Association of Abnormal Liver Function Parameters with HIV Serostatus and CD4 Count in Antiretroviral-Naive Rwandan Women

Jean Claude Dusingize,1 Donald R. Hoover,2 Qiuhu Shi,3 Eugene Mutimura,4 Emmanuel Rudakemwa,4 Victorien Ndacyayisenga,5 Léonard Gakindi,4 Michael Mulvihill,6 Jean D’Amour Sinayobye,1 Emmanuel Musabeyezu,4 and Kathryn Anastos6

Abstract

We determined the associations of HIV infection/CD4 count with markers of hepatocellular damage [elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT)] and liver synthetic function (decreased albumin) in HIV-infected (HIV+) antiretroviral therapy (ART)-naive and uninfected (HIV-) women enrolled in the Rwanda Women’s Interassociation Study and Assessment. Liver enzymes were measured with abnormality defined as either AST or ALT ≥1.25 times the upper limit of normal. Low serum albumin level was defined as <3.5 g/dl. Multivariable logistic regression analysis identified independent predictors of elevated AST/ALT and low serum albumin. HIV- women had the lowest prevalence (6.6%) of abnormal AST/ALT, with the highest prevalence (16.4%) in HIV+ women with CD4 <200 cells/µl (p = 0.01). The odds of having serum albumin <3.5 g/dl was 5.7-fold higher in HIV+ than HIV- women (OR = 5.68, 95% CI: 3.32–9.71). The risk of low albumin decreased from low to high CD4 count, with OR = 2.62, 95% CI: 1.66, 4.14 and OR = 1.57, 95% CI: 1.01, 2.43 in HIV+ women with a CD4 count <200 and 200–350 cells/µl, respectively vs. HIV+ with CD4 >350 (p <0.001 and p <0.05 for all comparisons). Our findings suggest that HIV-associated liver damage may occur in ART-naive patients. Although liver abnormality prevalences in this cohort of HIV-infected Rwandan women are less than reported in developed countries, caution is needed for risk assessment measures to monitor and screen HIV-infected patients pre- and post-ART initiation in African clinical settings to curtail potential risks associated with HIV infection.

Introduction

Human immunodeficiency virus (HIV) infection causes morbidity and mortality worldwide, and the number of HIV-infected patients has increased dramatically in the past decade.1–3 HIV infection causes systemic disease with many complications beyond acquired immunodeficiency syndrome (AIDS) illnesses that may not yet be recognized.4,5 While liver enzyme elevations are common in HIV-infected patients, their diagnosis or management may be difficult because of the intricacies involved in pathogenic mechanisms of liver functioning.6,7 In many HIV+ patients with elevated liver enzymes, the elevation is not explained by an identified underlying liver disease or toxin and thus may directly occur either due to antiretroviral drug toxicity or the HIV infection itself.

Additionally, liver enzyme abnormalities in HIV-infected persons may reflect concurrent hepatitis B (HBV) or hepatitis C (HCV) infection, which are more common among HIV+ than HIV- individuals.8,9 Other factors that independently contribute to liver damage that may be more common in HIV-infected persons include alcohol-related liver disease, nonalcoholic...
steatohepatitis associated with metabolic syndromes, and medication or illicit drug use. Studies from developed countries have reported correlations between HIV viral load and aminotransferase serum levels in HIV-infected antiretroviral (ART)-naive patients. However, a study conducted in Uganda found that the risk of clinically significant hepatotoxicity was low, even in HIV patients on ART and among HIV/HBV-coinfected persons. Nevertheless, there is emerging evidence that HIV infection, even in the absence of ART toxicity and other cofactors, may have a direct impact on the liver fibrosis pathogeneses, nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH), and on further progression to liver disease.

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are hepatic enzymes whose elevation indicates hepatocellular injury. Although reports of elevations in these hepatic enzymes are frequent in HIV-infected patients, direct reports of hepatocellular injury are limited, perhaps because of pitfalls in case definition. In addition to liver enzymes, which indicate hepatocellular damage, serum albumin is a measure of hepatic synthetic function with albumin levels decreased in chronic liver disease, such as cirrhosis, reflecting decreased synthesis. However, albumin levels are dependent on a number of other factors such as catabolism, hormonal factors, and urinary and gastrointestinal losses. These should be taken into account when interpreting low albumin levels. Several studies suggest possible associations of chronically elevated liver enzyme levels and an increased mortality in HIV-infected and HIV-uninfected patients irrespective of the causal mechanisms.

We determined the association between HIV infection and markers of hepatocellular damage (AST and ALT) and liver synthetic function (albumin) in ART-naive HIV-infected Rwandan women compared to an HIV uninfected group. In particular, hepatotoxicity measured by the levels of ALT or AST elevation was graded according to the AIDS Clinical Trial Group criteria. The goal of the study was to identify predictors of poor liver function in HIV-infected Rwandan women.

Materials and Methods

Study population

The Rwanda Women’s Interassociation Study and Assessment (RWISA) is an observational prospective cohort of 710 ART-naive (at enrollment) HIV-infected and 226 HIV-uninfected Rwandan women enrolled in 2005. Participants were recruited through grassroots women’s organizations and clinical care sites for HIV-infected patients. Inclusion criteria were age 25 years or older at study entry, willingness to give informed consent, agreement to be tested for HIV, participation in a baseline visit as an outpatient, and no history of receiving antiretroviral treatment with the allowed exception of single-dose nevirapine to prevent mother-to-child transmission of HIV. Informed consent included a video describing and demonstrating the study, followed by a group question and answer period, and then a private standard written informed consent process.

At study entry, participants provided historical information including sociodemographics, medical history, and symptoms. Anthropometric measurements and fasting blood specimens were taken. The interviews were conducted in the local language Kinyarwanda by trained interviewers with a nursing background. Research staff entered all interview and physical examination data directly into an ACCESS database. The study was funded by the National Institute of Allergy and Infectious Diseases and was approved by the Rwandan National Ethics Committee and the Montefiore Medical Center (Bronx, NY) Institutional Review Board. All RWISA participants for whom AST, ALT, and albumin measurements were performed at the enrollment visit are included in this analysis.

Laboratory methods

The liver enzymes ALT and AST and serum albumin were measured using COBAS Integra Chemistry Analyzer, Roche Diagnostics, Mannheim, Germany at King Faisal Hospital in Kigali. CD4 counts were determined with a FACS counter (Becton and Dickinson, Immunocytometry Systems, San Jose, CA). Diagnosis of HIV infection was determined by having a positive result for HIV-1 antibody ELISA kits (HIV Vironostika, Netherlands, and Murex HIV-1,2, Oxford, UK), which was confirmed by a positive result again with the same test.

Outcome variables

The primary outcomes were elevated transaminases (AST, ALT) and serum albumin. We defined abnormal liver enzymes according to the AIDS Clinical Trial Group Guidelines: liver enzyme elevations of <1.25, 1.25–2.5, 2.6–5, 5.1–10, or more than 10 times the upper limit of normal (ULN) define hepatotoxicity of grades 0, 1, 2, 3, and 4, respectively. For this study an abnormal liver enzyme was defined as an ALT/AST elevation of grade 1 (43 U/liter or 1.25 times the ULN) or higher, using 35 U/liter of ALT or AST as the ULN. Low serum albumin level was defined as an albumin value <3.5 g/dl, the lower limit of normal in the testing laboratory.

Statistical methods

Analyses were done for participants with and without HIV infection combined in order to assess the effect of HIV infection on the liver enzymes and serum albumin. Further analyses were done restricted to HIV+ participants by CD4 category (CD4 >350, 200 ≤ CD4 ≤ 350, and CD4 <200 cells/μl) to assess for the effect of disease progression on the liver enzymes and serum albumin. Descriptive statistics (means, standard deviations) were used to present continuous variables, and numbers and percentages for categorical variables. Analysis of variance compared mean serum albumin levels among groups defined by HIV status and CD4 count while Chi-square tests did so for categorical variables.

To identify predictors of poor liver function in this population we fitted a multivariable logistic regression model with all variables included in the model. Additionally, we did fit
linear regression models using serum albumin as a continuous variable, which gave results similar to those of the categorical models. However, for clinical relevance we believe linear models are not the best option to present and creating categories for levels of serum albumin abnormality is better as previously reported.13,21

Abnormal AST/ALT levels were combined both because this is normal clinical practice and due to low rates of abnormality (∼5%) in each. Furthermore, to use ALT and AST as continuous variables they would need to be split up for linear models, which is never done in clinical practice; in addition, each had a skewed distribution (kurtosis ∼10) even after log transformation. Variables included in these models were chosen by having a statistical association with amino-transaminase values and serum albumin in univariate analyses. SAS software, version 9.1.3 (Cary, NC), was used for all analysis. \( p < 0.05 \) was used to indicate a statistically significant association.

**Results**

Demographic, clinical, and laboratory parameters of participants are summarized by HIV/CD4 group (HIV−, HIV+ and for HIV+, CD4 >350, 200 < CD4 <350, and CD4 <200 cells/μl) (Table 1). Of the 936 participants, 855 (213 HIV−, 642 HIV+) had data on liver function tests from the enrollment visit. The HIV+ women were older than the HIV− women (58.2% vs. 21.2% over 40 years old; \( p < 0.001 \)). Among HIV− women, the prevalence of elevated AST and/or ALT was 6.6% compared to 12.6% in HIV-infected women, with the highest prevalence (16.4%) in HIV-infected women with CD4 <200 cells/μl. Mean serum albumin (g/dl) was systematically lower with more advanced HIV disease: 3.9 ± 0.4 in HIV− women and 3.6 ± 0.6, 3.5 ± 0.7, and 3.3 ± 0.6 g/dl in HIV+ women with CD4 count ≥350, 200–350, and <200 cells/μl, respectively (\( p < 0.001 \)). About 52% of HIV+ and 20% of HIV− women had serum albumin <3.5 g/dl.

**Markers of hepatocellular damage (ALT/AST) in HIV-positive subjects**

Table 2 shows factors associated with elevated ALT/AST using univariate (unadjusted) and multivariate (adjusted) logistic regression analysis for all subjects. The risk of having elevated ALT/AST was about 4.4-fold higher in HIV+ women compared to HIV− women (OR = 4.4, 95% CI: 1.91, 9.97). In analysis restricted to HIV+ subjects, there was no significant difference in liver enzymes among CD4 groups in either univariate or multivariate analysis indicating that the disease progression did not affect liver enzymes (Table 3). However, use of prophylactic drugs (Bactrim and/or Dapsone) was associated with elevated liver enzymes in both univariate and multivariate analysis (\( p = 0.045 \) and \( p = 0.03 \), respectively). We did not find any association between alcohol use, age, BMI, and income and elevated liver enzymes in univariate and multivariate analysis.

**Marker of synthetic liver function (serum albumin) in HIV-positive subjects**

In logistic regression analysis using models including all subjects (Table 4) the odds of having serum albumin <3.5 g/dl was 7.7-fold higher in HIV+ than HIV− women (OR = 5.68, 95% CI: 3.32, 9.71). In analysis restricted to HIV+ women (Table 5), the odds of having serum albumin <3.5 g/dl was 2.6-fold higher in HIV+ women with CD4 counts <200 and 1.6-fold higher in those with CD4 between 200 and 350 cells/μl (OR = 2.62, 95% CI: 1.66, 4.14 and OR = 1.57, 95% CI: 1.01, 2.43, respectively) compared to HIV− women with CD4

### Table 1. Baseline Characteristics of Study Population by HIV Status and CD4 Cell Count

| Participant characteristics | HIV positive | All HIV positive | p-value<sup>a,b</sup> |
|----------------------------|--------------|-----------------|-----------------------|
| HIV negative (n = 213)      | CD4 >350 (n = 177) | CD4 200–350 (n = 240) | CD4 <200 (n = 255) |
| Age (years)                 |              |                 |                       |
| <30                        | 33 (15.5)    | 47 (26.6)       | 48 (20.0)             | 53 (23.6) |<0.001 | 148 (23.1) |
| 30–40                      | 56 (26.3)    | 97 (54.8)       | 136 (56.7)            | 125 (55.6) |358 (55.8) |
| 41+                        | 124 (58.2)   | 33 (18.6)       | 56 (23.3)             | 47 (20.9)  |136 (21.2) |
| Income (Rwandan Francs)     |              |                 |                       |
| <10,000                    | 86 (44.5)    | 57 (32.8)       | 87 (36.8)             | 82 (37.6)  |0.06 |226 (35.9) |
| 10,000–35,000              | 74 (38.3)    | 96 (55.2)       | 119 (50.4)            | 101 (46.3) |316 (50.3) |
| >35,000                    | 33 (17.1)    | 21 (12.1)       | 30 (12.7)             | 35 (16.1)  |86 (13.7)  |
| Alcohol use, n (%)          |              |                 |                       |
| <00%                       | 52 (27.4)    | 36 (21.2)       | 51 (22.1)             | 46 (21.5)  |0.43 |133 (21.6) |
| Body mass index (kg/m²) Mean ± SD | 21.32 ±3.8 | 21.87 ±3.9 | 21.84 ±3.8 | 21.07 ±3.4 | 0.15 |21.58 ±3.7 |
| Albumin (mean ± SD), mg/dl  | 3.94 ±0.4    | 3.58 ±0.6       | 3.46 ±0.7             | 3.26 ±0.6  |<0.001 |3.43 ±0.6 |
| Creatinine, mg/dl (mean ± SD) | 0.85 ±0.19 | 0.91 ±0.2 | 0.93 ±0.2 | 0.94 ±0.2 |<0.001 |0.93 ±0.2 |
| Bactrim and/or Dapsone use in prior year n (%) | 38 (18.6) | 127 (72.9) | 219 (91.2) | 202 (91.4) |<0.001 |548 (86.3) |
| AST > or ALT >43 mg/dl      | 14 (6.6)     | 21 (11.8)       | 23 (9.6)              | 37 (16.4)  |0.01 |81 (12.6)  |
| Albumin <3.5 g/dl           | 42 (20.1)    | 72 (40.9)       | 119 (50.0)            | 138 (62.7) |<0.001 |329 (51.9) |

<sup>a</sup>p value is from chi-square test comparing all four HIV/CD4 groups (HIV negative, HIV+ CD4 >350, HIV+ CD4 200–350, HIV+ CD4 <200).

<sup>b</sup>Analysis of variance tested for differences among continuous variables among groups defined by HIV/CD4 groups.

n (%) for categorical variables or mean ± standard deviation for continuous variables.

ALT, alanine aminotransferase, AST, aspartate aminotransferase.
counts >350 cells/μl. Higher monthly income (>35,000 Rwandan francs (FRW) equivalent to 60$ US) was associated with a 40% lower risk of having low serum albumin compared to patients with lower income (<10,000 FRW or 17$) (OR = 0.61, 95% CI: 0.41, 0.99) after excluding the HIV group that was confounding the association between income and serum albumin. Higher BMI (>25 kg/m²) was protective against low serum albumin; the risk of having low serum albumin decreased by 70% compared to women with lower BMI (<18.5 kg/m²) (OR = 0.30, 95% CI: 0.16, 0.55). Older age (>40 years) was associated with lower serum albumin compared to younger age (<30 years) (OR = 2.2, 95% CI: 1.28, 3.71).

Discussion
In this study of ART-naive HIV-infected and HIV-uninfected Rwandan women, HIV serostatus was associated with

### Table 2. Factors Associated with Elevated Liver Enzymes (Aspartate Aminotransferase >43 or Alanine Aminotransferase >43 U/liter) in Unadjusted and Multivariate Analyses for All Subjects

| Parameter                          | Unadjusted OR (95% CI) | Overall p-value | p-value | Adjusted OR (95% CI) | Overall p-value | p-value |
|-----------------------------------|------------------------|-----------------|---------|----------------------|-----------------|---------|
| HIV+ vs. HIV-                      | 2.05 (1.14, 3.70)      | 0.02            |         | 4.36 (1.91, 9.97)    | <0.001          |         |
| Age (years)                        |                        |                 |         |                      |                 |         |
| <30                                | 1                      |                 |         |                      |                 |         |
| 30–40                              | 0.66 (0.39, 1.11)      | 0.11            | 0.70 (0.40, 1.21) | 0.19             |                 |         |
| >41                                | 0.72 (0.41, 1.27)      | 0.25            | 0.79 (0.41, 1.52) | 0.48             |                 |         |
| Income (Rwf)                       |                        |                 |         |                      |                 |         |
| <10,000                            | 1                      |                 |         |                      |                 |         |
| 10,000–35,000                      | 0.59 (0.37, 0.94)      | 0.03            | 0.52 (0.31, 0.87) | 0.01             |                 |         |
| >35,000                            | 0.76 (0.40, 1.46)      | 0.41            | 0.72 (0.36, 1.46) | 0.36             |                 |         |
| Alcohol use (yes vs. no)           | 1.41 (0.86, 2.31)      | 0.17            | 1.47 (0.88, 2.46) | 0.14             |                 |         |
| Body mass index (kg/m²)            |                        |                 |         |                      |                 |         |
| <18.5                              | 1                      |                 |         |                      |                 |         |
| 18.5–25                            | 1.32 (0.74, 2.34)      | 0.34            | 1.44 (0.78, 2.67) | 0.25             |                 |         |
| >25                                | 1.15 (0.54, 2.46)      | 0.71            | 1.40 (0.61, 3.19) | 0.43             |                 |         |
| Bacitracin and/or Dapsone use in prior year (yes vs. no) | 1.00 (0.63, 1.60) | 0.99 | 0.51 (0.28, 0.93) | 0.02 |                 |
| Serum creatinine >1 mg/dl vs. <1 mg/dl | 1.07 (0.67, 1.73) | 0.76 | 1.15 (0.69, 1.91) | 0.58 |                 |

All variables are included in the multivariate model.

### Table 3. Factors Associated with Elevated Liver Enzymes (Aspartate Aminotransferase >43 or Alanine Aminotransferase >43 U/liter in Unadjusted and Multivariate Analyses Restricted to HIV Positive Subjects

| Parameter                          | Unadjusted OR (95% CI) | Overall p-value | p-value | Adjusted OR (95% CI) | Overall p-value | p-value |
|-----------------------------------|------------------------|-----------------|---------|----------------------|-----------------|---------|
| CD4 groups                         |                        |                 |         |                      |                 |         |
| CD4 >350                          | 1                      |                 |         |                      |                 |         |
| CD4 200–350                        | 0.78 (0.42, 1.44)      | 0.43            | 0.86 (0.44, 1.70) | 0.66             |                 |         |
| CD4 <200                           | 1.44 (0.81, 2.57)      | 0.21            | 1.66 (0.88, 3.14) | 0.11             |                 |         |
| Age (years)                        |                        |                 |         |                      |                 |         |
| <30                                | 1                      |                 |         |                      |                 |         |
| 30–40                              | 0.65 (0.38, 1.13)      | 0.12            | 0.74 (0.42, 0.32) | 0.32             | 0.30            |         |
| >40                                | 0.74 (0.38, 1.44)      | 0.37            | 0.70 (0.34, 1.47) | 0.35             |                 |         |
| Alcohol use (yes vs. no)           | 1.65 (0.97, 2.81)      | 0.06            | 1.65 (0.95, 2.86) | 0.07             |                 |         |
| Income (Rwf)                       |                        |                 |         |                      |                 |         |
| <10,000                            | 1                      |                 |         |                      |                 |         |
| 10,000–35,000                      | 0.58 (0.35, 0.96)      | 0.03            | 0.55 (0.32, 0.95) | 0.03             |                 |         |
| >35,000                            | 0.67 (0.32, 1.42)      | 0.29            | 0.56 (0.25, 1.25) | 0.15             |                 |         |
| Body mass index (kg/m²)            |                        |                 |         |                      |                 |         |
| <18.5                              | 1                      |                 |         |                      |                 |         |
| 18.5–25                            | 1.06 (0.57, 1.95)      | 0.85            | 1.22 (0.64, 2.31) | 0.55             |                 |         |
| >25                                | 0.86 (0.37, 1.96)      | 0.71            | 1.17 (0.48, 2.82) | 0.73             |                 |         |
| Bacitracin and/or Dapsone use in prior year (yes vs. no) | 1.22 (0.78, 1.90) | 0.30 | 1.10 (0.67, 1.80) | 0.71 |                 |
| Serum creatinine >1 mg/dl vs. <1 mg/dl | 0.55 (0.30, 0.99) | 0.045 | 0.50 (0.26, 0.96) | 0.03 |                 |

All variables are included in the multivariate model.
markers of liver damage. The prevalence of liver transaminase abnormalities and impaired synthetic function was higher in HIV+ than HIV− women. Among the HIV-infected women there was no significant difference in liver enzymes across CD4 categories. Even though the prevalence of liver transaminase abnormalities was higher in HIV-infected women with CD4 <200 compared to CD4 >350, this difference was not statistically significant, suggesting that elevated liver enzymes are mainly due to HIV infection rather than HIV disease progression as a further contributing factor in this process.

Studies from resource-rich countries suggest that HIV infection is associated with a higher prevalence of elevated liver enzymes. A study of prevalence and factors associated with liver test abnormalities among HIV-infected persons in San Diego, California found that 27% of HIV+ patients had abnormal liver test results during a 6-month study period after ART initiation. However, the excess

Table 4. Factors Associated with Albumin (<3.5 vs. ≥3.5 g/dl) in Unadjusted and Multivariate Analysis for All Subjects

| Parameter                   | Unadjusted OR (95% CI) | Overall p-value | Adjusted OR (95% CI) | Overall p-value |
|-----------------------------|------------------------|-----------------|----------------------|----------------|
| HIV+ vs HIV−                | 4.29 (2.96, 6.22)      | <0.001          | 5.68 (3.32, 9.71)    | <0.001         |
| Age (years)                 |                        |                 |                      |                |
| <30                         | 1                      | 0.51            | 1                    | 0.003          |
| 30–40                       | 1.22 (0.85, 1.74)      | 0.27            | 1.20 (0.81, 1.77)    | 0.36           |
| >40                         | 1.21 (0.82, 1.79)      | 0.33            | 2.08 (1.31, 3.30)    | 0.002          |
| Income (Rwf)                |                        | 0.054           |                      | 0.28           |
| <10,000                     | 1                      |                 | 1                    |                |
| 10,000–35,000               | 0.94 (0.70, 1.26)      | 0.68            | 0.88 (0.63, 1.24)    | 0.46           |
| >35,000                     | 0.61 (0.39, 0.94)      | 0.02            | 0.68 (0.41, 1.11)    | 0.12           |
| Body mass index (kg/m²)     |                        | <0.001          |                      | <0.001         |
| <18.5                       | 1                      |                 | 1                    |                |
| 18.5–25                     | 0.56 (0.40, 0.80)      | <0.001          | 0.53 (0.36, 0.78)    | <0.001         |
| >25                         | 0.39 (0.24, 0.62)      | <0.001          | 0.39 (0.23, 0.66)    | <0.001         |
| Alcohol use (yes vs. no)    | 0.88 (0.63, 1.23)      | 0.44            | 1.02 (0.71, 1.46)    | 0.92           |
| Bactrim and/or Dapsone use  | 2.25 (1.65, 3.09)      | <0.001          | 0.97 (0.63, 1.51)    | 0.89           |
| Serum creatinine ≤1 vs. >1  | 1.11 (0.82, 1.50)      | 0.51            | 0.97 (0.69, 1.36)    | 0.86           |

Table 5. Factors Associated with Albumin (<3.5 vs. ≥3.5 g/dl) in Unadjusted and Multivariate Analysis Restricted to HIV-Positive Subjects

| Parameter                   | Unadjusted OR (95% CI) | Overall p-value | Adjusted OR (95% CI) | Overall p-value |
|-----------------------------|------------------------|-----------------|----------------------|----------------|
| CD4 groups                  |                        |                 |                      |                |
| CD4 >350                    | 1                      |                 | 1                    |                |
| CD4 200–350                 | 1.45 (0.98, 2.15)       | <0.06           | 1.57 (1.01, 2.43)    | <0.04          |
| CD4 <200                    | 2.44 (1.62, 3.67)       | <0.001          | 2.62 (1.66, 4.14)    | <0.001         |
| Age (years)                 |                        | 0.004           |                      |                |
| <30                         | 1                      |                 | 0.005                |                |
| 30–40                       | 1.11 (0.76, 1.64)       | 0.58            | 1.12 (0.74, 1.72)    | 0.58           |
| >40                         | 2.08 (1.29, 3.36)       | 0.003           | 2.18 (1.28, 3.71)    | 0.004          |
| Income (Rwf)                |                        | 0.08            |                      | 0.49           |
| <10,000                     | 1                      |                 |                      |                |
| 10,000–35,000               | 0.70 (0.50, 0.99)       | 0.04            | 0.84 (0.57, 1.23)    | 0.36           |
| >35,000                     | 0.62 (0.37, 1.02)       | 0.05            | 0.61 (0.41, 0.99)    | 0.04           |
| Body mass index (kg/m²)     |                        | <0.001          |                      | <0.001         |
| <18.5                       | 1                      |                 | 1                    |                |
| 18.5–25                     | 0.37 (0.24, 0.57)       | <0.001          | 0.38 (0.24, 0.61)    | <0.001         |
| >25                         | 0.26 (0.15, 0.45)       | <0.001          | 0.30 (0.16, 0.55)    | <0.001         |
| Alcohol use (yes vs. no)    | 0.95 (0.65, 1.40)       | 0.81            | 1.11 (0.73, 1.68)    | 0.63           |
| Bactrim and/or Dapsone use  | 0.85 (0.54, 1.35)       | 0.49            | 0.67 (0.39, 1.15)    | 0.14           |
| Serum creatinine ≤1 vs. >1  | 0.91 (0.65, 1.27)       | 0.57            | 0.97 (0.66, 1.41)    | 0.85           |

All variables are included in the multivariate model.
elevated liver enzymes observed in the latter study might be due to ART intake in contrast to our study in which all HIV+ women were ART naive. Contrary to studies conducted in developed countries, a prospective study of outpatients in Uganda found that the risk of clinically significant hepatotoxicity was low, even in patients on ART.13 Similarly, the prevalence of liver abnormalities observed in our study is lower than that reported in studies from developed countries among HIV-infected persons.16,22 However, other factors need be considered when comparing studies from sub-Saharan Africa and those from developed countries as HIV-infected persons in the resource-rich countries are more likely to have chronic HCV infection, which itself is associated with grade III–IV liver enzyme elevation,25 and to be obese with nonalcoholic fatty liver disease.

We observed a significant association of low serum albumin with HIV infection. This trend remains in multivariate models that adjust for other factors, which suggests the possibility that the liver injury could be partially due to the effect of HIV infection itself. Some studies suggest that HIV can alter the permeability of the gastrointestinal tract, leading to increased levels of circulating lipopolysaccharide that may affect liver function parameters,24 and in advanced HIV infection, there is an elevated rate of protein turnover, which persists irrespective of sufficient intake of calories and protein.25 Much of this is thought to be driven by an increase in circulating inflammatory factors. Elevated circulating concentrations of cytokines such as tumor necrosis factor (TNF), interleukin (IL)-6, and interferon (IFN)-x have been demonstrated in subjects with HIV infection and have significant effects on protein metabolism.25,26 A possible mechanism of the pathogenesis of liver damage in our study is that when HIV infection progresses and the CD4 count falls the whole-body protein turnover is increased. The whole-body protein turnover is markedly increased in stage IV HIV infection despite normal protein balance.25

Contrary to other studies we found no association between alcohol consumption and serum liver enzyme activities.27,28 The possible reason is that HIV-infected persons were educated on risk factors for HIV disease progression (that drug and alcohol use can interfere with their treatment or impair judgment and lead to risky behaviors) and thus avoided taking alcohol. Another possible reason is that having our study subjects consisting only of women could have decreased the effect of alcohol consumption as a recent study found that male gender was associated with liver enzyme elevations.13

Our study did not find any association between BMI and liver enzymes. The fact that BMI was not associated with elevated liver enzymes in our study population, contrary to studies from developed countries,26,30 may be explained by the fact that the large majority of women in our study population were lighter, with a mean BMI around 21 kg/m², and thus did not have a predisposition to hepatic steatosis. We did find, however, that a higher BMI was associated with a lower risk of low serum albumin; serum albumin <3.5 mg/dl was 70% and 62% lower in women with BMI >25 and 18.5–25 kg/m², respectively, compared to women with BMI <18.5 (p < 0.001). Previously published data from this population showed that HIV− subjects with low BMI tended to have serum albumin levels in the normal range, whereas the mean serum albumin among HIV+ women with low BMI was well below the lower limit of normal.31 This suggests a specific effect of advanced HIV disease in lowering serum albumin rather than a direct association of low albumin with low BMI. Our findings are similar to other studies among HIV-infected persons, which showed that albumin <3.5 mg/dl was associated with faster HIV disease progression and mortality in HIV-infected women,31,32 and suggests that impaired albumin synthesis is probably a consequence of HIV infection. Furthermore, the association between higher income and lower odds of serum albumin suggests that micronutrient intake and diet quality are affected by socioeconomic status (SES). In a study assessing whether social class predicts diet quality, Darmon and colleagues found that SES or income inequality variables may have a causal influence on diet quality.33

This study is limited by generalizability to men as the study population included only women. Second, we lacked data on hepatitis B and C viral infections and therefore we could not take into account coexisting liver infections that may have caused increases in liver enzymes. However, a recent study in Rwanda indicated no statistical differences in median ALT and AST levels at baseline and 12 months post-ART between HBV- and HCV-exposed and unexposed groups.34 Additionally, this population essentially had no exposure to illicit drug use (IDU), which may suggest that a low prevalence of HCV and HIV/HCV coinfections is likely to be less common in East Africa due to the differences in transmission routes.35 We utilized self-reported alcohol use, which is subject to underreporting due to the cultural stigma associated with alcohol consumption among women in Rwanda, but alcohol use in our setting appears to be very low.

In summary, our findings suggest that liver injury in ART-naive HIV-infected African women could partially be due to the effect of HIV infection itself, and that liver abnormalities were less common than previously reported in developed countries. Impaired liver synthesis is probably a consequence of advanced HIV disease. Future studies of the association between HIV infection and liver function in low-income settings, using direct or indirect liver damage measures (e.g., imaging) to improve recognition, diagnosis, and management, should be considered. In addition, prospective research on HIV infection, liver disease progression, and ART effects on reducing aminotransferase levels in these patients should be developed in order to determine the incidence of liver abnormalities and to establish causal relationships. Finally, given the critical importance of lipopolysaccharide and Kupffer cells in the pathogenesis of many forms of liver injury, the measurement of soluble CD14 might provide some indication of whether increased Kupffer cell activation might be driving the transaminase increase.

Acknowledgments

We acknowledge RWISA participants for their valuable time and commitment, and particularly acknowledge all research staffs for their contribution to this study.

This study was funded by supplements from the National Institute of Allergy and Infectious Diseases to the Bronx/Manhattan Women’s Interagency HIV Study (WHIS, U01-AI-35004), the Center for AIDS Research of the Albert Einstein College of Medicine and Montefiore Medical Center funded by the National Institutes of Health (NIH AI-51519),
the National Institute of Diabetes and Digestive and Kidney Disease (DK54615), and the Central Africa International Epidemiologic Databases to evaluate AIDS (5U01-AI-096299). Additional support was provided by the AIDS International Training and Research Program (Fogarty International Center, NIH D43-TW001403). Its contents are solely the responsibility of the authors and do not necessarily represent the official view of the NCRR or NIH. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author Disclosure Statement

The authors declare no competing financial interests.

References

1. Fauci AS: Twenty-five years of HIV/AIDS. Science 2006; 313(5786):409.
2. Blacker J: The impact of AIDS on adult mortality: Evidence from national and regional statistics. AIDS 2004; 18(Suppl 2):S19–26.
3. UNAIDS: AIDS Epidemic updates: Geneva Switzerland. Joint United Nations Programme on HIV/AIDS, 2006.
4. Morse CG and Kovacs JA: Metabolic and skeletal complications of HIV infection: The price of success. JAMA 2006;296(7):844–854.
5. Wanke CA: Epidemiological and clinical aspects of the metabolic complications of HIV infection: The fat redistribution syndrome. AIDS 1999;13(11):1287–1293.
6. Pol S, Lebray P, and Vallet-Pichard A: HIV infection and hepatic enzyme abnormalities: Intricacies of the pathogenic mechanisms. Clin Infect Dis 2004;38(Suppl 2):S65–72.
7. Nunez M: Hepatotoxicity of antiretrovirals: Incidence, mechanisms and management. J Hepatol 2006;44(1 Suppl): S132–139.
8. Zechini B, Pasquazzi C, and Aceti A: Correlation of serum aminotransferases with HCV RNA levels and histological findings in patients with chronic hepatitis C. The role of serum aspartate transaminase in the evaluation of disease progression. Eur J Gastroenterol Hepatol 2004;16(9): 891–896.
9. Sterling RK and Sulkowski MS: Hepatitis C virus in the setting of HIV or hepatitis B virus coinfection. Semin Liver Dis 2004;24(Suppl 2):61–68.
10. Paella FJ Jr, Delaney KM, Moorman AC, et al.: Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 1998;338(13):853–860.
11. Palmon R, Koo BC, Shoultz DA, and Dieterich DT: Lack of hepatotoxicity associated with nonnucleoside reverse transcriptase inhibitors. J Acquir Immune Defic Syndr 2002; 29(4):340–345.
12. Mata-Marín JA, Gaytan-Martinez J, Grados-Chavarría BH, et al.: Correlation between HIV viral load and aminotransferases as liver damage markers in HIV infected naive patients: A concordance cross-sectional study. Virol J 2009; 6:181.
13. Ocama P, Castelnuovo B, Kamya MR, et al.: Low frequency of liver enzyme elevation in HIV-infected patients attending a large urban treatment centre in Uganda. Int J STD AIDS 2010;21(8):553–557.
14. Ingliz P, Valantin MA, Duvivier C, et al.: Liver damage underlying unexplained transaminase elevation in human immunodeficiency virus-1 mono-infected patients on antiretroviral therapy. Hepatology 2009;49(2):436–442.
15. Crum-Cianflone N, Dilay A, Collins G, et al.: Nonalcoholic fatty liver disease among HIV-infected persons. J Acquir Immune Defic Syndr 2009;50(5):464–473.
16. Clark JM, Brancati FL, and Diehl AM: The prevalence and etiology of elevated aminotransferase levels in the United States. Am J Gastroenterol 2003;98(5):960–967.
17. Limdi JK and Hyde GM: Evaluation of abnormal liver function tests. Postgrad Med J 2003;79(932):307–312.
18. Ruhl CE and Everhart JE: Elevated serum alanine aminotransferase and gamma-glutamyltransferase and mortality in the United States population. Gastroenterology 2009; 136(2):477–485.
19. Koethe JR, Blevins M, Nyirenda C, et al.: Nutrition and inflammation serum biomarkers are associated with 12-week mortality among malnourished adults initiating antiretroviral therapy in Zambia. J Int AIDS Soc 2011;14:19.
20. Group. ACT. Table of grading severity of adult adverse experiences. US Division of AIDS, National Institute of Allergy and Infectious Diseases, Rockville, MD, 1996.
21. Sterling RK, Chiu S, Snider K, and Nixon D: The prevalence and risk factors for abnormal liver enzymes in HIV-positive patients without hepatitis B or C coinfections. Dig Dis Sci 2008;53(5):1375–1382.
22. Crum-Cianflone N, Collins G, Medina S, et al.: Prevalence and factors associated with liver test abnormalities among human immunodeficiency virus-infected persons. Clin Gastroenterol Hepatol 2010;8(2):183–191.
23. Sulkowski MS, Thomas DL, Chaisson RE, and Moore RD: Elevated liver enzymes following initiation of antiretroviral therapy. JAMA 2000;283(19):2526–2527.
24. Crane M, Iser D, and Lewin SR: Human immunodeficiency virus infection and the liver. World J Hepatol 2012;4(3): 91–98.
25. Macallan DC and Griffin GE: Metabolic disturbances in AIDS. N Engl J Med 1992;327(21):1530–1531.
26. Breen EC, Rezai AR, Nakajima K, et al.: Infection with HIV is associated with elevated IL-6 levels and production. J Immunol 1990;144(2):480–484.
27. Grant BF, Dufour MC, and Harford TC: Epidemiology of alcoholic liver disease. Sem Liver Dis 1988;8(1):12–25.
28. Ataloto PI, Kioivistho HM, Hietala JP, et al.: Effect of moderate alcohol consumption on liver enzymes increases with increasing body mass index. Am J Clin Nutr 2008; 88(4):1097–1103.
29. Ruhl CE and Everhart JE: Determinants of the association of overweight with elevated serum alanine aminotransferase activity in the United States. Gastroenterology 2003; 124(1):71–79.
30. Kovari H, Ledergerber B, Battegay M, et al.: Incidence and risk factors for chronic elevation of alanine aminotransferase levels in HIV-infected persons without hepatitis B or C virus co-infection. Clin Infect Dis 2010;50(4):502–511.
31. Mehta SH, Astemborski J, Sterling TR, et al.: Serum albumin as a prognostic indicator for HIV disease progression. AIDS Res Hum Retroviruses 2006;22(1):14–21.
32. Feldman JG, Burns DN, Gange SJ, et al.: Serum albumin as a predictor of survival in HIV-infected women in the Women's Interagency HIV study. AIDS 2000;14(7): 863–870.
33. Darmon N and Drewnowski A: Does social class predict diet quality? Am J Clin Nutr 2008;87(5):1107–1117.
34. Rusine J, Ondoa P, Asiimwe-Kateera B, et al.: High seroprevalence of HBV and HCV infection in HIV-infected adults in Kigali, Rwanda. PloS One 2013;8(5): e63303.

35. Taylor LE, Swan T, and Mayer KH: HIV coinfection with hepatitis C virus: Evolving epidemiology and treatment paradigms. Clin Infect Dis 2012;55(Suppl 1): S33–42.

Address correspondence to:
Jean Claude Dusingize
Regional Alliance for Sustainable Development
P.O. Box 5141
Kigali
Rwanda

E-mail: dusingize@gmail.com