Original Article

HCV Co-infection is Associated with Metabolic Abnormalities among HAART naive HIV-infected Persons

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ABSTRACT

Objectives: To determine the metabolic abnormalities among Hepatitis C Virus (HCV) coinfected HAART naïve HIV infected persons within the adult ARV clinic of the University College Hospital/University of Ibadan, Ibadan, Nigeria **Methods:** This was a retrospective study involving the review of clinical records of newly recruited HIV-infected persons in the adult antiretroviral (ARV) clinic over a 12month period (January - December 2006). Baseline results for fasting plasma glucose (FPG) and fasting lipid profile were retrieved. **Results:** Out of the 1,260 HIV infected persons seen during the study period, HCV co-infection was found in 75 (6%) persons. The median values for total cholesterol, LDL-cholesterol and HDL-cholesterol were lower in the HCV co-infected persons. HIV-HCV co–infection was associated with a 0.31 mmol/L depression in Total Cholesterol (TC). The median FPG concentration was significantly higher in HIV-HCV co–infected than HIV only infected persons (5.33mmol/L vs. 5.00mmol/L, p = 0.047). However, regression analysis showed there was no relationship between the HIV-HCV coinfected state and fasting glucose levels. **Conclusion:** HIV-HCV co-infection may be associated with a predictable decline in plasma cholesterol, but FPG may not be sufficient to demonstrate insulin resistance in these persons.

Keywords: *HCV, HIV, metabolic abnormalities*

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Introduction

HIV with Hepatitis C virus (HCV) co-infection is relatively common.[1] This is due to the sharing of common risk factors for transmission.[2] Prevalence of HCV co-infection varies across geographic regions depending on the predominant mode of HIV transmission. In places where a significant burden of HIV transmission is through intravenous drug use, prevalence of HCV co-infection can be up to 99%.[3] In regions with predominantly heterosexual HIV transmission such as sub-Saharan Africa, HCV co-infection prevalence ranges between 1.9-14.7%.[4-6] HCV coinfection does not seem to negatively impact the natural course of HIV infection.[1] It is, however, associated with increased risk of antiretroviral-associated hepatotoxicity.[7] On the contrary, the effect of HIV on the course of HCV infections is an accelerated rate of liver fibrosis with increased mortality rates.[8]

Both of these infections have been independently associated with a variety of metabolic abnormalities that affect both lipid and glucose metabolism. HIV infection is associated with a high prevalence of dyslipidemia and dysglycemia.[9] In the absence of treatment, more advanced HIV disease is associated with additional atherogenic changes such as hypertriglyceridemia and low HDL-C as well as glucose intolerance.[9-11] Similarly, studies suggest that chronic HCV infection is a metabolic disease characterized by hepatic steatosis, hypocholesterolemia and/or insulin resistance/diabetes mellitus.[12,13] Genotype specific mechanisms are believed to determine the metabolic abnormality observed in chronic HCV infection. This is suggested by the predominant metabolic effects of hypocholesterolemia and hepatic steatosis with HCV genotype 3 infections and insulin resistance (IR) and Diabetes Mellitus with non-G3 genotypes such as HCV G2 and genotypes 1 and 4.[14] A recent report suggests that the combined effects of

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HIV/HCV infection on glucose and lipid metabolism may also be affected by host genetic influences. The presence of interleukin 28 receptor alpha (IL28RA) polymorphisms and ADIPOQ rs2241766 G allele (GG/GT genotype) have been shown to influence the glucose and lipid abnormalities observed in HIV/HCV co-infected persons.[15,16]

The metabolic changes observed in HIV-HCV co-infected persons have clinical consequences. Insulin resistance has been shown to be associated with progression of hepatic fibrosis and reduction in both rapid virological response and sustained virological response to peginterferon and ribavirin.[17,18] The contrary may be true for hypocholesterolemia.[19] Reports also suggest that HCV co-infection may prevent hyperlipidemia which may be induced by HAART.[20,21] This study was undertaken to describe the effects of HIV-HCV coinfection on lipid and glucose metabolism among a Nigerian population of ART naïve HIV infected persons.

Materials and Methods

This was a retrospective study in which clinical and laboratory records of persons attending the adult ARV clinic of the University College Hospital/University of Ibadan, Ibadan, Nigeria were reviewed and analyzed. The UCH/UI ARV clinic was established in 2002. HIV infected persons were enrolled into the adult ARV clinic if they were aged 15 years or older. HIV infection was confirmed by a Western Blot assay. Pregnant HIV infected women were excluded from this study.

The medical records or case notes were reviewed to extract the physical examination findings, baseline laboratory investigation results; full blood count, and clinical chemistries (Alanine Transaminase, Urea, Glucose, Creatinine, and a Complete Lipid Profile). Similarly, the sputum AFB and Chest X-ray findings and Serological screening for Hepatitis B and C, baseline CD4 cells/mm3 and HIV-1 RNA load were reviewed. This study was conducted from January to December 2006 and ethical clearance was obtained from the IRB of UCH/UI Ibadan.

Fasting blood samples were collected into specimen collection tubes containing Potassium EDTA and Fluoride oxalate for the measurement of lipids and glucose respectively. Plasma total cholesterol, HDL cholesterol, triglycerides, and glucose estimations were done on a Roche Hitachi 902 auto-analyzer (Roche Diagnostics Co, Indianapolis, IN) using standard Roche enzymatic kits (Roche Diagnostics, Basel, Switzerland). LDL cholesterol was calculated using the Friedewald formula (LDL-Cholesterol (mmol/L) = Total Cholesterol (mmol/L)-[HDL Cholesterol (mmol/L) + Triglycerides (mmol/L) /2.17]. CD4+ counts were measured with *Partec Cyflow* (Partec GmBH, Munster, Germany) and HIV RNA viral load with *Roche Amplicor® HIV1 version 1.5* (Roche Diagnostics, GmbH, Mannheim, Germany). Screening for Hepatitis B was done by detection of hepatitis B surface antigen (HBsAg) using a 3rd generation enzyme-linked immunoabsorbent assay (ELISA); and for testing for HCV antibodies (anti-HCV) using a 3rd generation assay.

Statistical Analysis

Data obtained was analyzed using the Statistical Package for Social Sciences (SPSS) version 17. Descriptive statistics were reported as means with standard deviation and median with interquartile range. Means were compared using the Student t test, Medians were compared using the Mann-Whitney *U* test while proportions were compared using the z test. Spearman's correlation was used to determine associations between variables. Simple and multiple linear regressions were employed to describe the relationships between metabolic parameters and HCV status. Level of statistical significance was set at $p < 0.05$.

Results

A total of 1,316 ART-naïve HIV-infected persons were recruited into the adult ART programme during the period studied. The characteristics of these persons have been previously described (11). Out of these, 1260 persons had the result of hepatitis C screening and thus, were used for further analysis. The Socio-demographic characteristics and baseline laboratory results of the 1260 persons are shown in Table 1 and Table 2 respectively.

The percentage of persons with Hepatitis C virus coinfection with Total Cholesterol < 3.89 mmol/L and LDL cholesterol < 2.59 mmol/L was significantly more than those without HCV co-infection (74.7% vs. 54.2%, $p = 0.004$; 82.7% vs. 69.8%, $p = 0.010$, both respectively). Two hundred and nine persons (16.6%) had impaired fasting glucose (> 2.85 mmol/L). There was no significant difference in the percentage of persons with impaired fasting glucose among the HCV coinfected persons (14.7%) compared with those without HCV co-infection (16.8%).

Table 3 shows results of simple linear regression of glucose and the cholesterol fractions against HCV co-infection status. HIV/HCV coinfection predicted a statistically significant reduction in all the cholesterol containing fractions. No such relationship existed between the HCV coinfection and glucose or triglycerides. The result of a multiple linear regression model that included, age > 40years, weight, gender, CD4 count, log viral load and HCV co-infectivity status is shown in Table 4. The model summaries for TC; HDL-C; LDL-C; TG and

Table 1: Socio-Demographic characteristics of study persons

Subjects	All	HIV only	HIV HCV	*p* value
n[a] (%)	1260	1185 (94)	75 (6.0)	–
Age (yrs.)[+]	35.2 (9.9)	35.1 (10.0)	36.1 (8.8)	0.286
Female	854 (67.8)	810 (68.4)	44 (58.7)	0.082
Male[a]	406 (32.2)	375 (31.6)	31 (41.3)	
Married[a]	767 (60.9)	726 (67.3)	41 (54.7)	0.256
Post–primary education[a]	836 (66.3)	786 (66.3)	50 (66.7)	0.952

Values-[a] n (%); * Significant at p < 0.05

Table 2: Clinical and laboratory characteristics of study persons

Subjects	All	HIV only	HIV/HCV	p value
Total Cholesterol (mmol/L)#	3.65 (1.55)	3.65 (1.55)	3.44 (1.16)	<0.001*
HDL–Cholesterol (mmol/L)#	1.01 (0.62)	0.96 (0.62)	0.78 (0.54)	<0.001*
LDL– Cholesterol (mmol/L)#	2.05 (1.40)	1.99 (1.37)	1.68 (1.11)	0.006*
Triglycerides (mmol/L)#	1.28 (0.79)	1.27 (0.80)	1.33 (0.77)	0.052
Glucose (mmol/L)#	5.00 (1.28)	5.00 (1.28)	5.33 (0.94)	0.047*
Weight (kg)+	56.6 (12.9)	56.8 (13.0)	53.9 (12.3)	0.098
CD4 count (cells/mm3)#	185 (295)	191 (301)	125 (211)	0.015*
Viral Load (log(10) copies/ml)#	5.04 (5.54)	5.04 (5.53)	5.22 (5.84)	0.089

[#] median (Interquartile Range); [+]mean (standard deviation); * Significant at p < 0.05

Table 3: Simple linear regression of metabolic parameters with HIV/HCV coinfection status

Variable (mmol/L)	Regression Coefficient (β)	95% Confidence Interval	p–value
Total Cholesterol	–0.41	–0.68; –0.13	0.003*
HDL–Cholesterol	–0.14	–0.25; –0.03	0.013*
LDL–Cholesterol	–0.29	–0.51; – 0.07	0.011*
Triglycerides	0.11	–0.06; 0.28	0.196
Glucose	0.20	–0.10; 0.51	0.188

* Significant at $p < 0.05$

Table 4: Coefficients from multiple linear regression of metabolic, clinical and demographic parameters

Variable	Total Cholesterol (mmol/L)	HDL–Cholesterol (mmol/L)	LDL–Cholesterol (mmol/L)	Triglycerides (mmol/L)	Glucose (mmol/L)
HCV presence	– 0.065 (0.037)	– 0.048 (0.126)	– 0.068 (0.029)	0.040 (0.210)	0.050 (0.124)
Male	– 0.167 (0.000)	– 0.084 (0.015)	– 0.122 (0.000)	– 0.051 (0.145)	– 0.041 (0.244)
Age >40yrs	0.048 (0.131)	0.036 (0.270)	0.050 (0.123)	– 0.003 (0.929)	0.061 (0.067)
Log CD4 count	0.002 (0.966)	– 0.018 (0.624)	– 0.020 (0.569)	– 0.066 (0.72)	– 0.066 (0.073)
Log Viral RNA load	– 0.126 (0.000)	– 0.171 (0.000)	– 0.136 (0.000)	0.064 (0.065)	0.048 (0.168)
Weight	0.199 (0.000)	0.138 (0.000)	0.162 (0.000)	– 0.065 (0.066)	0.041 (1.157

Values are β (*p* value)

glucose are $R2 = 0.092$, F (6,963) = 16.17, $p < 0.005$; $R 2 = 0.063$, F (6,962) = 10.97, $p < 0.005$; $R 2 = 0.067$, F (6,963) = 11.56,$p < 0.005$; $R2 = 0.024$, F (6,962) = 3.89, $p < 0.005$; $R2 = 0.092$, F (6,958) = 2.334, $p < 0.030$, all respectively. The presence of HCV co-infection predicted a decrease in all the cholesterol containing fractions. This was, however, only significant for TC and LDL-C.Table 1:

Discussion

This study found a significant association between the presence of HCV co-infection and significant reduction in plasma TC, HDL-C and LDL-C in HAART-naïve HIV infected Nigerian adults attending the ARV. The median TC was lower in HCV co-infected persons compared with those without the co-infection. It was demonstrated that the HIV/HCV co-infected state resulted in a decrease of 0.31 mmol/L and a decrease of 0.27 mmol/L in TC and LDL-C respectively. Although the HIV/HCV group had a significantly higher median fasting plasma glucose concentration, regression analysis did not show any significant relationship. These findings, to the best of our knowledge, are the first to be reported from sub-Saharan

Africa on the metabolic consequences of HIV/HCV co-infectivity.

The differences noted between the HIV-HCV coinfected persons and those without are modest compared to that reported by Floris-Moore *et al.* among HIV-infected men.[22] On univariate analysis of their data, the differences between the mean of the HCV uninfected group was about 0.98 mmol/L and 0.71 mmol/L lower than the HCV infected subjects for TC and LDL-C respectively. This was further demonstrated on multivariate analysis which showed that the population of HCV infected men had TC and LDL-C lower than the HCV uninfected men by 0.84 mmol/L and 0.58 mmol/L respectively. A possible contributory factor to the differences observed may be due to the genotype of the co-infecting HCV in the studied populations. Prati *et al*.[23] demonstrated that HCV-associated hypocholesterolemia was most evident with genotype 3 (G3), intermediate with genotype 1 (G1) and not significant with genotype 2.[23] In Nigeria, HCV subtypes described among a group of HIV infected persons were predominantly HCV G1, present in 75% of the subjects and HCV G2 in the remaining 25%.[24] This is similar to findings in the general population as reported from 2 communities in Nigeria where among 60 persons with HCV infection, genotype 1 comprised 85% and genotype 2, 15%.[25] We could not find any reports of HCV G3 in Nigeria. On the contrary, Floris-Moore reports from a population where over 10% of HCV may be due to the HCV G3.[26] The likely presence of this notably hypolipidemic genotype may be responsible for the lower cholesterol reported by the latter group. This may also be suggested by the results of multivariate analysis for the association of HCV coinfected status with triglycerides. HCV G3 has been noted to be associated with relevant hypertriglyceridemia compared with HCV non G3 phenotypes.[27] While this association was demonstrated among the population studied by Floris-Moore *et al.*,[22] it was not demonstrated among our people. The distinct biochemical effects of HCV G3 was also demonstrated by its ability to interfere with distal cholesterol synthesis pathway resulting in lower levels of lathosterol, 7-dehyrocholesterol and cholesterol but not lanosterol among persons with chronic hepatitis C.[14] This effect was not observed among a similar group of HCV G2 infected persons. The specific mechanism underlying this genotype specific perturbation has not been explained.

Regression analysis did not show any association between fasting glucose values and the presence of HCV co-infection. Reports by Forrester *et al* [28], Polgreen *et al* [29] and Howard et al[30], also did not find any significant association between co–infection and elevations in fasting glucose. Nevertheless, the latter authors demonstrated a significant effect of HCV con-infection and increased insulin resistance within the same group of persons. This will suggest that our findings, with regards to glucose metabolism among our persons may not be at variance with the fairly well established association of HCV infection, HIV infection and HIV/HCV co-infection with increased risk of development of hyperglycemia. What our findings do suggest is that the fasting glucose study may not be the test of choice in demonstrating insulin resistance among HIV/HCV co-infected persons. This was also suggested by Gianotti *et al*.[31] Among a group of 84 persons with long-standing HIV infection, the oral glucose tolerance test identified 7 persons with impaired glucose tolerance/diabetes mellitus who had normal fasting glucose measurements. This was despite the demonstration of significantly higher HOMA-IR values among the IGT/DM group, suggesting that FPG was not sufficiently sensitive to the degree of insulin resistance associated with IGT/DM. This seeming discord may be explained by the fact that abnormalities in FPG and the 2 hour post glucose load identify 2 different forms of insulin resistance. While persons with disorders of fasting glucose have predominantly hepatic insulin resistance and normal muscle insulin sensitivity, individuals with disorders of 2HPG have normal to slightly reduced hepatic insulin sensitivity and moderate to severe muscle insulin resistance.[32] Milner *et al*.[33] have demonstrated that chronic hepatitis C is associated peripheral rather than hepatic insulin resistance. This may explain the absence of an association between HCV co-infection and impairment in fasting glucose measurements. This implies that fasting glucose measurements may not be sensitive to the detection of insulin resistance in HCV, and by extension, in HCV/HIV infected persons.

This study has demonstrated that in the presence of HCV co-infection, cholesterol values are significantly lower in the HIV infected persons. Although both of these infections are known to be associated with insulin resistance, fasting glucose measurement alone may not reveal the insulin resistance expected in them.

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Conflicts of interest

There are no conflicts of interest.

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