L (SD 1.0), LDL-C of 2.76 mmol/L (SD 0.90), HDL-C of 1.1 mmol/L (SD 0.75). The median FBG was at 4.97 mmol/L (SD 0.84) (Table 3). No participants were diagnosed with dyslipidemia prior to HIV diagnosis.

The prevalence of dyslipidemia was at 65.4% (95% CI: 59.2, 71.9) and was documented within 415 days from the time of HIV diagnosis. The most common lipid derangement is low HDL-C (74.7%) followed by elevated LDL-C (53%), elevated TG (35.2%) and elevated TC (20.5%). The most common pattern of dyslipidemia noted were as follows: isolated low HDL-C (28.3%), high LDL-C/low HDL-C (14%), and high TG/low HDL-C (14%). The prevalence of hyperglycemia before ART was 10.4% (95% CI: 8.0, 13.2) and was documented within 615 days from the time of HIV diagnosis. Majority had FBG within the IFG levels (92.4%). Two patients self-reported to be diagnosed with IFG prior to HIV diagnosis; one patient is on metformin. Dyslipidemia and hyperglycemia were both observed in 8.8% (95% CI: 6.7, 11.45) of the cohort. Among those patients diagnosed with both dyslipidemia and hyperglycemia before ART initiation, 28.6% fulfilled the criteria for metabolic syndrome.

After adjusting for age, sex, CD4 count, BMI, comorbidities (hypertension and hyperglycemia), time of delay in ART initiation, prophylactic antibiotic use (cotrimoxazole, azithromycin, dapsone), oral corticosteroid use and statin/fibrates use the logistic regression analysis confirmed the following factors were associated with dyslipidemia: concurrent hyperglycemia (AOR 3.8, 95% CI: 2.7, 7.4) and delay of ART initiation for >320 days from HIV diagnosis (AOR 1.5, 95% CI: 1.1, 2.3). Early initiation of ART had a protective effect on dyslipidemia (AOR 0.3, 95% CI: 0.1, 0.7). For hyperglycemia, after adjusting for age, sex, CD4 count, BMI, comorbidities (hypertension), time of delay in ART initiation, prophylactic antibiotic use (cotrimoxazole, azithromycin, dapsone), use of TB medications and OHAs, it showed that concurrent dyslipidemia was an associated factor (AOR 3.1, 95% CI: 1.4, 5.8) (Table 4).

Initiation of appropriate interventions for dyslipidemia were documented in 26.9% (112/415). Lifestyle modification is the only intervention prescribed in 54.5% (61/112). Pharmaceutical intervention which includes use of statins and fibrates were started in 19.6% (22/112) and 7.1% (8/112), respectively. On the other hand, both lifestyle modification and use of medications were advised in 18.8% (21/112).

Interventions for hyperglycemia were only documented in 10.6% (7/66). Lifestyle modification alone was advised in three participants while four participants were started on oral hypoglycemic agents (OHAs).

Table 1. Demographic, clinical and laboratory characteristics of 635 Filipino PLHIV with and without dyslipidemia

Demographics	Pre-ART			Post-ART		
	Dyslipidemic (n=415)	Non-dyslipidemic (n=220)	P	Dyslipidemic (n=309)	Non-dyslipidemic (n=326)	P
Mean age; SD (years)	29; 7.4	30; 7.5	0.180	33; 10.3	33; 10.2	0.183
Age ≥30	181 (43.6%)	88 (40%)	0.380	141 (45.6%)	128 (39.2%)	0.185
Male sex	408 (98.3%)	210 (95.5%)	0.030	299 (96.8%)	319 (97.9%)	0.395
Median CD4; IQR (cells/mm^3)	207; 196.3	206; 195.8	0.190	343; 223.1	343; 223.3	0.120
Median Nadir CD4; IQR (cells/mm^3)	161; 296	160;293	0.241	-	-	-
CD4 <200 cells/mm^3	207 (49.9%)	140 (63.6%)	0.002	57 (18.4%)	122 (37.4%)	0.030
WHO stage			0.153			0.267
1	169 (40.7%)	76 (34.5%)		111 (35.9%)	134 (41.1%)	
2	49 (11.8%)	22 (10.0%)		38 (12.3%)	33 (10.1%)	
3	92 (22.2%)	46 (21.0%)		63 (20.4%)	75 (23.0%)	
4	105 (25.3%)	76 (34.5%)		97 (31.4%)	84 (25.8%)	
Mean BMI; SD (kg/m^2)	21.5; 3.9	21.5; 3.8	0.682	23.1; 3.9	23.2; 3.9	0.686
BMI classification:			0.671			0.178
Normal	232 (55.9%)	125 (56.8%)		135 (43.7%)	153 (46.9%)	
Underweight	45 (10.8%)	29 (13.2%)		11 (3.6%)	17 (5.2%)	
Overweight	106 (25.5%)	48 (21.8%)		121(39.5%)	103 (31.6%)	
Obese	19 (4.6%)	8 (3.6%)		31 (10%)	23 (7.1%)	
Co-morbidities:						
Hypertension	15 (3.6%)	3 (1.3%)	0.104	9 (2.9%)	9 (2.8%)	0.178
Asthma/Allergy	42 (10.1%)	24 (10.9%)	0.181	29 (9.4%)	36 (11.04%)	0.202
Smoker, mean; SD (pack/years)	153 (36.9%),1.7; 5.2	69 (31.4%),1.7; 5.3	0.166,0.551	99 (32.0%), 1.7; 5.2	123 (37.7%), 1.7; 5.3	0.133,0.590
Alcohol beverage drinker	66 (15.9%)	29 (13.18%)	0.360	36 (11.6%)	59 (18.1%)	0.023
Delay in ART initiation; SD (days)	259; 384	421; 2591	0.038	-	-	
0-320 days	266 (64.1%)	167 (75.9%)	0.002	-	-	
>320 days	66 (15.9%)	37 (16.8%)		-	-	
Duration of ART use						<0.001
0-36 months	-	-		246 (79.6%)	296 (90.8%)	
≥ 36 months	-	-		63 (20.4%)	30 (9.2%)	
OI Prophylaxis / Other Medications						
Cotrimoxazole	196 (47.2%)	124 (56.4%)	0.028	-	-	
Azithromycin	148 (35.7%)	99 (45.0%)	0.022	-	-	
Isoniazid	58 (13.9%)	25 (11.4%)	0.353	-	-	
Fluconazole	45 (10.8%)	21 (9.5%)	0.610	-	-	
Anti-TB medications	79 (19.0%)	41 (18.6%)	0.903	-	-	
Dapsone	23 (5.5%)	19 (8.6%)	0.135	-	-	
Corticosteroid	9 (2.2%)	11 (5%)	0.052	-	-	<0.001
ART regimen						
NRTI: AZT based	-	-		133 (43%)	62 (19 %)	
Non-AZT based	-	-		176 (57%)	264 (81 %)	
NNRTI:						
EFV-based	-	-		278 (90%)	253 (77.6%)	<0.001
Non-EFV based	-	-		31 (10%)	73 (22.4%)	
NVP based	-	-		57 (18.4%)	26 (8%)	<0.001
Non-NVP based	-	-		252 (81.6%)	300 (92%)	
PI based	-	-		22 (7.1%)	15 (4.6%)	0.176
Non PI based	-	-		287 (92.9%)	311 (95.4%)	

ART – antiretroviral, SD – standard deviation, CD4 – cluster of differentiation 4, WHO – World Health Organization, BMI – Body Mass Index, WB – Western Blot, OI – opportunistic infection, TB – Tuberculosis, NRTI – nucleoside reverse transcriptase inhibitor, AZT – zidovudine, NNRTI – non-nucleoside reverse transcriptase inhibitor, EFV – efavirenz, NVP – nevirapine, PI – protease inhibitor

Metabolic abnormalities post-ART exposure

The mean duration of ART use was 978 days (SD 670). The mean lipid and fasting blood glucose level increased after ART initiation with TC at 4.9 mmol/L (SD 1.0), TG at 1.78 mmol/L (SD 1.1), LDL-C at 2.96 mmol/L (SD 0.87), HDL-C at 1.20 mmol/L (SD 0.39) and FBG at 5.2 mmol/L (SD 0.79) (Table 3).

Dyslipidemia was noted in 48.7% (95% CI 43.4, 54.4) of the study population and majority was observed within the first 36 months (79.3%). Majority had high LDL-C at 81.5%, high TC at 58.6%, high TG at 57.9% and low HDL-C at 52.1%. On the other hand, the most common dyslipidemia pattern was high TC/high TG/high LDL-C/low HDL-C in 21% followed by high TC/high TG/high LDL-C in 15.5%. The prevalence of hyperglycemia after ART was 15.6% (95% CI: 12.7, 19.0) with the majority (89.9%) falling within the IFG level. Dyslipidemia and hyperglycemia were both observed in 14.6% (95% CI: 11.8, 17.9) of the cohort after ART initiation. Among these, 43% fulfilled the criteria for metabolic syndrome.

After adjusting for age, sex, CD4 count, WHO stage, BMI, comorbidities, alcohol consumption and smoking history, duration of ART initiation and ART regimen and statins/fibrates use, logistic regression analysis confirmed the following factors associated with dyslipidemia: WHO stage 4 (AOR 2.1, 95% CI: 1.3, 3.7), hyperglycemia (AOR 16.1, 95% CI: 6.5, 35.7), >36 months of ART use (AOR 8.7, 95% CI: 6.4, 14.2) and EFV based ART (AOR 2.8, 95% CI: 1.3, 4.4). Low CD4 count was protective against dyslipidemia (AOR 0.5, 95% CI: 0.2, 0.8). Adjusting for age, sex, CD4 count, WHO stage, BMI, comorbidities, alcohol consumption and smoking history, duration of ART initiation and ART regimen, and OHAs use logistic regression analysis showed that age ≥30 (AOR 2.1, 95% CI: 1.7, 3.4), dyslipidemia (AOR 17.8, 95% CI: 7.6, 36.1), being

Table 2. Demographic and clinical characteristics of 635 Filipino PLHIV with and without hyperglycemia

Demographics	Pre-ART			Post-ART		
	Hyperglycemic (n=66)	Non-hyperglycemic (n=569)	P	Hyperglycemic (n=99)	Non-hyperglycemic (n=536)	P
Mean age; SD (years)	29; 7.5	30; 7.5	0.710	35; 11.6	35; 11.4	0.990
Age ≥30	29 (43.9%)	240 (42.2%)	0.784	56 (56.6%)	213 (39.7%)	0.002
Male sex	64 (97%)	544 (95.6%)	0.851	97 (98.0%)	521 (97.2%)	0.659
Median CD4 count; IQR (cells/mm^3)	206; 196.1	207; 195.9	0.292	346; 223.4	342; 223.0	0.055
Median Nadir CD4; IQR (cells/mm^3)	160;296	160;293	0.364	-	-	-
CD4 <200 cells/mm^3	32 (48.5%)	315 (55.4%)	0.420	20 (20.2%)	159 (29.7%)	0.172
WHO stage			0.818			0.544
1	29 (43.9%)	216 (38.0%)		34 (34.3%)	211 (39.3%)	
2	7 (10.6%)	63 (11.1%)		8 (8.0%)	62 (11.6%)	
3	11 (16.7%)	127 (22.3%)		26 (26.3%)	112 (20.9%)	
4	19 (28.8%)	162 (28.4%)		31 (31.4%)	150 (27.9%)	
Mean BMI; SD (kg/m^2)	21.3; 3.8	22.8; 3.7	0.003	23.1; 4.0	23.2; 4.0	0.06
BMI classification:			0.169			0.084
Normal	36 (54.5%)	321 (56.4%)		36 (36.4%)	252 (47.0%)	
Underweight	3 (4.5%)	71 (12.5%)		4 (4.0%)	24 (4.5%)	
Overweight	18 (27.3%)	136 (23.9%)		47 (47.5%)	177 (33.0%)	
Obese	5 (7.6%)	22 (3.9%)		8 (8.1%)	46 (8.6%)	
Co-morbidities:						
Hypertension	3 (4.5%)	15 (2.6%)	0.376	4 (4.0%)	14 (2.6%)	0.431
Asthma/Allergy	8 (12.1%)	57 (1.0%)	0.176	10 (10.1%)	54 (10.0%)	0.466
Smoker, mean; SD (pack/years)	23 (34.8%),1.7; 5.3	199 (35.0%),1.7; 5.3	0.984,0.412	28 (28.3%), 1.7; 5.2	194 (36.2%),1.7; 5.3	0.129,0.607
Alcohol beverage drinker	7 (10.6%)	88 (15.5%)	0.295	8 (8.0%)	87 (16.2%)	0.037
Delay in ART initiation; SD (days)	250; 312	327; 1691	0.999	-	-	
0-320 days	44 (66.7%)	389 (68.4%)	0.849	-	-	
>320 days	12 (18.2%)	106 (18.6%)		-	-	
Duration of ART use						<0.001
0-66 months	-	-		94 (95.0%)	526 (98.1%)	
≥ 66 months	-	-		5 (5.0%)	10 (1.9%)	
OI Prophylaxis / Other Medications						
Cotrimoxazole	25 (37.9%)	295 (51.8%)	0.032	-	-	
Azithromycin	16 (24.2%)	231 (40.6%)	0.010	-	-	
Isoniazid	11 (16.7%)	72 (12.7%)	0.360	-	-	
Fluconazole	7 (10.6%)	59 (10.4%)	0.952	-	-	
Anti-TB medications	9 (13.6%)	111 (19.5%)	0.249	-	-	
Dapsone	1 (1.5%)	41 (7.2%)	0.078	-	-	
Corticosteroid	2 (3.0%)	18 (3.2%)	0.953	-	-	
ART regimen						<0.001
NRTI: AZT based	-	-		50 (50.5%)	145 (27.0%)	
Non-AZT based	-	-		49 (49.5%)	391 (73.0 %)	
NNRTI:						
EFV based	-	-		91 (91.9%)	440 (82.1%)	0.015
Non-EFV based	-	-		8 (8.1%)	96 (17.9%)	
NVP based	-	-		17 (17.2%)	66 (12.3%)	0.188
Non-NVP based	-	-		82 (82.8%)	470 (87.7%)	
PI based	-	-		8 (8.1%)	29 (5.4%)	0.297
Non PI based	-	-		91 (91.9%)	507 (94.6%)	

ART – antiretroviral, SD – standard deviation, CD4 – cluster of differentiation 4, WHO – World Health Organization, BMI – Body Mass Index, WB – Western Blot, OI – opportunistic infection, TB – Tuberculosis, NRTI – nucleoside reverse transcriptase inhibitor, AZT – zidovudine, NNRTI – non-nucleoside reverse transcriptase inhibitor, EFV – efavirenz, NVP – nevirapine, PI – protease inhibitor

Table 3. Laboratory characteristics of 635 Filipino PLHIV pre- and post-antiretroviral exposure

Laboratory Parameters	Pre-ART	95% CI	Post ART	95% CI	p
TC; SD (mmol/L)	4.5; 1.1	4.4, 4.7	4.9;1.0	4.8, 5.1	<0.001
TG; SD (mmol/L)	1.6; 1.0	1.5, 1.8	1.8;1.1	1.7, 1.9	0.024
LDL-C; SD (mmol/L)	2.8; 0.1	2.7, 2.9	2.9;0.1	2.9, 3.1	<0.001
HDL-C; SD (mmol/L)	1.1; 0.5	1.0, 1.1	1.2;0.4	1.2, 1.3	<0.001
FBG; SD (mmol/L)	4.9; 0.8	4.9, 5.1	5.2;0.8	5.1, 5.3	<0.001

overweight (AOR 1.8, 95% CI: 1.3, 2.9) and AZT based ART (AOR 1.4, 95% CI: 1.3, 2.9) were the identified associated factors for hyperglycemia (Table 4).

Dyslipidemia and hyperglycemia were both present in 14.6% (93/635). In this cohort, 23.9% of the participants were already noted to have dyslipidemia before ART and remained to be dyslipidemic after initiation. Meanwhile, only 2% of the participants were hyperglycemic before ART and remained to be after ART.

Intervention for these metabolic abnormalities is lacking. Initiation of interventions for dyslipidemia were documented in 44.3% (137/309). Lifestyle modification alone was advised in 46.7% (64/137), statins and fibrate use were at 18.9% (26/137) and 6.6% (9/137), respectively. Both lifestyle modification and anti-dyslipidemia medications were started in 27.8% (38/137). For hyperglycemia, initiation of intervention is at 14.1% (14/99). Ten participants were advised lifestyle modification only while 4 were started on OHAs.

Table 4. Multivariate analysis of the factors associated with Dyslipidemia and Hyperglycemia pre- and post-ART initiation (N=635)

Dyslipidemia					
Pre-ART			**Post-ART**		
Factors	**AOR (95%CI)**	**p**	**Factors**	**AOR (95%CI)**	**p**
Hyperglycemia before ART	3.8 (2.71, 7.4)	0.001	WHO stage 4	2.1 (1.3, 3.7)	0.021
Delay of ART initiation from WB: > 320 days	1.5 (1.12, 2.31)	0.032	Hyperglycemia after ART	16.1 (6.5, 35.7)	<0.001
ART started before WB diagnosis	0.3 (0.18, 0.65)	0.011	ART duration > 36 months	8.7 (6.4, 4.2)	<0.001
			Latest CD4 count <200	0.5 (0.2, 0.8)	0.005
			EFV-based regimen	2.8 (1.3, 4.4)	<0.001
Hyperglycemia					
Pre-ART			**Post-ART**		
Factors	**AOR (95%CI)**	**p**	**Factors**	**AOR (95%CI)**	**p**
Dyslipidemia before ART	3.1 (1.4, 5.8)	0.001	Age ≥ 30	2.1 (1.7, 3.4)	0.004
			Dyslipidemia after ART	17.8 (7.6, 36.1)	<0.001
			Overweight	1.8 (1.3, 2.9)	0.023
			AZT-based regimen	1.4 (1.1, 3.2)	0.051

ART – antiretroviral, OR – odds ratio, AOR – adjusted odds ratio, CD4 – cluster of differentiation 4, WHO – World Health Organization, WB – Western Blot, AZT – zidovudine, EFV – efavirenz

DISCUSSION

Dyslipidemia and hyperglycemia were evident among Filipino PLHIV. We report a dyslipidemia prevalence of 65% prior to ART exposure. This prevalence is similar to previous studies.[5,6,23] Low HDL-C and the combination of low HDL-C and high TG were the two most common patterns of dyslipidemia observed among ART-naïve individuals and agrees with the patterns observed in prior studies of dyslipidemia among ART naïve regardless of race.[23-27]

Our study showed a high prevalence of patients with high LDL-C level (53%) and a low prevalence of high TC (20.5%). Prior studies showed trends towards lower TC level[24,26-28] but other studies did not show this effect.[29] Conflicting results are also evident on the pattern of LDL-C.[25,30] Previous studies have shown that HIV infection initially affects the TC, followed by other components.[31] One study reported that a low CD4 count increased the odds of dyslipidemia by eleven times.[32] Although low CD4 count did not reach statistical significance in our study, we hypothesize that the risk of dyslipidemia was mitigated by the presence of malnutrition, debilitation, malabsorption, or hepatic dysfunction.[33,34] Our results however, support the association between the progressive decline in HDL-C and the increase in TG level with worsening immunosuppression.[24-28,30]

Our study reports a 10.4% hyperglycemia prevalence before ART initiation. This is higher than the 2.6% prevalence of DM among ART-naïve individuals in an American study but is similar to the 11.7% hyperglycemia prevalence in a study done in Thailand.[35,36] Our result is consistent with literature demonstrating increased rates of IFG and DM among Asians compared to Caucasians adjusting for the same BMI.[37] Among our patients with hyperglycemia, an overwhelming majority (92.4%) met criteria for IFG, consistent with a prior study.[36] These figures are consistent with the pathophysiology of hyperglycemia in PLHIV, where IFG and impaired glucose tolerance (IGT) precede weight loss and progress to the development of DM.[18]

Among those patients diagnosed with both dyslipidemia and hyperglycemia before ART initiation, 28.6% (16/56) fulfilled the criteria for metabolic syndrome. Its manifestation cannot be completely attributed to traditional risk factors for metabolic syndrome, such as age and BMI, and might be complicated by the duration of HIV infection and prolonged immune activation. The co-existence of both dyslipidemia and hyperglycemia in 8.8% of the ART-naïve individuals is a testament to the shared risk factors in the etiogenesis of both diseases. This is strengthened by the fact that dyslipidemia was the only significant risk factor for hyperglycemia after multivariate logistic regression.

It is interesting that our study showed 1.5 times increased odds of developing dyslipidemia with a significant delay in ART initiation (e.g, more than 320 days) from time of HIV diagnosis. On the other hand, high risk patients who were started on ART prior to HIV confirmation, had a 70% decreased risk of developing dyslipidemia when compared to those who were started after the delay in HIV diagnosis. These findings suggest that prolonged, uncontrolled HIV infection itself somehow promotes the dyslipidemic state. This association was not observed for hyperglycemia.

In this study, the proportion of dyslipidemic subjects' post-ART is lower compared to the proportion pre-ART despite an increase in BMI. This finding might be due to the institution of non-pharmacologic and pharmacologic intervention for dyslipidemia before ART and continued post-ART. Although a low number received intervention, they likely helped to correct metabolic abnormalies. In addition, the initiation of ART may have reduced the inflammatory HIV milieu linked to the development of dyslipidemia.

Despite this finding, our data found a greater proportion of subjects fulfilled the criteria for metabolic syndrome

after ART initiation. This supports the combined effect of HIV infection and its treatment to the development of lipid abnormalities (elevated TG and decreased HDL), hyperglycemia and central obesity.[17-19]

In our study, the most common lipid derangements post-ART are elevated TC and LDL-C. Their role as the main driver for the development of metabolic syndrome in our cohort needs further investigation. Dyslipidemia in metabolic syndrome was brought about by increased tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), downregulation of tyrosine kinase Ron while insulin resistance (IR) is due to increased soluble urokinase plasminogen activator receptor (suPAR) and adipokine production from adipocytes.[19]

The level of the various lipid parameters and serum glucose level after ART initiation in our cohort was higher compared to a similar cohort on first-line ART.[23] This may be because of inflammation caused by other AIDS defining illnesses and co-infections.[32] After ART exposure, there was an increase in the proportion of dyslipidemic patients with elevated TC (58%) and elevated LDL-C (81%). Though the atherogenic index of plasma (AIP) was not computed in this study, the described lipid profile is recognized as an important risk factor for cardiovascular events.[38]

Patients who were classified under WHO stage 4 had almost a two-fold increased odds of dyslipidemia after ART initiation. This suggests there is greater immune activation among those with co-infections and severe immunosuppression even after ART initiation.[39,40] We found that the persistence of low CD4 count (<200 cells/mm^3) after ART exposure had a protective effect against dyslipidemia. This result is consistent with another multi-center study implicating the insufficient duration of ART exposure as the cause of the persistent low CD4 count and the low dyslipidemia risk.[41]

The duration of ART exposure is a well-known risk factor for dyslipidemia.[14] In this cohort, there was an eight-fold increased risk of dyslipidemia with ART exposure of more than 36 months. PIs are classically often linked to metabolic consequences, but this study failed to demonstrate this observation, likely because of the low number of patients on PIs in our cohort. However, this study strengthens the association of dyslipidemia and the use of EFV[3,13,42] which are postulated to affect the process of triglyceride–cholesteryl ester exchange.

The prevalence of hyperglycemia after ART showed a 5.2% increase compared to the pre-ART period. The risk for hyperglycemia exists but the degree of derangement was not as prominent as dyslipidemia.[43] In our study, traditional risk factors such as age ≥30, and weight gain after ART initiation[7,19] were also associated with the development of hyperglycemia. Whether the increase in weight was from improved nutrition or from ART-induced lipodystrophy is unclear. This study showed that being overweight is a risk factor for hyperglycemia, but the association was not observed among the obese due to the small number of patients in that category. This study also validated the association of AZT-based regimen with hyperglycemia.[3] These findings are linked to mitochondrial dysfunction from persistent HIV infection and ART related mitochondrial toxicity that perpetuates the high oxidative stress milieu.[44] Mitochondrial dysfunction affects fatty acid beta-oxidation which in turn causes accumulation of nonmetabolized fatty acids. This is also linked to HIV-associated lipodystrophy syndrome that is characterized by alterations in fat deposition coupled with metabolic complications like dyslipidemia, IR and lactic acidemia.[44] Moreover, chronic immune activation involving monocytes and macrophages contribute to phagocytosis of LDL-C forming foam cells (classical monocytes), secretion of pro-inflammatory cytokines and generate reactive oxygen species (intermediate monocytes) that is associated with occurrence of metabolic complications and disease progression.[45]

In general, lifestyle modification is the recommended initial intervention for the metabolic syndrome. However only 23% of dyslipidemic and 7.2% of hyperglycemic patients in this cohort were advised lifestyle modification. The low application of this recommendation might be due to poor medical chart documentation. In addition, laboratory results may not have been given clinical importance since most patients were relatively young.

Statins in the form of rosuvastatin, pravastatin and atorvastatin were used in only 14% and fibrates in only 3.7% of our study cohort. The low use of hypolipidemic agents might be due to fear of drug-drug interaction with medications (ART, rifampicin), or lack of awareness of guideline recommendations. The decision to start statins should depend on the patient's cardiovascular risk stratification and the benefit of reduction should outweigh the potential side effects and cost of treatment.

Similarly, OHAs were used only in a minority of patients since 90% of hyperglycemic subjects were diagnosed with IFG. IFG is initially managed with lifestyle modification before resorting to OHAs. Metformin is the initial OHA of choice in most patients with IFG or DM, but exercise caution regarding its use among PLHIV due to ART interactions, worsening cachexia, impaired appetite and increased hypoglycemia risk.[29] Insulin, which is recommended for severe DM, was not used in this cohort, but is devoid of ART interactions.[46]

The strengths of this study include an analysis of HIV and non-HIV related risk factors pre- and post-ART and the effect of delayed ART institution. However, the retrospective nature of the study prohibited us from calculating important variables such as waist-hip ratio, measures of visceral adiposity and plasma insulin levels. Other limitations of this study include the lack of documentation of metabolic derangements among those

who died, the scarcity of laboratory data to document diagnosis of dyslipidemia and hyperglycemia prior to HIV diagnosis and the uncertainty that all bloodwork were obtained as fasting.

CONCLUSION

The prevalence of dyslipidemia and hyperglycemia is high in a relatively young cohort of Filipino PLHIV. However, pharmaceutical and non-pharmaceutical interventions remain to be low. Preventive strategies against these metabolic derangements should be integrated in the healthcare program for HIV. Strategies include early HIV diagnosis and immediate initiation of ART among new cases, frequent and intensive monitoring of these metabolic parameters while on ART, appropriate dietary modifications and prompt initiation of treatment.

The results of this study serve as a call to make INSTI-based ART the first line ART in the country because of fewer effects on these metabolic parameters,. These non-infectious complications should be given equal attention to reduce the burden to the overwhelmed healthcare system brought by the HIV epidemic.

A prospective cohort is recommended to consider changes in important variables like immune activation levels, other anthropometric measurements (waist-hip ratio, visceral adiposity) and inflammatory markers on activated monocytes and its relation to the development of these metabolic abnormalities. Future research should investigate the association of these metabolic derangements and the noted risk factors to the development of cardiovascular outcomes.

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