

Screening Outcomes of Hepatitis B and E among HIV Patients on HAART in Osogbo, South Western Nigeria

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Abstract

Background: The lives of patients living with HIV/AIDS have improved in terms of longer life expectancy and quality. This has seen the emergence of complications of the disease and the drugs such as metabolic syndrome and re-emergence of tuberculosis. Co-infection with other viruses especially the hepatic viruses has also become a major source of concern. The aim of this research is to determine the incidence of hepatitis B and E among this group of patients. **Methods and Findings:** Blood samples were collected from 156 consecutive HIV positive patients on HAART, informed consent having been obtained previously. The patients were screened both for hepatitis B and E using standard procedures. A questionnaire was administered to all participants. The results are illustrated with tables following analysis with SPSS version 10. It was found that 24.5% were positive for hepatitis E while 7.8% were positive for hepatitis B. It was also found that educational status was the only statistical significant variable for HEV co-infection. Taking the value of alanine transaminase to be 12 U/L as upper limit of normal, the mean value for HEV positive patients obtained was 13.8U/L while for those HBV positive was 10U/L. **Conclusion:** From the findings, more emphasis should be placed on improving education of the populace. More research should be carried out to determine what subtypes of the viruses are present and their effects on the hepatic system using preferably non-invasive techniques. Also the variability of hepatic enzymatic activity needs more analysis.

Keywords

Aids, Transmission, Viral, HAART, Hepatic

1. Introduction

Since the advent of highly active antiretroviral therapy (HAART) introduced in 1996 [1], there has been an increase in the quality and length of life of patients placed on these drugs. The disease condition acquired Immune deficiency Syndrome (AIDS) has gradually evolved into a chronic condition however with subsequent side effects of the drugs and side effects of AIDS itself emerging as the patients live longer. Complications of the drugs have been well documented e.g. Zidovudine and anaemia. Other well documented complications include metabolic syndrome (hypertriglyceridemia, low high-density lipoprotein cholesterol, and insulin resistance). This has been shown to increase the risk of cardiovascular events in these groups of patients [2]. Drugs associated with this include stavudine [3], lopinavir/ritonavir. Other complications are co-infection with tuberculosis and co-infection with other viruses [4] [5] [6].

Co-infections with other viruses such as west Nile virus, cytomegalovirus and Parvovirus B19 have been well documented [7]. A lot of emphasis has been placed on co-infection with hepatitis C because of the effect of HIV/HCV has on the hepatic system. It could lead to liver fibrosis, cirrhosis and a particular aggressive form of hepatic carcinoma [4]. Since it is possible for other viruses to be present alongside HIV in a patient who is HIV positive, it is important to investigate such a patient for the presence of other viruses especially the hepatic viruses. Once HIV is diagnosed in a patient the patient is then screened for these viruses and managed based on the findings [5]. In a study carried out in our facility it was found that 23.2% were found to be co-infected with HCV [4]. These patients are therefore prone to the more aggressive effects of HIV/HCV mentioned above, and should be managed appropriately. In another study among the same group of patients increases of hepatic enzymes were also observed and a further study revealed that these patients were potentially prone on the long term to hepatic osteoarthropathy [5] [8] similar to findings obtained in other parts of the world. Interestingly it was noted that females were more prone than males to these adverse events.

A considerable amount of studies have been carried out worldwide on HIV/Hepatitis C virus (HIV/HCV) co-infection, and it would appear that more emphasis has been placed on this dual infection than has been on hepatitis B virus co-infection with HIV (HBV/HIV co-infection) even though they are both of significant clinical importance. However Hepatitis B (HBV) co-infection with HIV is another dual viral co-infection of significant epidemiological importance [9] [10]. Though it can also be transmitted via blood, sexual activity and sharing of needles among drug addicts are more common routes of infection with HCV. It is estimated that 10% of HIV positive individuals are also HBV positive. Complications associated with hepatitis B and C are currently among the leading causes of hospital admission and death in the HIV-infected population. Therefore, adequate management of hepatitis B and C infection is now being considered a priority in HIV-co-infected patients. HBV is the leading cause of chronic liver disease and a leading cause of death, accounting for up to half of all cases of cirrhosis and hepatocellular carcinoma [11].

An estimated 400 million people are infected with HBV, with the majority of cases occurring in regions of Asia and Africa where the virus is endemic. There, up to 70% of adults show serologic evidence of current or previous infection, and 8 to 15% have chronic HBV infection. In Nigeria high rates have been reported in various parts of the country. There is an increase in morbidity and mortality in HBV/HIV infected patients than in those infected with either virus alone. These co-infected individuals have progression to chronic hepatitis B almost five times faster than those infected with hepatitis B alone. They are also 17 more time likely to die than those infected with HBV virus alone. There are higher levels of hepatitis B viraemia and have a higher risk of cirrhosis and hepatocellular carcinoma. HBV/HIV co-infection is of particular significance in pregnant women. They have expression of HBV DNA and HBeAg which makes transmission to the fetus easier and more efficient. In general HIV immunosuppression can cause a reduction in HBV surface antibody such that the individual is unable to mount an effective defence leading to reactivation of chronic hepatitis B and subsequent sequelae [12]-[17].

Human immunodeficiency virus (HIV) and hepatitis B virus (HBV) exact a high toll on infected patients. Both can lead to chronic disease, cancer, and death, and neither can be eradicated with the use of current therapeutic medication. Drug resistance often develops after patients have received treatment for some time and is usually followed by the loss of clinical advantages. Co-infection with the two viruses exacerbates the negative effects. Studies have revealed that co-infection with HBV is associated with lower CD4 counts [12]. Thus it is essential in a center such as ours dedicated to the prevention and management of HIV to determine the incidence of HBV/HIV in our group of patients.

It has been suggested that all HIV patients should be screened for HBsAg, and those found to be negative should undergo further screening for HBcAb and HBsAb as those would provide evidence of immunological control of previous infection or vaccination. All HBsAg-positive patients should be counseled about reducing the risk of HBV transmission to close contacts. It is known that HBV can be more infectious than HIV and can be transmitted to household contacts via dried blood, open cuts, and shared toothbrushes or razors. Sex partners, household members, children with close physical contact are also prone. Those who share injections, with the patient should be screened for HBV and vaccinated if they are not actively infected.

Hepatitis E virus (HEV) is another virus that can occur in association with HIV. It is a non enveloped RNA virus also belonging to the family hepeviridae. The route of transmission being feco-oral, Hepatitis E virus epidemics are therefore associated with poor sanitation and hygiene. Its incidence varies with geographical location. The virus has been successfully isolated in pigs and deer making it zoonotic. Being an emerging infection it has become of considerable significance worldwide, though it appears very little attention is being paid to the virus in Nigeria presently. However, studies from Ibadan in south west Nigeria have revealed infection rates as high as 12.2% [18]. HEV has a predilection for immune-compromised patients which somewhat distinguishes it

from the other hepatitis viruses. These immune compromised patients could undergo an acute infection which could be missed clinically and biochemically [18].

Organ transplantation is becoming an increasingly frequent mode of treatment for a wide variety of diseases worldwide and in Nigeria transplant centers are emerging in various parts of the country involving both the public and private health sector, hence, the necessity for more emphasis on screening for the virus. As mentioned above an important sustaining condition for the survival of this virus in humans is immunoparesis [18].

Studies on HEV/HIV co-infection in Nigeria appear to be scanty and isolated. Though a study among health care workers (HCW) in Ibadan in south west Nigeria revealed higher levels of HEV-antibody (44%) among HCW than controls [19].

A reason for this could be that HCW because of the nature and setting of their various occupations (nurses, lab. scientists, medical doctors, etc.) they are more prone to blood borne viral infections than other populations [20]. This also indicates that more studies need to be carried out regarding HIV and other viruses in our clinical instance especially those that are blood borne. Indeed it could be that we are on the threshold of a situation whereby hepatitis E is included among the mandatory viruses (HBV, HCV, HIV) that need to be screened for before declaring a potential candidate "fit" as a blood donor, though much more indepth research and analysis need to be carried out. It is interesting to note that like HCV, HEV has also been reported as a nosocomial infection.

The prevalence of HEV in USA and Europe has been reported as being between 1% - 5%, while those reported in developing areas of the world range from 10% - 100% . In Asia and regions of northern Africa infections rates of between 22.5% to 100%.

2. Materials and Methods

Study population: Blood samples were collected from 156 consecutive HIV positive individuals on antiretroviral therapy (ART) with adequate data from administered questionnaires. The participants gave informed consent to be included in the study.

The study was carried out in Osogbo the capital city of Osun state in Nigeria. It is an urban setting with a population of 3,416,959. The residents are majorly Yoruba however there are other ethnic groups including Hausas, Igbos and those of Edo state origin. The weather pattern is typically tropical, periods of heavy rain fall alternating with dry spells. For the diagnosis of HIV testing kits from three different manufacturers were utilized such as Unigold, Statpak and Determine using recognized standard methods. In diagnosing HBV infection, third generation enzyme immunoassay kit produced by DIAPRO (Italy) was used where-in the serum specimen was diluted with DILSPE and 100µl of the diluted specimen, alongside the negative controls in triplicate and positive controls were added to different wells, leaving the first well as blank. After the micro plate was incubated and wells washed, all the wells were treated with enzyme conjugate except the first blanking well. The micro plate was incubated again and the chromogen/substrate mixture was added after the second washing. The reactions were stopped

with sulphuric acid and the optical density (OD) was read at 450 nm immediately. The cut-off value for the batch was determined and individual results were interpreted as negative (<0.9); positive (>1.1) and equivocal (0.9 - 1.1) as appropriate. For the diagnosis of HEV infection, using reagents and wells supplied by Diapro, Italy, wash buffer was diluted 1 to 20 with distilled water. A 50 µl each of positive control, negative control and specimen was added into their respective wells. Then, 50 µl HRP-Conjugate antibody was added to each well except the Blank. The plate was incubated for 60 minutes at 37°C and the wells were washed 5 times with wash buffer, allowing the micro wells to soak for 30 - 60 seconds. A volume of 50 µl of TMB solution A and 50 µl TMB solution B was added into each well including the Blank, and the plate was incubated at 37°C for 10 minutes avoiding light. The enzymatic reaction between the TMB solutions and the HRP-Conjugate antibody produced blue color in positive control and anti-HEV positive sample wells.

Using a multichannel pipette, 50 µl stop solution was added into each well. Intensive yellow color developed in positive control and HBsAg positive sample wells. The absorbance was read at 450 nm, using 630nm as reference wavelength. The results were then subjected to statistical analysis using SPSS version 10.

3. Results

Of all the 156 participants 128 were female and 28 male. The majority 37.8% had attained secondary education, while 33.3% had been to university. Eight percent reported having no education at all. Self-employment was the main source of income in most cases at 65.4%, while 3.8% were unemployed (**Table 1**). Twenty six (16.7%) were civil servants and 4.5% had achieved professional status. 82.7% were married, while 9.6% were single and 7.7% widowed. There was no evidence of organ transplantation throughout the study (**Table 2**). Majority of the participants had a CD4 count above 500 (62.8% **Table 2**). All those positives for hepatitis B had been through the educational system (**Table 3**).

Only 17.3% agreed to having had blood transfusion previously while 17.9% reported using condoms with every sexual encounter. 23.1% used condoms occasionally while 45.5% denied using condoms at all.

Of the travel history, the majority 87.2 % had no significant travel history. Only 9.0% had a positive travel history. There was no history of organ transplant in any of the cases. 26.3% percent had pregnancy less than two years ago and 37.2% reported pregnancy over four years ago. Reviewing the infections as dual infections with HIV *i.e.* HIV and HBV, for HBV/HIV dual infection the majority was married and 7.8% of these were positive for HBV. Regarding education the majority of positive cases were among those who had attained tertiary education. Most (78%) had no history of blood transfusion and of those positive (HIV/HBV) only 1 (3.6%) agreed to using condoms for every sexual encounter.

Most of them (92.6%) had no travel history. For dual infection with HEV according to marital status the widowers had the highest rate of infection at 16.7%, educational

Table 1. Socio-demographic distribution of HIV study population.

Sex	
Female	128 (82.1)
Male	28 (17.9)
Religion	
Christianity	87 (55.8)
Islam	69 (44.2)
Occupation	
Artisan	15 (9.6)
Professional	7 (4.5)
Civil servant	26 (16.7)
Self employed	102 (65.4)
Unemployed	6 (3.8)
Marital status	
Single	15 (9.6)
Married	129 (82.7)
Widowed	12 (7.7)
Educational status	
Primary	37 (23.7)
Secondary	59 (37.8)
Tertiary	52 (33.3)
None	8 (5.1)

Table 2. Distribution of predisposing factors to Hepatitis B & E among HIV positive respondents.

Transfusion	
No	129 (82.7)
Yes	27 (17.3)
Condom use	
Always	28 (17.9)
Occasionally	36 (23.1)
Not at all	71 (45.5)
Travel history	
No	136 (87.2)
Yes	14 (9.0)
Pregnancy	
<2 Years ago	41 (26.3)
Years	13 (8.3)
>4 Years	58 (37.2)
History of diarrhoea	
No	150 (96.2)
Yes	6 (3.8)
Organ transplant	
No	156 (100)
CD4 count	
Below 200	26 (16.7)
200 - 499	32 (20.5)
500 & Above	98 (62.8)

status ($p = 0.002$) was the only statistically significant variable and the highest percentage of those positive for HEV had no form of education at all. Those with secondary school education had the lowest rate of infection at 3.4%. Of the transfusion history, 7.4% had a positive history. 24.5% were positive for HEV while 7.8% were positive for

Table 3. Association between socio-demographic characteristics and presence of hepatitis B.

Risk factors	Hepatitis B		Chi-square value	P value	Remark
	Negative (%)	Positive (%)			
Marital status					
Single	15 (100.0)	0 (0.0)	2.24	0.327	NS
Married	119 (92.2)	10 (7.8)			
Widowed	12 (100.0)	0 (0.0)			
Educational status					
None	8 (100.0)	0 (0.0)	0.766	0.858	NS
Primary	35 (94.6)	2 (5.4)			
Secondary	55 (93.2)	4 (6.8)			
Tertiary	48 (92.3)	4 (7.7)			
Transfusion					
Yes	27 (100)	0 (0.0)	2.236	0.135	NS
No	119 (92.2)	10 (7.8)			
Condom use					
Every	27 (96.4)	1 (3.6)	1.009	0.799	NS
Occasionally	33 (91.7)	3 (8.3)			
Not at all	67 (94.4)	67(94.4)			
Travel					
No	126 (92.6)	10 (7.4)	1.571	0.456	NS
Yes	14 (100.0)	0 (0.0)			

HBV. Of those positive for both HEV and HBV alanine transaminase levels were not statistically significant.

4. Discussion

Our study population revealed that 128 were female and 28 were male. This is not surprising as all studies we have carried out on HIV expose the higher incidence of HIV in females than males which has been established in other studies. Overall the majority of our subjects were married (82.7%) (Table 1). 24.5% were positive for HEV. This is on the high side when compared to 11.7% obtained by Hassing *et al.* in a study carried out in Holland in 2014. This might be explained by the more affluent society that study was carried out with cleaner healthier environment and higher quality of health care. It was also noted that HEV positivity was equally prevalent among different CD4+ groups which is similar to our findings (Table 2) [21]. It should be mentioned at this point that HEV infection has been linked with poverty in the developing world such as Nigeria. [22]. Increasing incidence of co infection of HEV and HIV with age has been reported in South Iran, 47.7% occurring in those over 50 years.

The only statistically significant epidemiological association of HEV infection was with educational status. This is strikingly similar to studies carried out in other parts of Nigeria. In Plateau state Nigeria formal education was also one of the significant variables associated with HEV [23]. The more educated the society is, the more likely higher emphasis would be placed on positive environmental issues such as cleanliness, positive attitude to health care and other important factors ensuring a healthier environment. Other risk factors identified by the study included marital status, location and farming as a profession. In our study marital status revealed that the highest number of

HEV positive cases were among those who were widowed and married (Table 4). HEV infection is an acute self limiting infection that is responsible for up to 20% of deaths in pregnant women. None of our female participants were pregnant and reports of the infection among pregnant women are somewhat low [24]. However in India high infection rates have been reported with increased severity of infection [25] [26]. This further underlines the fact that location, surroundings etc. have a significant role to play in HEV infection rates.

Blood transfusion is also a risk factor for HEV infection. Of those positive for HEV in our study, 2 (7.4%) (Table 2) had a positive history of blood transfusion. Transfusion safety has been of paramount importance for the transfusion services worldwide and with time the transfusion safety has been constantly improving due to mandatory screening of blood and blood products with regular introduction of more sensitive tests. Currently screening of blood and blood products for HEV is not done and there are also no recommendations. But the question is largely unanswered whether parenterally transmitted HEV is a risk to transfusion safety. It may well be that screening for HEV would be added to the battery of screening tests especially as SOTs (solid organ transplants) become a more frequent treatment option.

In our cohort there was no history of organ transplants, however this cannot escape mention because it is well known and accepted that patients with reduced immunity are prone to the effects of HEV infection. In a study in the Netherlands, it was found that patients with solid organ transplants (SOTs) were at a definite higher risk of HEV infection.

Table 4. Association between socio-demographic characteristics and presence of hepatitis E.

Risk factors	Hepatitis E		Chi-square value	P value	Remark
	Negative (%)	Positive (%)			
Marital status					
Single	15 (100)	0 (0.0)	2.612	0.271	NS
Married	119 (92.2)	10 (7.8)			
Widowed	10 (83.3)	2 (16.7)			
Educational status					
None	5 (62.5)	3 (37.5)	14.398	0.002	S
Primary	32 (86.5)	5 (13.5)			
Secondary	57 (96.6)	2 (3.4)			
Tertiary	50 (62.5)	2 (3.8)			
Transfusion					
No	119 (92.2)	10 (7.8)	0.004	0.951	NS
Yes	25 (92.6)	2 (7.4)			
Condom use					
Every	28 (100)	0 (0.0)	3.886	0.274	NS
Occasional	33 (91.7)	3 (8.3)			
Not at all	63 (88.7)	8 (11.3)			
Travel out					
No	126 (92.6)	10 (7.4)	0.709	0.702	NS
Yes	13 (92.9)	1 (7.1)			

Nine of 12 patients who had SOT were treated postoperatively with a tacrolimus-based regimen, which has been associated with increased risk for HEV infection [27]. In time SOTs as a treatment option in this part of the world would increase as health care systems strive to improve in quality along with best practices worldwide.

In our study, 7.8% of the HIV positive patients were co-infected with HBV and were all married. This is somewhat lower to figures obtained in Italy where 15.4% of cases were found to be co-infected [28]. However, coming down to Africa in Burkinafaso, 12.17% out of 115 pregnant HIV positive patients were found to be positive for HBV. Though in Mali only a co-infection rate of 1.13% was obtained [29]. In South Africa, co-infection rates as high as 20% were detected by investigators [29]. Another study in Nigeria revealed co-infection rates of 11.9%. It can be deduced from this wide swings of co-infection rates that co-infection is largely dependent on particular environments. This in turn would now involve variables within the location such as hygiene, access to quality healthcare and educational status among others. However unlike with HEV, educational status was not statistically significant ($p = 0.002$) (Table 3). It has been suggested that HBV infection is more likely to occur in HIV infected individuals than in none infected persons probably due to reduced immunity. Interestingly it has also been suggested that HBV infection routes differ to those of HIV. Studies have linked HIV transmission to stronger association with sexual activity, while transmission routes involving HBV are majorly vertical. At this point it may be relevant to note that transmission routes for hepatitis C virus infection (HCV) have been strongly associated with parenteral routes. The point being that even though all three viruses may be present in an individual, each virus has its own unique and “preferred” transmission route. This is very important especially when it regards developing methods aimed at reducing or preventing transmission altogether [30]-[35]. The study revealed that levels of alanine transaminase in those both positive for HEV and HBV were not particularly significant (Table 5). It was found that 24.5% were positive for hepatitis E while 7.8% were positive for hepatitis B. It was also found that educational status was the only statistical variable for HEV co-infection. Alanine transaminase levels were not significantly affected in this study. Taking 12 U/L as upper limit of normal, the mean average for HEV positive patients was 13.8U/L while for those HBV positive was 10U/L (Table 5 and Table 6). Patients positive for HEV and revealing normal alanine transaminase levels are not unknown as was shown in a study carried out in Australia [36]. Another study suggested that persistent elevation of alanine transaminase levels were suggestive of chronic cases of HEV infection [37]. That study also seemed to indicate that co-infection with HCV was more likely to be the cause of raised alanine transaminase levels even in the presence of HEV [37]. The majority of our patients had CD4 counts of above 500. This should not be unexpected as they were all on HAART and clinically stable with absence of recurrent fever, candidiasis or other clinical indicator of immune deficiency. However it should be noted that the British HIV association has stated in its treatment options for co-infected patients with HBV, that even those with CD4 counts above 500 should be given the option of commencing treatment.

Table 5. Mean AGE and ALT levels in those both positive and negative for HBV.

	ALT	Age
Positive	10	40.28
Negative	10.6	41.30

Table 6. Mean age and alt levels in those both positive for HEV.

	ALT	AGE
Positive	13.08	47.83
Negative	9.76	39.72

5. Conclusion

As HIV/AIDS patients continue to live longer due to the introduction of highly active antiretroviral therapy (HAART) in 1996, the emergence and relationship of co-infection with other viruses especially the hepatic viruses and their adverse contributions to the infection have become global causes of concern. However, more research has to be undertaken to increase our knowledge in this part of the world on the effect of HIV co-infection with other viruses in order to improve treatment outcomes and reduce transmission rates. The established role of educational status in the incidence of HEV cannot be over emphasized. More should be done to increase the educational status of the populace more so in developing countries.

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