

RESEARCH NOTE

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Evaluation of hepatic and kidney dysfunction among newly diagnosed HIV patients with viral hepatitis infection in Cape Coast, Ghana

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Abstract

Objective: HIV positive individuals infected with viral hepatitis B (HBV) or C (HCV) are at an increased risk of progression to kidney and liver failures. Therefore, prior to initiation of antiretroviral therapy, early diagnosis and initiation of appropriate treatment protocols are imperative for co-infected individuals. This study evaluated the prevalence of HBV and HCV, and extent of liver and renal dysfunction among 90 newly diagnosed HIV patients attending the Cape Coast Teaching Hospital HIV clinic.

Results: Levels of alanine aminotransferase, aspartate-platelet ratio index and estimated glomerular filtration rate were used respectively to diagnose hepatotoxicity, liver fibrosis and chronic kidney disease (CKD). Association analyses were evaluated by Pearson's Chi-square test or Fisher's exact test and considered significant at $p < 0.05$. Using rapid diagnostic tests, 75.6% ($n = 68$) had HIV1 mono-infection, 24.4% ($n = 22$) had HIV1/HBV co-infection while 0.0% ($n = 0$) had HIV1/HCV co-infection. The prevalence of hepatotoxicity, liver fibrosis, and CKD were 7.8% ($n = 7$), 2.2% ($n = 2$), and 15.5% ($n = 14$) respectively. Similar proportions of HIV1/HBV and HIV1 were diagnosed with liver fibrosis ($p = 0.431$). In relation to hepatotoxicity Grade, a high proportion of HIV1/HBV were diagnosed with Grade 2 ($p = 0.042$). Also, severely reduced kidney function (CKD stage 4) was observed in only HIV1/HBV ($n = 2$, 9.1%, $p = 0.053$).

Keywords: HIV, HBV, Clinical proxies, Hepatotoxicity, Chronic kidney disease

Introduction

Human immune deficiency virus (HIV) infection remains a public health problem worldwide with about 36.9 million infections as at 2017. Sub Saharan Africa bears the greatest burden with about 25.7 million cases [1]. Generally, viral hepatitis B (HBV) and C (HCV) infections are common among people living with HIV/AIDS (PLWHA) because they tend to share the same routes of transmission [2]. Worldwide, about 5–20% of PLWHA are co-infected with HBV [3]. In Sub-Saharan Africa, the

prevalence of HIV/HBV co-infection ranges between 0 and 28.4% [4, 5]. Globally, the prevalence of HIV/HCV co-infection is about 6.2% with about 2.3 million people affected [6].

The introduction of antiretroviral therapy (ART) for HIV treatment has led to reduced mortality among people living with HIV/AIDS (PLWHA) [7]. However, non-HIV related conditions such as hepatic and renal dysfunction are increasingly recognized to contribute to morbidity and mortality in HIV patients [8]. Attributive factors could be co-infection with HBV and HCV coupled with hepatotoxic/nephrotoxic impacts of ART [8, 9].

While the hepatological impact of HBV and HCV infections is well recognized, strong associations have

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been observed between these viral infections and renal disease [10, 11]. The pathogenesis and pathology of renal disease caused by these viruses has been extensively reviewed elsewhere [12]. Increasingly, co-infections with viral hepatitis are recognized to complicate clinical profiles [13], and among pregnant women, an increased disease burden has been reported [14, 15]. For HIV positive patients on ART, co-infection with HBV and/or HCV could exacerbate liver and kidney dysfunction. Therefore, early diagnosis of co-infected individuals and the initiation of appropriate treatment protocols are imperative. Although the World Health Organization (WHO) recommends screening of all newly diagnosed HIV individuals for HBV and HCV [16], most resource-limited countries including Ghana are yet to include this in their HIV control programmes [17]. Therefore, we undertook this pilot study to determine the prevalence of HBV and HCV and associated co-morbid conditions such as hepatic and renal dysfunction in newly diagnosed HIV infected patients attending the Cape Coast Teaching Hospital HIV clinic, prior to initiation of ART.

Main text

Methods

Study area, design and population

The study was undertaken at Cape Coast Teaching Hospital in the Cape Coast Metropolitan area of the Central Region of Ghana. This was a hospital-based retrospective cross-sectional study undertaken from January to May 2017. Newly diagnosed HIV patients who were attending the Cape Coast Teaching Hospital HIV Clinic were recruited into the study after informed consent was sought. At the clinic, patients confirmed to have HIV were assessed clinically by physicians to determine the WHO clinical stage and their suitability for treatment. The patients then undertook liver and kidney function tests, and full blood count test. HBV and HCV testing were performed during their subsequent visit prior to initiation of ART.

Data collection and processing

Demographic data (including age, sex, marital, occupational and educational statuses) and HIV clinical stage; which is based on the WHO clinical staging of HIV [18] were obtained from patients' records.

Laboratory test results were retrieved from patients' records. Full blood count data collected included hemoglobin concentration (g/dL) and platelet count ($10^9/L$). Other results collected included creatinine concentration, alanine aminotransferase (ALT) concentration and aspartate aminotransferase (AST) concentration.

Hepatotoxicity was diagnosed if ALT concentrations were ≥ 50.0 U/L, and was categorized as Grades 1, 2 and 3

and 4, with ALT value of 50.0–99.9 U/L, 100.0–199.9 U/L and ≥ 200.0 U/L respectively [19]. To determine whether a patient has liver fibrosis, we calculated the aspartate-platelet ratio index using the formula: $APRI = (AST/ULN) \times 100 / \text{platelet count } (10^9/L)$ (<https://www.hepatitisc.uw.edu/page/clinical-calculators/apri>). Where ULN represents the upper limit of normal range values for AST. Normal liver function was defined by $APRI < 1.5$, while liver fibrosis was defined by $APRI > 1.5$.

To determine renal function of the patients, estimated glomerular filtration rate (eGFR) was obtained using the online eGFR calculator at <https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators/ckd-epi-adults-conventional-unit>. Parameters including serum creatinine concentration in mg/dL, race and gender were used [20]. Chronic kidney disease (CKD) stages were categorized based on the Kidney Disease Outcomes Quality Initiative classification by the National Kidney Foundation [21]. For this study, CKD was defined by CKD stages 3, 4 and 5 (with eGFR 30–59 mL/min/1.73 m², 15–29 mL/min/1.73 m² and < 15 mL/min/1.73 m² respectively) while normal kidney function was defined by CKD stages 1 and 2 (with eGFR ≥ 90 mL/min/1.73 m² and 60–89 mL/min/1.73 m² respectively) [21, 22].

Hepatitis B and C testing

Testing for HBV infection was undertaken using the Hepatitis B combo test kit (Gemc Technology Group, Zhengzhou, Henan, China). Briefly, about 2.5 μ L of capillary blood was taken from a finger prick. About 0.5 μ L of the capillary blood each was spotted into wells assigned to HBsAg, HBsAb, HBeAg, HBeAb and HBcAb and a buffer solution applied immediately. HCV infection was tested using rapid anti-HCV test strip (Intec Products, Xiamen, China). For both HBV and HCV tests, the procedure, results reading and interpretations were conducted with strict adherence to the manufacturer's protocol.

Statistical analysis

Data were entered into excel and the analyses done with Graphpad Prism 6 (GraphPad Software Inc., San Diego, USA) and SPSS Version 20 (IBM Corporation, Chicago, USA). Parametric variables were presented as mean and standard deviation and compared by unpaired Student t-test. Non-parametric variables were described as median and interquartile range and compared by Mann–Whitney test. Categorical variables on the other hand were presented as proportions, with 95% confidence interval and compared by Pearson's Chi-square test or Fisher's exact test.

Results

Socio-demographic characteristics of study participants

The mean age ± SD of the 90 participants was 42.8 ± 8.2, and most (n = 63, 70.0%) were aged between 36 and 55 years (Table 1). Majority of the participants were married (n = 76, 84.4%), and most of them were females (n = 58, 64.4%) (Table 1). Although 92.2% (n = 83) of the participants had lower forms of education (none or basic form of formal education), about 94.6% (n = 85) had some form of employment (Table 1).

Prevalence of viral hepatitis B or C in newly diagnosed HIV infections

All the 90 participants tested positive for HIV1 with none testing positive for HIV2. Among the participants, 24.4% (n = 22) tested positive for both HBsAg and HbCAb, 5.6% (n = 5) tested positive for HBsAb, 2.2% (n = 2) tested positive for HBeAg and 8.9% (n = 8) tested positive for HBeAb. The prevalence of HIV1 mono-infection was 75.6% (n = 68) and that of HIV1/HBV co-infection was 24.4% (n = 22). We did not record any HCV infection.

Diagnosis of HIV clinical stages

Majority of the participants, 71.1% (n = 64, 95% CI 60.7–79.7), were diagnosed with HIV stage 1. Of the remaining participants, 14.4% (n = 13, 95% CI 8.5–23.5) had HIV stage 2, 7.8% (n = 7, 95% CI 3.7–15.6) had HIV stage 3 and 6.7% (n = 6, 95% CI 3.0–14.2) had HIV stage 4.

Table 1 Distribution of socio-demographic characteristics among the study participants (n = 90)

Category	Sub-category	n (%)	95% CI
Age	18–35	20 (22.2)	26.3, 31.4
	36–55	63 (70.0)	43.8, 46.5
	56+	7 (7.8)	55.5, 65.6
Sex	Female	58 (64.4)	53.9, 73.8
	Male	32 (35.6)	26.2, 46.1
Marital Status	Married	76 (84.4)	75.2, 90.7
	Widowed	2 (2.2)	0.5, 8.7
	Single	10 (11.1)	6.0, 19.6
	Divorced	1 (1.1)	0.2, 7.7
	Cohabiting	1 (1.1)	0.2, 7.7
Occupational status	Employed	85 (94.6)	88.6, 98.4
	Student/unemployed	5 (4.4)	1.6, 11.4
Highest educational level	None	50 (55.6)	45.0, 65.6
	Basic	33 (36.7)	27.2, 47.3
	Secondary	6 (6.7)	3.0, 14.2
	Tertiary	1 (1.1)	0.2, 7.7

Socio-economic determinants were presented as numbers and proportions [n (%)], with 95% confidence intervals (95% CI). None and basic: lower forms of education, secondary and tertiary: higher forms of education

Comparison of socio-economic variables between the different groups of HIV infections

The mean age between the HIV1 mono-infection and HIV1/HBV co-infection groups was similar (p = 0.984, Table 2). Also, infection with either HIV1 or HIV1/ HBV was independent of age group (p = 0.808), gender (p = 0.927), marital status (p = 0.819), level of education (p = 0.480) and occupational status (p = 0.569) (Table 2).

Prevalence of hepatic damage, liver fibrosis and CKD among the newly diagnosed HIV infections

The levels of hematological indices [Hb (p = 0.917) and PLT (p = 0.460)], liver chemistry [ALT (p = 0.821) and AST (p = 0.123)] and renal chemistry [creatinine (p = 0.351)] tests were observed to be similar in both HIV1 and HIV1/HBV groups (Table 3). The prevalence of hepatotoxicity, liver fibrosis, and chronic kidney disease (CKD) were 7.8% (n = 7), 2.2% (n = 2), and 15.5% (n = 14) respectively. Similar proportions of the HIV1

Table 2 Association between socio-demographic factors and HIV infection type

Characteristics	HIV1 mono-infection (n = 68)	HIV1/HBV co-infection (n = 22)	p-value
Age, mean ± SD	42.9 ± 10.4	42.8 ± 8.2	0.984
Age group, n (%)			
18–35	15 (16.7)	5 (5.6)	0.808
36–55	47 (52.2)	16 (17.8)	
56+	6 (6.7)	1 (1.1)	
Sex, n (%)			
Female	44 (48.9)	14 (15.6)	0.927
Male	24 (26.7)	8 (8.9)	
Marital status, n (%)			
Married	56 (62.2)	20 (22.2)	0.819
Widowed	2 (2.2)	0 (0.0)	
Single	8 (8.9)	2 (2.2)	
Divorced	1 (1.1)	0 (0.0)	
Cohabiting	1 (1.1)	0 (0.0)	
Occupational status, n (%)			
Employed	64 (71.2)	22 (24.4)	0.569
Student/unemployed	4 (4.4)	0 (0.0)	
Highest educational level, n (%)			
None	24 (26.7)	9 (10.0)	0.480
Basic	37 (41.1)	13 (14.4)	
Secondary	6 (6.7)	0 (0.0)	
Tertiary	1 (1.1)	0 (0.0)	

Unpaired t-test was used to compare the exact ages between the mono-infected and co-infected participants. Where SD = standard deviation of the mean ages. Association analyses between infection type and the socio-economic determinants were done using Pearson's Chi-square test or Fisher's exact test. A two-tailed p-value was considered significant at p < 0.05

Table 3 Association between HIV clinical data and HIV infection type

Clinical data	Description	HIV1 mono-infection (n = 68)	HIV1/HBV co-infection (n = 22)	p-value
		Median (IQR)		
Hb (g/dL)		10.0 (8.5–11.8)	10.4 (8.8–11.4)	0.917
PLT (10 ⁹ /L)		208 (165.0–245.0)	230 (167.3–256.3)	0.460
ALT (U/L)		28.1(18.1–34.7)	25.6 (17.3–45.3)	0.821
AST (U/L)		30.6 (23.8–45.0)	33.0 (27.5–58.9)	0.123
Creatinine (mg/dL)		80.0 (65.1–106.2)	89.8 (62.0–118.2)	0.351
	ALT (U/L)	Hepatotoxicity, n (%)		
Absent	< 50.0	64 (91.4)	19 (86.4)	0.355
Present	≥ 50.0	4 (5.9)	3 (13.6)	
Grade 1	50.0–99.9	4 (5.9)	1 (4.5)	0.042
Grade 2	100.0–199.9	0 (0.0)	2 (9.1)	
Grade 3 and 4	≥ 200.0	0 (0.0)	0 (0.0)	
	APRI	Liver fibrosis, n (%)		
Absent	< 1.5	67 (98.5)	21 (95.5)	0.431
Present	> 1.5	1 (1.5)	1 (4.5)	
	eGFR (mL/min/1.73 m ²)	CKD, n (%)		
Absent	≥ 60	58 (85.3)	18 (81.8)	0.696
Present	< 60	10 (14.7)	4 (18.2)	
Stage 1	≥ 90	40 (58.8)	10 (45.5)	0.053
	Normal GFR			
Stage 2	60–89	18(26.5)	8 (36.4)	
	Mildly reduced GFR			
Stage 3	30–59	10 (14.7)	2 (9.1)	
	Moderately reduced GFR			
Stage 4	15–29	0 (0.0)	2 (9.1)	
	Severely reduced GFR			
		n (%)		
HIV stages	Stage 1	47 (52.2)	17 (18.9)	0.86
	Stage 2	10 (11.1)	3 (3.3)	
	Stage 3	6 (6.7)	1 (1.1)	
	Stage 4	5 (5.6)	1 (1.1)	

Mann–Whitney test was used to compare levels of Hb, PLT, ALT and AST. Where IQR = interquartile range. Association analyses of infection type with hepatotoxicity, liver fibrosis CKD or HIV stages were done using Pearson's Chi-square test or Fisher's exact test. A two-tailed *p*-value was considered significant at *p* < 0.05

and HIV1/HBV groups were diagnosed with hepatotoxicity (*p* = 0.355), liver fibrosis (*p* = 0.431) and CKD (*p* = 0.696) (Table 3). In relation to the hepatotoxicity Grade, a high proportion of those with HIV1/HBV were diagnosed with Grade 2 (*p* = 0.042, Table 3). Also, severely reduced kidney function (CKD stage 4) was recorded in only those with HIV1/HBV (*n* = 2, 9.1%), and such an observation was nearly significant (*p* = 0.053, Table 3). That notwithstanding, no differences in HIV clinical stages were observed between the two groups (*p* = 0.86, Table 3).

Discussion

HIV infection complicated by HBV and HCV infection increases the risk of morbidity and mortality compared

with HIV mono-infection. Because treatment increases the survival of co-infected individuals compared with the untreated, it is recommended to routinely check for HBV and HCV status of all newly diagnosed patients. However, in most resource-limited countries including Ghana, this recommendation is yet to be included in HIV control programmes. In this pilot study, all newly diagnosed patients were HIV1 positive with none testing positive for HIV2 infection. In Ghana, 98.5% of HIV infections are due to the type 1 mono-infection, with the rest being dual type 1 and 2 infections [23]. The 22.4% prevalence of HIV/HBV co-infection falls within the range of 0 to 28.4% reported in sub Saharan Africa [7]. This prevalence was as expected, as most HBV acquisition in Sub-Sahara Africa, including Ghana, is before age

6 years, thus, HIV/HBV co-infection usually mirrors the national HBV prevalence [5, 24]. We did not record any case of HIV/HCV co-infection, probably because, the prevalence of this co-infection tends to be lower in sub Saharan Africa; where intravenous drug injection is less prevalent [6]. However, Ntiamoah in 2015 reported an HIV/HCV prevalence in Ghanaian pregnant women as 4.1% [25] whereas Brandful et al. reported a prevalence of 8.2% among patients attending sexually transmitted disease clinics in 1999 [26].

To determine the impact of HIV/HBV co-infection on liver morbidity such as hepatotoxicity and liver fibrosis in our study participants, we utilized surrogates such ALT, AST, APRI and degree of hepatotoxicity. We observed no significant differences in these surrogates, that notwithstanding, studies in Tanzania reported a significantly higher AST and ALT concentration in HIV/ HBV co-infected individuals compared with HIV mono-infected [27, 28]. Though several non-invasive measurements exist for diagnosing liver fibrosis [29, 30], the APRI is recommended by the WHO for assessing the presence of liver fibrosis in the absence liver biopsy [17, 31]. Using > 1.5% APRI proxy, the study reports a prevalence of 2.2% of liver fibrosis among the participants, which is lower compared with high levels of liver fibrosis reported elsewhere in Sub Saharan Africa [27, 32, 33]. Even though HIV/HBV co-infected patients are at an increased risk of developing liver fibrosis compared with HIV mono-infected individual [34], our findings revealed that co-infection was independent of liver fibrosis. The prevalence of hepatotoxicity was 7.8%, which compares with the 6.5% reported in Ethiopia [35], however, the higher rate in this study could be due to the presence of co-infection with HBV.

The use of tenofovir and/or lamivudine in ART combination for treating HIV complicated with HBV co-infection has been recommended irrespective of the immune state of the patients [36]. However, these drugs have been found to increase the risk of developing nephrotoxicity in these patients [35, 37, 38]. Therefore, assessment of the renal function prior to treatment has been recommended [16, 37]. The 15.5% prevalence of CKD in the newly diagnosed compares with a high rate of 22.9% recorded in Nigeria [39]. kidney failure may result from HIV-associated nephropathy, which is common in the Africans with contributory factors such as co-infection with HBV or HCV [40, 41]. Therefore, our finding of higher proportions of HIV1/ HBV co-infected individuals with severe forms of CKD (CKD 4) buttresses such findings.

Conclusion

In summary, the study observed that, prior to initiation of ART, severe forms of hepatotoxicity (hepatotoxicity

Grade 2) and CKD (CKD stage 4) were common among HIV1/ HBV co-infections. The findings buttress the need for resource-limited countries to routinely screen for hepatitis B at HIV clinics, so as to initiate appropriate treatment protocols.

Limitation

The sample size for the study was small, thus, future studies with a larger sample size is recommended to substantiate our findings. The underlying aetiology of liver and kidney dysfunction was unknown for the participants. Also, the study could not diagnose CKD in participants with eGFR values > 60, since urine albumin, an alternative mean value for determining CKD was not measured.

Abbreviations

HBV: hepatitis B virus; HCV: hepatitis C virus; CKD: chronic kidney disease; PLWHA: people living with HIV/AIDS; Hb: hemoglobin; PLT: platelets; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal; eGFR: estimated glomerular filtration rate; APRI: aspartate aminotransferase to platelet ratio index; WHO: World Health Organization.

Acknowledgements

We are most grateful for the enormous support by the clinicians and staff at the HIV referral unit of the Cape Coast Teaching Hospital.

Authors' contributions

OCKH and SE conceived and designed the study. Clinical assessment of patients was done by OCKH and DOY. AL and IA conducted hepatitis B/C testing. Retrieval of laboratory data was done by OCKH, DO, WJT and NGA. NGA and WJT entered the data. NGA and OCKH analysed the data, and drafted the manuscript. GKH and PAA critically reviewed the manuscript. All authors read and approved the final manuscript.

Funding

Not applicable.

Availability of data and materials

The datasets supporting the findings of this article are available in this manuscript.

Ethics approval and consent to participate

Ethical approval for the study was sought from and granted by School of Medical Sciences Scientific Ethical Review Board, University of Cape Coast, Ghana. A further approval letter was granted by the ethics committee of the Cape Coast Teaching Hospital which enabled the commencement of this study. Written informed consent was provided by each study participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 10 March 2019 Accepted: 24 July 2019
Published online: 31 July 2019

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