Dyslipidemia in an HIV-Positive Antiretroviral Treatment-Naive Population in Dar es Salaam, Tanzania

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Abstract: Limited data are available on dyslipidemia in HIV-infected patients in resource-limited settings. We performed a cross-sectional analysis in antiretroviral therapy (ART)–naive, non-fasting HIV-infected patients in Tanzania between November 2004 to June 2008. Robust linear regression modeling was performed. Lipid parameters were assessed in 12,513 patients [65% women; median (interquartile range) age, 36 (30–42) years; CD4 count, 143 (51–290) cells/mm^3]. Low high-density lipoprotein was prevalent in 67% and increased triglyceride in 28%. High triglyceride and low high-density lipoprotein levels were associated with low CD4 counts ($P < 0.001$). In this ART-naive Tanzanian population, dyslipidemia was highly prevalent and associated with advanced disease. The impact of ART on these changes requires further exploration.

Key Words: ART-naive, cardiovascular disease, dyslipidemia, HIV positive, Tanzania

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INTRODUCTION

In 2008, it was estimated that 33.4 million individuals were living worldwide with HIV and that 30 million were from low-income and middle-income countries.[1] In developed countries, improved lifespan due to antiretroviral therapy (ART) has resulted in an increased incidence of non-communicable diseases among HIV-infected patients[2] with similar rises in resource-limited settings (RLS) expected as ART rollout continues. Dyslipidemia is a well-known risk factor for cardiovascular disease (CVD), one of the most common noncommunicable diseases in HIV-infected populations. A number of studies from the developed world have documented a high rate of dyslipidemia in HIV-infected individuals both on and off ART.[3–5] However, there is very little data on dyslipidemia and subsequent cardiac risk among HIV-infected individuals in RLS. In the few studies from RLS that have been conducted, low-to-normal total cholesterol (TC) and low-density lipoprotein (LDL), elevated triglyceride (TG), and decreased high-density lipoprotein (HDL) among ART-naive individuals have been observed.[6–10] Unfortunately, data from developed countries on CVD and CVD risk factors cannot necessarily be extrapolated to RLS due to differences in patient populations and HIV subtypes,[6,11] therefore, additional studies from RLS are needed. The study of dyslipidemia in patients not yet on therapy is particularly important in RLS to examine the independent effect of HIV itself on CVD risk and inform the choice of subsequent ART. In this study, we assessed the prevalence of dyslipidemia and associated risk factors among HIV-infected patients at the time of enrollment, before ART initiation in an urban HIV Care and Treatment program, in Tanzania.

METHODS

Study Population

This study was conducted between November 2004 to June 2008 at 12 HIV Care and Treatment Clinics affiliated with Management and Development for Health (MDH) HIV/AIDS Care and Treatment Program and supported by President's Emergency Plan For AIDS Relief in Dar es Salaam. At the time of this study, the HIV prevalence in Dar es Salaam was 5.7%.[12] Patients included in this study met the following criteria: complete or partial lipid panel performed before ART initiation, >15 years of age, and not pregnant at the time of enrollment. Enrollment into MDH—supported

Care and Treatment Clinics followed a written informed consent and ethical approval, which was obtained from Muhimbili University of Health and Allied Sciences and the Harvard School of Public Health.

Study Design

Clinical care of all HIV-infected patients followed Tanzanian guidelines.[13] At all sites, patients were enrolled and had their HIV diagnosis, clinical stage, and blood drawn before possible ART initiation. Laboratory testing included the following: CD4 count, complete blood count, hemoglobin (Hgb), blood urea nitrogen, creatinine, alanine amino transferase (ALT), lipid panel, and glucose.

Laboratory Methods

TC, TG, and HDL cholesterol was tested using the Cobas Integra 400 Plus analyzer (Roche Diagnostics Ltd. CH-6343, Rotkreuz, Switzerland). Low-density lipoprotein (LDL) was derived from an indirect measurement using the Friedewald formula.[14] Non-HDL was determined using the following formula: Non-HDL = TC−HDL. CD4 was measured using the FACS Calibur system (Becton Dickinson, San Jose, CA).

Statistical Analysis

Dyslipidemia was defined according to US National Cholesterol Education Program III guidelines.[15] Increased non-HDL was defined as >160 mg/dL. Wilcoxon Rank sum test and χ^2 tests were used to compare the baseline characteristics. Robust linear regression models were used to examine the association between lipid outcomes and their potential predictors.[16] All multivariate analyses were adjusted for age, gender, site, season, and calendar year of ART initiation in the model. Additional potential confounders including age, sex, body mass index (BMI), ALT, Hgb, were identified through stepwise regression after forcing these variables into the model and were included if their *P* value <0.20. The median score test was used to assess the significance of any trends observed. The significance tests were 2-sided, and *P* values less than 0.05 were considered statistically significant. Statistical analyses were performed with SAS, Release 9.1 (Cary, NC). The adjusted means of triglyceride and HDL cholesterol were calculated using the robust regression model.

RESULTS

Baseline Characteristics

Twelve thousand five hundred thirteen patients were included in the analysis. Demographics are shown in Table 1. Twelve thousand five hundred thirteen patients had TC, 11,807 had TG, 1874 had non-HDL and HDL, 1853 had LDL, and 1787 had all 4 lipid parameters. At baseline, the median TG was 113 mg/dL (range: 83–159 mg/dL), TC 142 mg/dL (range: 109–177 mg/dL), HDL 32 mg/dL (range 21–45 mg/dL), LDL 88 mg/dL (range: 66–111), and non-HDL 110 mg/dL (range 89.7–135.0 mg/dL). TG was >150 mg/dL in 28% of patients, TC was >200 in14% of patients, and HDL was <40 mg/dL in 67% of patients. LDL was >130 in 12% of patients and non-HDL was >160 mg/dL in 9 % of patients (Fig. 1A). Prevalence of dyslipidemia by specific categories is shown in Figure 1A for all subjects and in Table 1 for all subjects (n = 12,513) and those with a full lipid panel (n = 1787). Dyslipidemia was found in 76% of patients with full lipid panels.

TABLE 1. Subject Characteristics at Baseline (Total Cohort n = 12,513 and Those With a Full Lipid Panel n = 1787)

	Median (IQR) or %, n = 12,513	Median (IQR) or %, n = 1787
Age (yrs)	36 (30–42)	36 (30–43)
Female (%)	65	67
Body mass index (kg/m^2)	20.1 (17.8–23.1)	20.7 (18.4–23.7)
CD4 (Cells/mm^3)	143 (51–290)	170 (64–320)
CD4 category (cells/mm^3)		
<50	25	20
50–99	15	14
100–199	22	23
200+	38	44
WHO Stage at baseline		
I	14	17
II	17	22
III	43	45
IV	26	16
Hgb level (g/dL)	10.2 (8.4–11.9)	10.6 (8.9–12.1)
ALT (u/L)	20 (13–31)	17.2 (11.7–28)
Prevalence of increased triglyceride (%)	28	22
Prevalence of reduced HDL (%)	67	67
Prevalence of increased LDL (%)	12	12
Prevalence of increased total cholesterol (%)	14	10
Prevalence of increased non-HDL (%)	9	9

Triglyceride

There was no significant difference in TG levels between males and females. TG levels increased with age ($P < 0.001$). After adjusting for age, gender, site, season, and clinical indicators (including BMI, ALT, and Hgb), TG was independently and inversely associated with CD4 cell count and was most elevated in the lowest CD4 cell count category (*P* value for nonlinearity < 0.0001). TG levels increased at CD4 cell count levels below approximately 300 cells per cubic millimeter (Fig. 1B). There was a significant independent positive correlation between WHO stage and TG level ($P < 0.001$). In the lowest BMI category, the median TG was 127 mg/dL and decreased as the BMI increased ($P < 0.001$). There was a significant independent inverse relationship between TG and Hgb levels; more pronounced anemia (Hgb < 7.0 g/dL) was associated with higher TG levels ($P < 0.001$).

High-Density Lipoprotein

HDL levels were significantly lower in male versus female patients ($P < 0.001$). After adjusting for age, gender, site, season, and clinical indicators, HDL was independently positively associated with CD4 count (*P* value for nonlinearity < 0.0001) (Fig. 1B). WHO stage was inversely related to

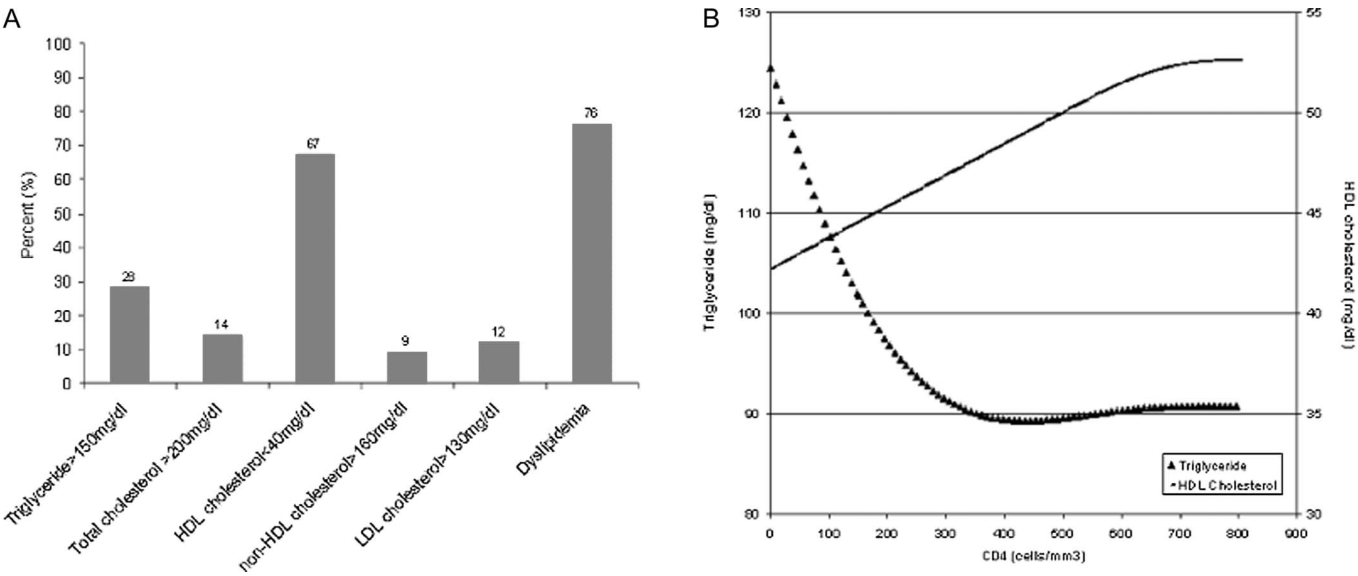

FIGURE 1. A, Prevalence of dyslipidemia at the time of enrollment into the HIV care program. The study site is the Management and Development for Health (MDH), Harvard PEPFAR Care and Treatment Program, Dar esSalaam, Tanzania. Dyslipidemia was defined according to US National Cholesterol Education Program (NCEP) III guidelines[15] as total cholesterol (TC) > 200 mg/dL, low-density lipoprotein (LDL) cholesterol > 130 mg/dL, triglycerides (TG) > 150 mg/dL, high-density lipoprotein (HDL) cholesterol < 40 mg/dL, non-HDL cholesterol (non-HDL) < 160 mg/dL. Sample sizes for each lipid measurement were as follows: Non-HDL and HDL = 1,874, LDL = 1,853, TC = 12,513, and TG = 11,807. B, Triglycerides and HDL in relation to CD4 levels. Stepwise restricted cubic spline models were fit to the robust regression of triglycerides and HDL on CD4, which was adjusted for age, gender, site season, calendar year, and clinical indicators, including BMI, hemoglobin level, and ALT.[36]

HDL. As the patient population progressed from stage I to stage IV, HDL decreased significantly ($P \leq 0.001$). HDL was significantly correlated with BMI; the lowest HDL levels were seen in the lowest BMI category ($P \leq 0.005$).

Low-Density Lipoprotein

LDL was significantly lower in male patients versus female patients ($P \leq 0.001$). As age increased, there was a significant increase in LDL ($P = 0.037$). After adjusting for age, gender, site, season, and clinical indicators, LDL was lowest in patients with BMI <17 and increased with higher BMI's ($P \leq 0.001$). There was an independent positive association between LDL and CD4 cell count ($P \leq 0.002$) and LDL and Hgb (P value < 0.001).

Total Cholesterol

TC was significantly lower in male versus female patients ($P \leq 0.001$). As age increased, there was a significant positive trend with increasing TC ($P = 0.003$). After adjusting for age, gender, site, season, and clinical indicators, the TC was lowest in patients with BMI <17 and increased at higher BMI's ($P \leq 0.001$). TC increased with increasing CD4 cell count ($P \leq 0.001$). WHO stage was independently inversely correlated with TC; as WHO stage increased from I to IV, TC decreased ($P \leq 0.001$). Hgb was lower in patients with lower TC levels ($P = 0.001$).

Non-HDL

Non-HDL was significantly lower in the male versus female patients ($P \leq 0.001$).

As age increased, there was a significant positive trend ($P = 0.001$) with increasing non-HDL. After adjusting for age, gender, site, season, and clinical indicators, non-HDL trended up with increasing BMI ($P \leq 0.001$). Hgb was lower in patients with lower non-HDL levels ($P = 0.001$). There was no significant relationship found between non-HDL and CD4 count or WHO stage.

DISCUSSION

In the largest study of HIV-infected ART-naive patients in the developing world to date, we observed a high prevalence of dyslipidemia and noted significant differences in the type and extent of dyslipidemia based on the degree of immunosuppression. In our cohort of HIV-infected ART-naive patients, a large percentage met criteria for dyslipidemia, which was significantly higher than that observed in HIV-negative patients from other Tanzanian settings.[17] In studies from developed countries, HIV-infected patients seem to be at significantly higher risk of CVD than noninfected individuals.[18–20] In the DAD cohort, where elevated rates of dyslipidemia were evident but a different definition of dyslipidemia was used, a 26% increase in risk in the frequency of myocardial infarction (MI) was observed per year of exposure to ART ($P < 0.001$). The increased risk of MI was attenuated controlling for dyslipidemia, suggesting dyslipidemia contributed in part to the increased MI rates.[19] Considering the increasing rates of obesity, diabetes and other CVD risk factors observed among HIV-noninfected persons in RLS,[21–24] similar trends in CVD morbidity and mortality would be expected to occur among HIV-infected patients in RLS as ART rollout continues.

In our cohort, the majority of dyslipidemia was characterized by abnormal HDL or TG levels, with normal or low TC, non-HDL, and LDL levels as previously observed in other treatment-naive HIV-infected populations.[3,4,5,25,26] It should be noted that the pattern of dyslipidemia that has been observed in ART-naive patients is different from the pattern seen in ART-treated individuals, who tend to have higher levels of LDL, non-HDL, and TC. Data on dyslipidemia among HIV-infected patients in RLS is scarce. In a study by Manuthu et al,[8] which compared lipid values among 295 ART-naive and treated patients in Kenya, the overall prevalence of dyslipidemia was 63.1%. The majority of dyslipidemia was characterized by high TG (22.5%) and low HDL (51.3%) levels in ART-naive patients. In 2 other recent studies from Rwanda and Uganda, a similar pattern was found.[9,10] The clinical relevance of this pattern of dyslipidemia lies in the potential risk it confers for the development of premature CVD.[10]

We observed a distinct pattern of rising TG and decreasing HDL, LDL, and TC levels with progressive immune dysfunction. This pattern of dyslipidemia, and its strong correlation with disease stage, has also been observed in other treatment-naive populations in both developed and developing countries.[25–27] In a study by Feingold et al,[26] hypertriglyceridemia was also found to be associated with disease progression and HIV viremia. Recently, studies suggest that low CD4 count is associated with atherosclerotic disease and increased MI rates among HIV patients.[28–30]

The pathogenesis underlying the association between immune dysfunction and dyslipidemia remains unclear. Hypertriglyceridemia may be related to inflammation and subsequent cytokine effects seen in advanced disease.[25] Hypertriglyceridemia may also be related to decreased hepatic clearance possibly related to the role of apolipoprotein E.[4,25,31] Rose et al[32] has proposed that low HDL levels may be linked to an HIV-secreted soluble transactivator protein (Tat) in the plasma causing reduced cholesterol mobilization from hepatic cells. Finally, HDL hepatic metabolism may be redirected towards apo-B–containing lipoproteins by factors related to HIV infection and inflammation.[27,32]

This study had several limitations. It was a retrospective analysis that did not include a negative control group and, therefore cannot provide proof of causality between HIV, immunosuppression, and the development of dyslipidemia. We were limited in fully assessing CVD risk because our database lacked detailed information regarding the patients' medical, social, nutritional, and family history. Another limitation was that lipid samples were nonfasting. As a result, TG levels may be falsely elevated and thus the prevalence of dyslipidemia may be less than we observed. If the triglyceride measures over 400 mg/dL, the LDL sample, which is calculated indirectly by the Friedewald equation, will not be completely accurate.[33] However, TG levels were over 400 mg/dL in only 1.08% of patients. To gain additional insight into this analysis in the setting of such limitations, we also chose to report non-HDL cholesterol which provides an assessment of all apolipoprotein B–containing lipoproteins considered to be atherogenic and improves accuracy in nonfasting lipid samples.[34] The prevalence of increased non-HDL cholesterol was less than for the other lipid parameters. A smaller percentage of patients had all lipid parameters measured due to differing practice patterns among the physicians who cared for patients in this cohort, but full data were available in a large number of patients. Despite these limitations, this study provides a detailed analysis of dyslipidemia in very large cohort of HIV-infected patients in a RLS.

In summary, a high prevalence of dyslipidemia was seen among ART-naive HIV-positive patients in this cohort. Patients with the most advanced HIV disease had significantly elevated TG and low HDL levels, a pattern that may contribute to increased risk of CVD. These findings underline the importance of establishing a patient's CVD risk factor profile before ART initiation because subsequent ART choice depends on this.[35] Further study is required to assess the impact of ART on CVD disease and its risk factors in the RLS. Given the increased prevalence of dyslipidemia, CVD risk prevention counseling and management should be integrated into HIV care in RLS.

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