

# EFFECT OF HEPATITIS C VIRUS INFECTION ON SELECTED LABORATORY VALUES IN PREGNANT WOMEN WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

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## ABSTRACT

**Background and Objectives:** Both hepatitis C and Human Immunodeficiency viruses affect laboratory indices. The objective of this study was to describe the impact of both viruses on laboratory indices among 1,821 HIV-positive pregnant women.

**Methods:** This was a cross-sectional retrospective study at the University College Hospital, Ibadan

**Results:** Twenty-six (1.7%) women were HCV positive, 139 (8.8%) were HBsAg positive and 1, 407 (89.3%) were negative for both viruses. Three patients (0.19%) were positive for both viruses. These patients, the HBsAg positive women and 246 with no result for either virus were excluded from analysis. The HCV positive women had lower hematocrit ( $27.3\% \pm 4.5$  vs.  $28.4\% \pm 4.6$ ,  $p=0.29$ ), lower WBC ( $5, 200$  vs.  $5, 500$  cells/ml,  $p=0.766$ ) but higher platelet count ( $209, 000$  vs.  $199, 000$  cells / ml,  $p=0.019$ ). The co-infected group had higher CD4 ( $380$  vs.  $326$  cells/ml,  $p=0.319$ ), higher urea ( $16.0$  vs.  $11.0$ mg/ml,  $p=0.013$ ) but comparable ALT ( $16.0$  vs.  $15.0$  iu/ml,  $p=0.95$ ), log viral load ( $4.08 \pm 1.22$  vs.  $4.08 \pm 1.11$ ,  $p=0.97$ ) and creatinine levels ( $0.6$  vs.  $0.6$ ,  $p=0.329$ ). Only the difference in urea level was statistically significant.

**Conclusion:** While values were comparable between both groups, the synergistic effect of both viruses makes it necessary for health-care providers to closely monitor patients.

**Keywords:** Hepatitis C, HIV, Pregnancy, Laboratory indices

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## INTRODUCTION

It has been estimated that about 170 million people (3.0% of world population) are infected with hepatitis C virus (HCV) making it a global health problem.<sup>1</sup>The risk factors for HCV infection vary depending on the region of the world. In the developed regions of the world, percutaneous

exposure through injection drug use is the primary mode of transmission of HCV.<sup>2</sup>In the developing regions of the world, however, predominant modes of HCV infection include inadequately screened blood transfusions and unsafe medical injections.<sup>1, 3</sup> Other modes of HCV transmission include mother-to-child transmission (a major route of infections with young

children)<sup>4</sup> and sexual transmission.<sup>5</sup> Although the mechanism is unclear, a higher risk of vertical transmission of HCV to infants born to Human Immunodeficiency virus (HIV) co-infected mothers has been reported.<sup>6</sup> The HIV and HCV share similar routes of transmission; hence HCV is more common in individuals infected with HIV than in the general population.<sup>7</sup>

Several workers have examined the impact of HIV infection on HCV progression with reports of increased risk for progression to cirrhosis or decompensated liver disease and increased risk for liver related death in co-infected patients.<sup>8, 9, 10, 11, 12, 13</sup> Factors influencing HCV disease progression in HIV co-infected patients include level of CD4 immunosuppression (especially patients with CD4 cell counts less than 500 cells/l),<sup>14</sup> older age at infection and excess alcohol intake.<sup>10</sup> Finally, with HCV acting as a carcinogen hepatocellular carcinoma (HCC) has been reported to occur at a younger age in HIV/ HCV co-infected patients.<sup>15</sup>

Similarly, the impact of HCV infection on the course of HIV disease has also been examined with various studies reporting that HCV infection appears to be associated with an increased risk of the progression of HIV to AIDS and increased risk of AIDS-related mortality.<sup>9, 16, 17</sup> In particular, HCV viral load has been found to have a detrimental effect on HIV progression, with increasing HCV viral load being associated with increased risk for progression to AIDS and risk for AIDS related mortality.<sup>16</sup> Other ways that HCV may impact care of the HIV-positive individual is its role as a strong predictor of the development of hepatotoxicity,<sup>18, 19</sup> transient increases in HCV viral load and transaminases with introduction of HAART.<sup>7</sup> The evidence from these studies is that while HIV is clearly associated with accelerated liver disease and reduced survival in HCV infected patients, HCV on the other hand is an independent factor associated with HIV progression to AIDS and AIDS related death.

With the increasing access to highly active anti-retroviral therapy (HAART) in sub-Saharan Africa (SSA), it is expected that AIDS-related deaths will decline. It must however be noted that there may be a sharp increase in the number of deaths among HIV/ HCV coinfecting individuals due to end-stage liver disease. This is because both viruses affect the liver individually<sup>20</sup> and collectively.<sup>21</sup> In addition, both viruses have been reported to have an impact on hematological

indices and renal function.<sup>22, 23</sup> Finally, an understanding of the impact of HCV on immunologic and virologic parameters of HIV – infected persons is necessary to inform prevention and management strategies. This study was designed to evaluate the impact of HCV co-infection on selected baseline laboratory values among a large population of HIV infected pregnant women in Nigeria.

## **MATERIALS AND METHODS**

The records of HIV-infected pregnant women who presented for care between January 1<sup>st</sup> 2006 and 31<sup>st</sup> December 2013, at the Prevention of mother-to-child transmission (PMTCT) unit of the University College Hospital, Ibadan (UCH) were reviewed. The University College Hospital Ibadan Antiretroviral Program offers PMTCT services provided by the Government of Nigeria with support initially from the HARVARD- President's Emergency Plan for AIDS Relief but now the AIDS Prevention Initiative in Nigeria (APIN) program. HIV-positive pregnant women access these services having been referred from the UCH antenatal clinic, and other clinics in the environs.

Variables recorded at the first clinic visit include socio-demographic characteristics and hepatitis B and C status. In addition, selected baseline biochemical indices, haematological indices, CD4 cells counts and viral load are also determined. These baseline laboratory testing are conducted using 3<sup>rd</sup> generation enzyme-linked immunosorbent assay (ELISA) for detection of hepatitis B surface antigen (HBsAg), testing for HCV antibodies (anti-HCV) using third (3<sup>rd</sup>) generation assays, and measurement of CD4 + T lymphocyte (CD4) count by flow cytometry. Full blood count was performed using KN-21N Haematology Analyzer (Sysmex, Kobe, Japan). Serum alanine transaminase (ALT) was measured using enzymatic methods (automated Hitachi 902 machine), and plasma HIV RNA (viral load) by Roche Ampiclor RNA PCR assay). These methods have been described in an earlier publication.<sup>24</sup>

### **Data Analysis**

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS Inc, Chicago, Ill), version 15. The baseline laboratory values

of HCV – infected and uninfected HIV-positive pregnant women were analyzed and compared. Continuous variables were presented as median or mean and standard deviation while categorical variables were presented as frequencies / percentages. Associations between categorical variables were investigated using Chi square test while student's t-test or Mahn-Whitney test (for non-normally distributed variables) was used to test for significant difference in continuous variables. P value was set at <5%.

### Ethical Considerations

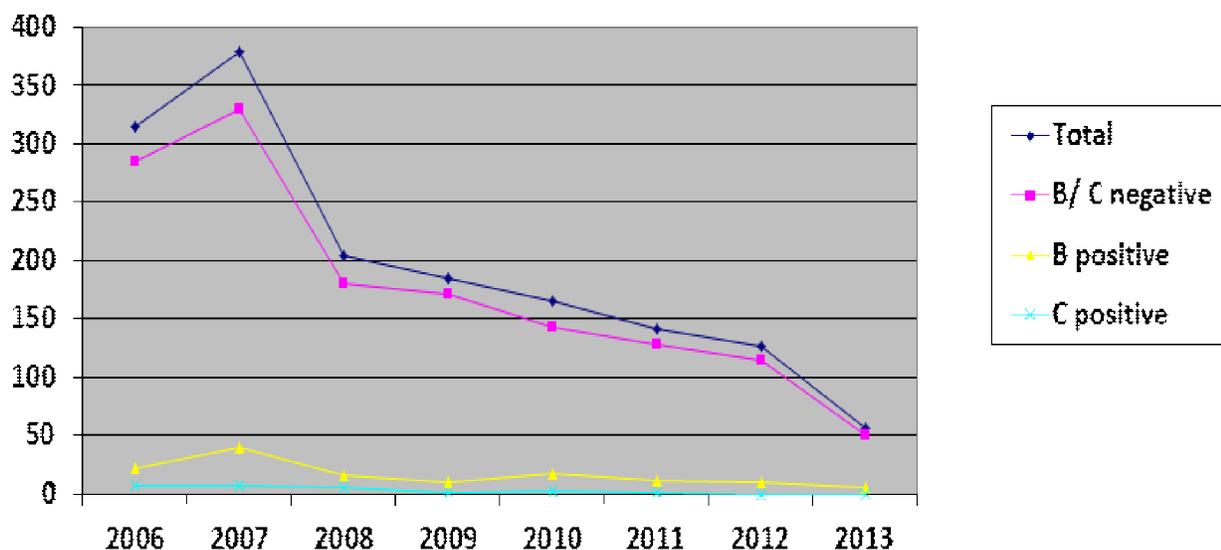
The antiretroviral treatment program is an operational research that was approved by the University of Ibadan/University College Hospital Ibadan Joint Institutional Review Board. Informed consent forms are signed by all patients during enrollment procedures. The program maintains an electronic data base of all patients enrolled and their

laboratory results. The electronic medical record systems for the patient data are implemented on a password-protected computer systems for the purpose of privacy and confidentiality of data. Patients' folders containing case report forms are kept in safe cabinets with locks in the medical records section and access is restricted to authorised persons only.

### RESULTS

During the period of study, one thousand, eight hundred and twenty- one (1, 821) women presented for care. Two hundred and forty-six (246) of the women had no result available for screening tests for either HBV or HCV and so were excluded from the analysis. Figure 1 shows the distribution of the patients by hepatitis status over the years under consideration.

Fig. 1. Hepatitis status over the years



Twenty-six (1.7 %) women were positive for HCV, 139 (8.8%) were positive for HBV and 1, 407 (89.3%) were negative for both HBV and HCV. Three patients were positive for both HBV and HCV. Patients with HBV infection were excluded from final analysis.

The mean age ( $\pm$  S.D.) of the patients was 29.2 years ( $\pm$  7.1). The HCV\HIV co-infected women were younger than those without co-infection, 26.8 years ( $\pm$  6.3) and 29.0 years ( $\pm$  5.3) respectively( $p = 0.04$ ).

The co-infected women had lower haematocrit ( $27.3\% \pm 4.5$  vs.  $28.4\% \pm 4.6$ ,  $p=0.29$ ),

lower white blood cell count (5, 200 cells / ml vs. 5, 500 cells / ml,  $p=0.766$ )but higher platelet count (209, 000 cells / ml vs. 199, 000 cells /ml). The difference in platelet count was statistically significant ( $p=0.019$ ). The co-infected group had higher CD4 (380 cells /ml vs. 326 cells/ ml,  $p=0.319$ ), higher blood urea (16.0 mg/ ml vs. 11.0mg/ml,  $p=0.013$ ) but comparable ALT (16.0 iu/ml vs. 15.0 iu/ml,  $p=0.95$ ) Log viral load ( $4.1 \pm 1.2$  vs.  $4.1 \pm 1.1$ ,  $p=0.97$ ) and serum creatinine levels (0.6 vs. 0.6,  $p=0.329$ ). Only the difference in urea level was statistically significant.

**Table 1:** Selected laboratory values for HIV/ hepatitis C co-infected and hepatitis B/C negative HIV positive pregnant women

Variable	Total	Hepatitis C positive	Hepatitis B/C negative	P value
&Age (years)	29.16 ± 7.14	26.77 6.53	28.95 5.33	0.04
&Gestational age (weeks)	26.03± 7.96	25.45 8.47	26.04 7.95	0.73
&Haematocrit (%)	28.47 4.52	27.33 4.45	28.41 4.64	0.29
*White blood cell (1,000/ml)	5.5 (4.0-19.8)	5.2 (2.8- 10.5)	5.5 (4.0- 19.8)	0.766#
*Platelet count (1,000/ml)	200.0 (13.5- 1,444.0)	209.0 (131.0 – 526.0)	1999.0 (13.5- 1,444.0)	0.019#
*CD4 (cells/ml)	323.0 (0- 3102)	380.0 (43- 1456)	326.0 (0-3102)	0.319#
& Log viral load	4.08 (1.11)	4.08 (1.22)	4.08 (1.11)	0.97
*ALT (iu/ml)	15.0 (1-642)	16.0 (1- 111)	15.0 (1-642.0)	0.95#
*Urea (mg/ml)	11.0 (8-257)	16.0 (6.0- 76.0)	11.0 (1.0-257)	0.013#
*Creatinine (mg/ml)	0.6 (1- 26.0)	0.6 (0.3- 1.1)	0.6 (0.1- 26.0)	0.329#

& Mean values

\*Median values with range

# Mann-Whitney value

## DISCUSSION

The selected baseline laboratory characteristics of HIV-infected and HIV/HCV co-infected pregnant women in this study were similar with the exception of platelet count and blood urea level with the co-infected women having higher values. The ALT level though similar in both groups of women, the value of 16.0iu/ml reported among the co-infected group was higher than the 7.9 iu/l reported by Obienu among general HIV-positive population.<sup>25</sup> However, this value was lower than the 26iu/l reported by Otegbayo et al also among HIV-positive adults in Ibadan,<sup>24</sup> and the 33 iu/l reported by Miri Dashe *et al* among HIV-negative pregnant women.<sup>26</sup> While the value reported in our group of co-infected pregnant women is not suggestive of pathology, cholestasis is a recognized histological feature of HIV/HCV coinfection.<sup>25</sup> A special form of hepatitis, fibrosing cholestatic hepatitis (FCH), which has a strong association with immunosuppression (including chronic hepatitis B and C with immune suppression) has been described. It has been reported to be rapidly progressive and sometimes fatal.<sup>25, 27</sup> The hallmarks of this form of liver injury include marked hepatocytic injury, severe cholestasis, and periportal and pericellular fibrosis.<sup>25,28, 29</sup> It has been suggested that fibrosing cholestatic hepatitis results from unimpeded viral replication within hepatocytes.<sup>30</sup> Similarly, HIV infection accelerates the histological progression of HCV infection, so that HIV/HCV

coinfected individuals develop cirrhosis and end-stage liver disease in a shorter period of time.<sup>31, 32</sup> This rapid histological progression may also manifest as higher levels of bilirubin in co-infected individuals. However, bilirubin and alkaline phosphatase were not evaluated in our study because it is not a part of the protocol operated by the PEPFAR-HARVARD program.

It must also be noted that several workers have evaluated the impact of HCV-HIV co-infection on the risk of hepatotoxicity following commencement of ART.<sup>33, 34</sup> These authors were able to demonstrate that although there is an increased risk of rise in hepatic transaminases, however, HCV does not significantly impact response to ART in the short term.

Haemoglobin concentration was lower in the HIV/HCV co-infected patients compared with the HCV mono-infected control subjects. The value of 27.3% ± 4.5 reported in our study is lower than 29.0% by Obienu *et al*<sup>25</sup> among adult HIV-positive population, 29.3% reported by Ramon *et al*<sup>35</sup> among HIV positive pregnant women from Abidjan and 35.4% by Miri-Dashe among HIV-negative pregnant women.<sup>26</sup> In a similar manner, the white blood cell count value of 5, 200 cells/ ml was lower in the co-infected group but higher than 4, 040 cells/ml reported by Obienu in the general HIV positive population.<sup>25</sup> It is however lower than 5, 936 cells/ ml reported by Ramon *et al* (HIV-positive pregnant women in

Abidjan)<sup>35</sup> and 6,400 cells / ml by Dashe (HIV-negative pregnant women in Jos).<sup>26</sup>

A synergistic effect of both infections on haematological indices has been suggested. Possible causes for the anaemia seen in HIV-positive individuals include the effect of changes in cytokine production on haematopoiesis,<sup>36</sup> decreased erythropoietin concentration<sup>37</sup> and opportunistic infections such as *Mycobacterium avium complex* (MAC).<sup>25</sup> In a similar manner, when HCV-mono-infection is untreated, anaemia may also result from different types of immune-mediated cytopaenias, haemolytic anaemia<sup>38</sup> or pure red cell aplasia.<sup>39</sup> Similarly, leukopaenia is inherent in HIV infection. Critical events include lymphocyte depletion and granulocytopenia.<sup>40</sup> The pathogenesis for this includes autoimmune mechanisms<sup>25</sup> and impaired granulopoiesis.<sup>41</sup>

In contrast to the haematocrit and white blood cell count values, the platelet count was higher in our group of HCV positive pregnant women. The platelet count of 209, 000 cells / ml was higher than the 175, 000 cells/ ml among the general adult HIV-positive population,<sup>25</sup> lower than the 224, 000 cells/ml from Abidjan ( HIV-positive pregnant women)<sup>35</sup> but similar to the 207, 000 cells/ ml among HIV-negative pregnant women.<sup>26</sup>

A synergistic effect of both viruses on platelet count with resultant thrombocytopenia has also been suggested.<sup>25</sup> Possible mechanisms for the thrombocytopenia in the HIV-positive individual include accelerated platelet clearance due to immune complex disease,<sup>25, 42</sup> the direct infection of megakaryocytes may result in defective platelet production and apoptosis of the infected megakaryocytes.<sup>25, 43</sup> In a similar manner, thrombocytopenia is not uncommon in chronic HCV infection ; possible mechanisms include absence of liver – derived thrombopoietin,<sup>44</sup> advanced liver disease and manifest cirrhosis<sup>45</sup> and direct cytopathic involvement of megakaryocytes.<sup>46</sup> Finally, HCV-associated immunoglobulins may induce thrombocytopenia via an immunological mechanism similar to that operating in immune thrombocytopenic purpura.<sup>25</sup> It is not immediately clear the reason why the levels were higher in our cohort.

In this study, there were no significant differences in CD4+ T-cell counts and HIV RNA levels at baseline. This is similar to the findings by other authors who examined the impact of HIV-HCV co-

infection in immunological and virologic parameters in sub-Saharan Africa and developed countries.<sup>47-50</sup> In addition, those authors also noted no significant differences in CD4+ T cell counts and HIV RNA levels after ART initiation when HIV-HCV co- infected and HIV-monoinfected groups were compared. However, they noted slightly less robust changes in CD4+ T cell counts after ART initiation in the HIV-HCV co-infected patients.<sup>47,51</sup> Nonetheless, it is believed that this poorer immunologic recovery after ART initiation has little if any effect on overall morbidity or mortality.<sup>47,52</sup> Similarly, several workers have found no effect of HCV on HIV virologic response after ART initiation.<sup>47,51,53</sup> This suggests there is minimal effect of HCV on the efficacy of ART in controlling HIV viral replication.

The significantly elevated urea level among the HCV co-infected patients might be a precursor to HIV-associated nephropathy. However, urinary protein was not evaluated in this study as it is not part of the baseline evaluation in our program. Reassuringly, the serum creatinine levels were similar in both groups of women and within normal levels. HIV- associated nephropathy is characterized by rapidly progressive renal failure that evolves over weeks to months to end-stage renal disease.<sup>54</sup> Its cardinal laboratory feature is that of proteinuria >1gm/day.<sup>23</sup> Risk factors include being African American and having low CD4 cell count (< 100/mm<sup>3</sup>). Undetectable HIV RNA may be protective.<sup>55</sup> Renal biopsy shows extensive collapsing glomerulosclerosis, tubular ectasia, and tubulointerstitial disease.<sup>54</sup> HCV-associated renal disease, on the other hand, is often a manifestation of HCV-associated mixed cryoglobulinemia. Patients may present with dermatologic signs along with haematuria, proteinuria and sometimes renal failure.<sup>23</sup> Laboratory findings include HCV RNA in plasma and cryoglobulins in blood. Therapy directed at hepatitis (PEG- interferon plus ribavirin) may result in amelioration of the renal disease.

In conclusion, while the laboratory (haematological, biochemical , immunological and virological ) values evaluated in this study were comparable when HCV/ HIV co-infected patients were compared to HIV mono-infected patients, the synergistic effect of both viruses on the values make it necessary for health care providers to continue to closely monitor these patients.

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