

# Selected biochemical and hematological abnormalities in Nigerians with human immunodeficiency virus and hepatitis C virus coinfection

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**Background:** Liver disease has emerged as a major cause of morbidity and mortality in patients with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) coinfection, now that antiretroviral therapy has become more effective and has prolonged life expectancy in HIV-infected patients. The main objectives of this study were to determine the prevalence of HIV/HCV coinfection and the pattern of hematological and biochemical abnormalities associated with such dual infection.

**Methods:** In this study, patients with HIV infection (cases) were tested for anti-HCV antibodies. There was a control group made up of apparently healthy individuals who came to hospital for medical examination for various reasons. They also had an anti-HCV antibody test. Those who tested positive for anti-HCV antibodies among the cases and control subjects were further evaluated for hemoglobin concentration, total white cell count, platelet count, and liver function.

**Results:** One hundred and eighty HIV-infected patients and 180 control subjects participated in the study. The seroprevalence of anti-HCV antibodies in the HIV-infected patients and control subjects were 6.7% and 4.4%, respectively ( $P=0.57$ ). Serum total bilirubin, conjugated bilirubin, and alkaline phosphatase were significantly higher in the HIV/HCV coinfecting patients compared with their HCV mono-infected counterparts ( $P=0.0396$ ,  $0.0001$ , and  $0.0016$ , respectively). The mean hemoglobin, white cell count, platelet count, and CD4+ T lymphocyte count were significantly lower in the HIV/HCV coinfecting patients than the HCV mono-infected control group ( $P=0.0082$ ,  $0.0133$ ,  $0.0031$ , and  $0.0001$ , respectively).

**Conclusion:** The seroprevalence of anti-HCV antibodies in HIV-infected Nigerian patients is 6.7%. Patients with HIV/HCV coinfection have lower blood counts, higher serum bilirubin, and higher serum alkaline phosphatase compared with patients having HCV mono-infection.

**Keywords:** human immunodeficiency virus, hepatitis C virus, coinfection, biochemical, hematological abnormalities

## Introduction

Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) are global health problems. Due to shared routes of transmission, coinfection with the two viruses is common and represents an emerging area of interest both in clinical practice and research.<sup>1</sup>

In the US, 15%–30% of HIV-infected individuals are coinfecting with HCV.<sup>2,3</sup> However, the proportion of HIV-infected patients with HCV varies substantially according to the HIV risk factor. Among patients who acquired HIV from blood product transfusion or intravenous drug use, even higher rates (60%–90%) of HCV

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coinfection have been reported, whereas risk factors such as sexual transmission have lower rates.<sup>4</sup>

The mortality related to HIV has dropped considerably over the past 10–15 years with the introduction of highly active antiretroviral therapy.<sup>5</sup> Following the introduction of highly active antiretroviral therapy, there has been a sharp increase in the number of deaths due to end-stage liver disease among the HIV-HCV coinfecting population.<sup>6,7</sup> This has led to increased research into the evaluation and management of coinfecting patients.

Sexual transmission is the predominant source of the spread of the HIV/AIDS epidemic in sub-Saharan Africa.<sup>8</sup> Consequently, the HIV/HCV coinfection rate is expected to be lower than that in developed countries. In Gambia it was reported as 0.6%.<sup>9</sup> In Nigeria, prevalence rates ranging from 4.5% to 10.3% have been reported in various studies.<sup>10–13</sup> However, there are no published studies regarding HIV/HCV coinfection in south east Nigeria.

Management of each of these viral infections requires a rigorous process of proper clinical evaluation and laboratory testing which are mandatory, not only at the initiation of treatment, but have to be repeated several times in the course of follow-up. The process becomes even more complex when there is coinfection. Both viruses affect the liver individually,<sup>14–17</sup> and collectively.<sup>18–21</sup> It follows that the clinician needs to have a good idea of certain parameters of liver function in HIV/HCV coinfecting patients before, during, and after treatment. Therefore, this study was designed to determine the prevalence of HCV infection in HIV-infected patients and to evaluate selected biochemical and hematological indices.

## Methods and materials

This was a cross-sectional study of consecutive treatment-naïve HIV-infected patients seen at the University of Nigeria Teaching Hospital Enugu between May 2007 and April 2009. The study was approved by the University of Nigeria Teaching Hospital research ethics committee and informed consent was obtained from each participant before inclusion. There was a control arm made up of age-matched and gender-matched HIV-negative persons who came for pre-employment medical examination, a premarriage medical examination, or voluntary blood testing.

Venous blood (5 mL) was obtained from the cases and control subjects. Anti-HCV antibody was assayed in the two groups using a third-generation enzyme linked immunosorbent assay which utilizes recombinant HCV antigen manufactured by DRG International, Marburg, Germany.

This test has a sensitivity of 95%, a specificity of 97.5%, and a coefficient of variation  $\leq 15\%$ . Biochemical tests were also carried out on the sera of the HIV-infected patients (cases) and control subjects using the Bayer® Plus clinical chemistry analyzer. Hematological tests for the determination of hemoglobin, white cell count, and platelet count were carried out on the cases and control subjects using an automated hematology analyzer (Sysmex XT 2000i; Sysmex Corporation, Kobe, Japan). CD4+ T lymphocyte count was determined in HIV-infected patients using the CyFlow® Counter (Partec, Swedesboro, NJ).

## Statistical analysis

The data were analyzed using SPSS version 15.0 (SPSS Inc, Chicago, IL). Continuous variables were summarized as means  $\pm$  standard deviation, while categorical variables were presented as percentages. Differences between proportions were determined using the Chi-squared test, and *P* values  $\leq 0.05$  were considered statistically significant.

## Results

There were 180 HIV-infected patients (80 males [44.4%] and 100 females [55.6%]). There were also 180 control subjects (91 males [50.6%] and 89 females [49.4%]). The mean age of the HIV-infected patients was  $36.4 \pm 8.4$  years while the mean age of the control subjects was  $37.0 \pm 7.9$  years. Twelve HIV-infected patients (6.7%) and eight control subjects (4.4%) were anti-HCV positive. The difference between the proportions was not statistically significant (*P* = 0.57). Table 1 illustrates the anti-HCV serology status of the HIV-infected patients and control subjects.

Selected hematological indices in the cases and controls are depicted in Table 2. Mean hemoglobin concentration, mean leukocyte count, mean platelet count, and mean CD4+ T lymphocyte count were significantly lower in the HIV/HCV coinfecting patients compared with the HCV mono-infected individuals (*P* = 0.0082, 0.0133, 0.0031, and 0.0001, respectively). Conversely, serum total and conjugated bilirubin were significantly higher in the HIV/HCV coinfecting group compared with the HCV mono-infected group (*P* = 0.0396 and 0.0001, respectively). Serum alkaline phosphatase was

**Table 1** Anti-HCV in HIV-infected patients and control subjects

Group	Anti-HCV positive	Percentage
HIV-infected patients (n = 180)	12	6.7
Control subjects (n = 180)	8	4.4
Total (n = 360)	20	5.6

**Abbreviations:** HCV, hepatitis C virus; HIV, human immunodeficiency virus.

**Table 2** Selected hematological abnormalities in HIV/HCV coinfection and HCV mono-infection

Parameter	HIV/HCV coinfection	HCV mono-infection	t value	P value
Mean hemoglobin concentration (g/dL)	9.66 ± 1.80	12.47 ± 1.4	3.16	0.0082*
Total WBC ( $\times 10^9$ cells/ $\mu$ L)	4.04 ± 1.27	5.96 ± 0.89	2.95	0.0133*
Platelet count ( $\times 10^9$ cells/ $\mu$ L)	175.1 ± 80.85	333.6 ± 59.66	3.76	0.0031*
CD4+ T lymphocyte count (cells/ $\mu$ L)	220.5 ± 53.73	505.8 ± 90.4	5.81	0.0001*

**Note:** \*Statistically significant.

**Abbreviations:** HCV, hepatitis C virus; HIV, human immunodeficiency virus; WBC, white cell count.

significantly higher in the HIV/HCV coinfecting patients compared with their HCV mono-infected counterparts ( $P = 0.0016$ ). Table 3 shows selected biochemical abnormalities in the cases and controls.

## Discussion

In this study, the seroprevalence of anti-HCV antibodies in the HIV-infected patients was 6.7% while in the control group it was 4.4%. The difference was not statistically significant. There is a possibility that some of the HIV-infected patients may have tested falsely negative for anti-HCV because of profound immunosuppression, as shown by the significantly lower mean CD4+ T lymphocyte count. This pattern has been reported by other investigators.<sup>22,23</sup> In such situations, an HCV RNA assay would be the appropriate method for evaluating HCV infection. Unfortunately, that was not done in this study because of funding and technical constraints. Further studies including viral load estimation will shed more light on this.

Serum total and conjugated bilirubin were significantly higher in the HIV/HCV coinfecting patients compared with the HCV mono-infected patients ( $P = 0.0396$  and  $0.0003$ , respectively). Cholestasis is a recognized histological feature of HIV/HCV coinfection.<sup>24</sup> Whether the observed higher conjugated bilirubin level in the HIV/HCV coinfecting group is related to this histological finding cannot be inferred because liver biopsy was not part of the study.

Furthermore, there is a special form of hepatitis known as fibrosing cholestatic hepatitis which has a strong associa-

tion with immunosuppression. It is a rapidly progressive, sometimes fatal, form of liver injury originally reported in liver transplant recipients with recurrent hepatitis.<sup>25</sup> It has now been recognized frequently in chronic hepatitis B patients and hepatitis C patients under immunosuppression.<sup>26</sup> The histologic hallmarks in the liver include marked hepatocytic injury, severe cholestasis, and periportal and pericellular fibrosis.<sup>27,28</sup> In contrast with the pathogenesis of chronic hepatitis in immunocompetent patients attributed to cellular immune-mediated hepatocytolysis, fibrosing cholestatic hepatitis has been postulated to result from unimpeded viral replication within hepatocytes, culminating in a direct cytopathic effect in the setting of immunosuppression.<sup>29</sup> High-level expression of viral antigens (HbsAg and HbcAg) has been visualized directly by immunohistochemical staining in affected livers and measured by quantitative analysis, such as radioimmunoassay of tissue homogenates.<sup>30</sup> The possibility that higher serum conjugated bilirubin levels in HIV/HCV coinfecting patients represents an early stage in progression to fibrosing cholestatic hepatitis remains to be confirmed.

HIV infection modifies the natural history of HCV infection by accelerating the histological progression of HCV infection, leading to cirrhosis and end-stage liver disease in a shorter period of time.<sup>18,31–33</sup> Another way to explain the higher level of serum conjugated bilirubin in the HIV/HCV coinfecting group is to regard it as a manifestation of rapid histological progression to cirrhosis. The clinical importance of this observation is that such biochemical

**Table 3** Selected biochemical abnormalities in HIV/HCV coinfection and HCV mono-infection

Parameter	HIV/HCV coinfection	HCV mono-infection	t value	P value
Alanine transaminase (IU/L)	7.9 ± 1.29	8.0 ± 1.96	0.1122	0.9127
Aspartate transaminase (IU/L)	11.46 ± 1.73	11.16 ± 2.23	0.2755	0.7881
Total bilirubin ( $\mu$ mol/L)	23.89 ± 8.72	14.1 ± 3.95	2.334	0.0396*
Conjugated bilirubin ( $\mu$ mol/L)	13.55 ± 2.27	6.92 ± 1.43	5.808	0.0001*
Alkaline phosphatase (IU/L)	102.3 ± 17.37	58.2 ± 20.46	4.165	0.0016*
Total protein (g/L)	68.48 ± 6.90	69.36 ± 1.35	0.279	0.7854
Albumin (g/L)	34.60 ± 3.096	36.58 ± 3.527	1.066	0.3094

**Note:** \*Statistically significant.

**Abbreviations:** HCV, hepatitis C virus; HIV, human immunodeficiency virus; WBC, white cell count.

abnormalities may represent surrogate markers of liver disease progression. Larger prospective studies will be more elucidatory.

Hemoglobin concentration was significantly lower in the HIV/HCV coinfecting patients compared with the HCV mono-infected control subjects. This may be due to an additive or synergistic effect of the two infections in the coinfecting group. Anemia is a very common finding in patients with HIV infection, particularly in individuals with more advanced HIV disease.<sup>34</sup> The causes include changes in cytokine production with subsequent effects on hematopoiesis,<sup>35–37</sup> decreased erythropoietin concentration,<sup>38,39</sup> opportunistic infectious agents, such as *Mycobacterium avium* complex<sup>40</sup> and Parvovirus B19.<sup>41</sup> Other less common mechanisms include vitamin B12 deficiency<sup>42</sup> and autoimmune destruction of red blood cells.<sup>43</sup> Similarly, in untreated HCV mono-infection, different types of immune-mediated cytopenias might be severe and clinically significant. However, hemolytic anemia and severe thrombocytopenia are the most frequently observed cytopenias.<sup>44</sup> Pure red cell aplasia has also been reported in association with HCV infection.<sup>45</sup>

The mean platelet count was significantly lower in the HIV/HCV coinfecting patients compared with the HCV mono-infected group. Again, this may be due to an additive or a synergistic effect of the two infections. Thrombocytopenia was first associated with the acquired immune deficiency syndrome before the discovery of HIV.<sup>46</sup> The mechanisms involved include accelerated platelet clearance due to immune complex disease,<sup>47–49</sup> antiplatelet glycoprotein antibodies,<sup>50,51</sup> and/or anti-HIV antibodies that crossreact with platelet membrane glycoprotein (antigenic mimicry).<sup>52,53</sup> Direct infection of megakaryocytes results in defective platelet production and megakaryocytic apoptosis.<sup>54,55</sup> Similarly, thrombocytopenia is common in chronic HCV infection and the mechanisms include advanced liver fibrosis and manifest cirrhosis,<sup>56</sup> lack of hepatic-derived thrombopoietin,<sup>57</sup> direct cytopathic involvement of platelets and megakaryocytes,<sup>58,59</sup> and HCV-associated immunoglobulins which induce thrombocytopenia via an immunological mechanism similar to that operating in immune thrombocytopenic purpura.<sup>60</sup>

Leukopenia is inherent in HIV infection. Apart from lymphocyte depletion, which is the critical event, granulocytopenia is a problem commonly encountered with HIV infection.<sup>61</sup> The pathogenesis is multifactorial, including an autoimmune mechanism<sup>62,63</sup> and impaired granulopoiesis.<sup>64,65</sup>

In conclusion, the seroprevalence of anti-HCV antibody in HIV-infected Nigerian patients is 6.7%. Coinfecting

patients are more likely to have deranged hematological and biochemical parameters compared with HCV mono-infected patients. This may be due to an additive or a synergistic effect of the two infections.

## Disclosure

The authors report no conflicts of interest in this work.

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