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Dyslipidemia in an HIV-positive, antiretroviral treatment-naïve 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 (RLS). We performed a cross-sectional analysis in ART-naïve, non-fasting HIV-infected patients in Tanzania between November 2004-June 2008. Robust linear regression modeling was performed. Lipid parameters were assessed in 12,513 patients (65% women; median (IQR) age, 36 (30–42) years; CD4 count, 143 (51–290) cells/mm3). Low HDL was prevalent in 67% and increased TG in 28%. High triglyceride and low HDL levels were associated with low CD4 counts (P<0.001). In this ART-naïve Tanzanian population, dyslipidemia was highly prevalent and associated with advanced disease. The impact of ART on these changes requires further exploration.

Keywords

HIV positive; ART-naïve; Dyslipidemia; Tanzania; Cardiovascular disease

INTRODUCTION

In 2008 it was estimated that 33.4 million individuals were living worldwide with HIV, and that 30 million were from low- and middle-income countries. In developed countries, improved lifespan due to antiretroviral therapy (ART) has resulted in an increased incidence...
of Non-Communicable Diseases (NCDs) among HIV-infected patients\textsuperscript{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 NCDs in HIV-infected populations.\textsuperscript{2} A number of studies from the developed world have documented a high rate of dyslipidemia in HIV-infected individuals both on and off ART.\textsuperscript{3,4,5} 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 TC and LDL, elevated TG, and decreased HDL among ART-naïve individuals have been observed.\textsuperscript{6,7,8,9,10} 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\textsuperscript{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, prior to ART initiation in an urban HIV Care and Treatment program, in Tanzania.

\section*{METHODS}

\subsection*{Study population}
This study was conducted between November 2004-June 2008 at 12 HIV Care and Treatment Clinics (CTCs) affiliated with MDH (Management and Development for Health), 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%.\textsuperscript{12} Patients included in this study met the following criteria: complete or partial lipid panel performed prior to ART initiation, >15 yrs. of age, not pregnant at the time of enrollment. Enrollment into MDH-supported CTCs followed a written informed consent and ethical approval, which was obtained from Muhimbili University of Health and Allied Sciences (MUHAS) and the Harvard School of Public Health (HSPH).

\subsection*{Study Design}
Clinical care of all HIV-infected patients followed Tanzanian guidelines.\textsuperscript{13} At all sites, patients were enrolled and had their HIV diagnosis, clinical stage and blood drawn prior to possible ART initiation. Laboratory testing included: CD4 count, complete blood count (CBC), hemoglobin (Hgb), blood urea nitrogen (BUN), creatinine, alanine amino transferase (ALT), cholesterol panel and glucose.

\subsection*{Laboratory Methods}
Total cholesterol (TC), triglyceride (TG) and high density lipoprotein (HDL) cholesterol was tested using the Cobas Integra 400 Plus analyzer (Roche Diagnostics). Low density lipoprotein (LDL) was derived from an indirect measurement using the Friedewald formula.\textsuperscript{14} Non-HDL was determined using the formula: Non-HDL= TC-HDL. CD4 was measured using the FACS Calibur system (Becton Dickinson).

\subsection*{Statistical analysis}
Dyslipidemia was defined according to US National Cholesterol Education Program (NCEP) III guidelines.\textsuperscript{15} Increased non-HDL was defined as > 160 mg/dL. Wilcoxon Rank sum test and $\chi^2$ 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.\textsuperscript{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, 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 two-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

12,513 patients were included in the analysis. Demographics are shown in Table 1. 12,513 patients had TC, 11,807 had TG, 1,874 had non-HDL and HDL, 1,853 had LDL and 1,787 had all four 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 in 14% 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 (Figure 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.

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 non-linearity <0.0001). TG levels increased at CD4 cell count levels below approximately 300 cells/m$^3$ (Figure 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).

HDL

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 non-linearity <0.0001)(Figure 1B). WHO stage was inversely related to HDL. As the patient population progressed from stage I to stage IV, HDL decreased significantly (P=<0.001). HDL was significantly correlated with BMI; the lowest HDL levels were seen in the lowest BMI category (P=<0.005).

LDL

LDL was significantly lower in male patients versus female patients (P=>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=>0.001). There was an independent positive association between LDL and CD4 cell count (P <=0.002) and LDL and Hgb (P-value<0.001).

TC

TC was significantly lower in male versus female patients (P=>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=<0.001). TC increased with increasing CD4 cell count (P=<0.001). WHO stage was independently inversely correlated with TC; as WHO stage increased from I to IV, TC decreased (P= <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=<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=<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-naïve 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-naïve patients, a large percentage met criteria for dyslipidemia which was significantly higher than that observed in HIV-negative patients from other Tanzanian settings. In studies from developed countries, HIV-infected patients appear to be at significantly higher risk of CVD than non-infected individuals. 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 HAART (P<0.001), and the increased risk of myocardial infarction was attenuated controlling for dyslipidemia, suggesting dyslipidemia contributed in part to the increased MI rates. Considering the increasing rates of obesity, diabetes and other CVD risk factors observed among HIV-non-infected persons in RLS, 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-naïve HIV-infected populations. It should be noted that the pattern of dyslipidemia that has been observed in ART-naïve 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., which compared lipid values among 295 ART-naïve 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-naïve patients. In two other recent studies from Rwanda and Uganda, a similar pattern was found. The clinical relevance of this pattern of dyslipidemia lies in the potential risk it confers for the development of premature CVD.

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-naïve populations in both developed and developing countries. In a study by Feingold et al., 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.
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.\textsuperscript{25} Hypertriglyceridemia may also be related to decreased hepatic clearance possibly related to the role of apolipoprotein E.\textsuperscript{4, 25, 31} Rose, et al. 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.\textsuperscript{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 non-fasting. 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.\textsuperscript{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 non-fasting lipid samples.\textsuperscript{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-naïve, 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 prior to ART initiation since subsequent ART choice depends on this.\textsuperscript{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.

Acknowledgments

All authors played a role in editing the article and approved the text as submitted to JAIDS. Catharina Armstrong designed the study and wrote the manuscript. Enju Liu and James Okuma performed the data analysis and assisted in the interpretation of statistical data. Claudia Hawkins, Steve Grinspoon, Wafaie Fawzi, Donna Spiegelman, Chalamilla Guerino and Marina Njelekela reviewed and edited the manuscript.

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References


Figure 1.
A: The study site is the Management and Development for Health (MDH), Harvard PEPFAR Care and Treatment Program, Dar es Salaam, Tanzania. Dyslipidemia was defined according to US National Cholesterol Education Program (NCEP) III guidelines 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) <160mg/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: Stepwise restricted cubic spline models were fit to the robust regression of triglycerides and HDL on CD4, adjusted for age, gender, site season, calendar year and clinical indicators including BMI, hemoglobin level and ALT.
Table 1
Subject characteristics at baseline (total cohort n=12,513 and those with a full lipid panel n=1,787)

<table>
<thead>
<tr>
<th></th>
<th>Median (IQR) or % n=12,513</th>
<th>Median (IQR) or % n=1,787</th>
</tr>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>36(30–42)</td>
<td>36(30–43)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>65</td>
<td>67</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>20.1(17.8–23.1)</td>
<td>20.7 (18.4–23.7)</td>
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<tr>
<td>CD4 (Cells/mm³)</td>
<td>143(51–290)</td>
<td>170(64–320)</td>
</tr>
<tr>
<td>CD4 category (Cells/mm³)</td>
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</tr>
<tr>
<td>&lt;50</td>
<td>25</td>
<td>20</td>
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<td>50–99</td>
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<td>100–199</td>
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<td>200+</td>
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<tr>
<td>WHO Stage at baseline</td>
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</tr>
<tr>
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<td>III</td>
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<td>45</td>
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<tr>
<td>IV</td>
<td>26</td>
<td>16</td>
</tr>
<tr>
<td>Hemoglobin level (g/dl)</td>
<td>10.2(8.4–11.9)</td>
<td>10.6(8.9–12.1)</td>
</tr>
<tr>
<td>ALT (u/l)</td>
<td>20(13 –31)</td>
<td>17.2(11.7–28)</td>
</tr>
<tr>
<td>Prevalence of Increased Triglyceride (%)</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td>Prevalence of Reduced HDL (%)</td>
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<td>67</td>
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<tr>
<td>Prevalence of Increased LDL (%)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Prevalence of Increased Total Cholesterol (%)</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>Prevalence of Increased non HDL (%)</td>
<td>9</td>
<td>9</td>
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