Hepatitis B and HIV co-infection is still treated using lamivudine-only antiretroviral therapy combination in Uganda

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Abstract

Background: Hepatitis B virus (HBV) and HIV are endemic in Uganda. Co-infection is common and leads to rapid progression of liver disease. Burden of co-infection is unknown yet most patients are on lamivudine-only ART where resistance is frequent. Most patients are initiated on antiretroviral therapy (ART) without knowing their HBV status.

Objectives: To determine burden of co-infection and HBV viral suppression among patients on ART in NorthernUganda.

Methods: We recruited HIV infected adult patients on ART in a cross-sectional study. Age, sex, ART regimen and duration were recorded. Hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBcAb) and liver panel were performed. For those HBsAg+, hepatitis B e antigen (HBeAg) and HBV DNA were performed. CD4 cell count was recorded.

Results: Three hundred patients were recruited. Twenty (6.7%) were co-infected, while 41% were anti-HBcAb+. Overall 188 (62.7%) were on lamivudine- only HBV active drug. Median ART duration 2 years (IQR 1-5), mean CD4+ cell count 317 cells/microlitre (SD 255-557). Of 20 HIV/HBV co-infected, 11/20 (55%) were on lamivudine-only ART, median duration 1.5 years. Nineteen (95%) had undetectable HBV DNA. Seventeen (85%) were HBeAg negative. Mean CD4+ cell count 327 cells/microlitre (SD 197-482).

Conclusion: A large proportion of patients were on lamivudine- only HBV-active ART. Resistance may occur long term thus testing for HBV and correct ART is recommended

Key words: HIV, HBV, Co-infection, Treatment

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Introduction

Hepatitis B virus (HBV) infection is common in Uganda with a national prevalence of 10% reported in 2009. However, the epidemiology varies considerably in the different regions in Uganda . The Northern region has the highest prevalence of between 20% to 25%.[1] On the other hand human immune deficiency virus (HIV) is also endemic in Uganda with a national average of 7.3%.The two viruses share modes of transmission, thus co-infection is expected to be high. Previous studies in Uganda have reported co-infection rates of 10% to 23%.[2,3]

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Human Immmune deficiency virus (HIV) infection is associated with rapid progression of liver disease in persons who are co-infected with HBV. This is even more relevant currently when antiretroviral therapy (ART) has improved life expectancy for patients with HIV even in resource limited settings. This situation has led to liver disease becoming one of the most important causes of early death among the HIV infected individuals in the Western world.[4-6] Even where treatment and monitoring is widely available, liver disease still accounts for up to 20% of deaths in HIV positive patients.[7] In the areas most affected by HBV and HIV infections, high co-infection rates worsen the prognosis in dually infected individuals. Rates of hepatitis B serological conversion and viral clearance have been shown to be lower in patients co-infected with HIV, leading to accelerated rates of progression to cirrhosis.[8]

Lamivudine, tenofovir and emtricitabine, used in HIV infection are as well effective against HBV. Use of these drugs in the overall ART combination has led to significant improvement in outcome of co-infected patients. However, resistance to lamivudine (and emtricitabine) occurs very frequently. In co-infected patients the incidence of resistance reaches up to 90% over 5 years of treatment.[9] Resistance will lead to reversal of the gains achieved by using ART. All the complications that occur in co-infected patients who are not on ART will become tenable when lamivudine resistance occurs. Tenofovir however, has not shown significant resistance over 5 years of use in co-infected patients.[10] An ART combination containing tenofovir+ lamivudine or tenofovir+ emtricitabine is recommended in co-infected patients.[4,11,12] Such guidelines are not in existence in most sub-Saharan African countries despite the latter carrying the highest burden of co-infections worldwide. This could partly be because of lack of evidence of resistance patterns.

Unfortunately since most of our patients are initiated on therapy without testing for HBV and majority have been on lamivudine monotherapy (for HBV in co-infected patients) inadvertently there may be a lot of resistance in the patient population especially where the burden of both infections is high. Hepatitis B viral loads and liver function tests may be indicators of resistance and possible HBV flares. In this study we determined the burden of co-infection and HBV viral suppression among patients who have already been on ART in the Northern part of Uganda which carries a high burden of HBV and HIV.

Patients and methods

We conducted a cross-sectional study among patients attending the HIV clinic in Gulu regional referral hospital. At the time we started data collection this clinic, had 1,744 patients active on ART. Close to 200 clients attend the clinic everyday and most of the patients were on ART combinations containing either zidovudine/lamivudine or tenofovir/lamivudine in addition to nevirapine or efavirenz as first line combinations. A few patients were on alluvia with any of the above combinations for second line.

All patients attending the clinic who where 18 years or more and on ART were eligible to participate in the study. They were recruited after signing informed consent document. Because of the large numbers, we recruited the first 20 patients who fulfilled the eligibility criteria on each clinic day as long as the participant had not been recruited before in this study.

We collected data on age, sex, marital status, widow or widower as well as clinical information: history of yellow eyes, family history of liver diseases, ART regimen and duration on ART, any other drugs. We drew 10 milliliters of venous blood for further investigations, divided into purple top and red top containers, each carrying 5 milliliters. We performed hepatitis B surface antigen (HBsAg) test using HBsAg card (Cypress Diagnostics, Langdorp, Belgium) using a drop of whole blood. Results of these tests were read in 20 minutes and reported as positive or negative. The remaining samples were then transported to the main laboratory where further testing was performed. For all patients, liver panel was performed using Eon one chemistry analyzer (Viral Diagnostics, Victoria, Australia), with reagents from Cypress Diagnostics (Langdorp, Belgium). The upper limit of normal (ULN) for alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was 40 IU/mL.

On the other hand ULN for total Bilirubin, albumin, total protein, gamma glutamyl transferase , and alkaline phosphatase (ALP) were reported as 17 micromol/L, 50 g/L , 83 g/L , 54 U/L and 125 U/L respectively. In addition, hepatitis B core antibody (HBcAb) was performed on all patients while HBeAg testing was done on samples that had initially tested positive for HBsAg. The testing for HBcAb and HBeAg were done using Biomeriuex miniVidas automated immunoassay analyzer (Biomerieux, Marcy l'Etoile, France). The same HBsAg positive samples were subjected to HBV DNA testing using real time polymerase chain reaction (RT PCR) using COBAS AmpliPrep/COBAS TaqMan HBV Test, v2.0 by Roche, with a lower limit of quantification (LLOQ) of 20 IU/mL. Patients were requested to allow use of their CD4 cell count results performed routinely in this clinic.

HBV viral loads was deemed to have been suppressed if it was below the lower limit of quantification of 20 IU/mL.

The study was approved by School of Medicine Research Ethics committee of Makerere University as well as the Uganda National Council for Science and Technology.

Data was entered in a Microsoft access program and exported to stata- version 12 for analysis. The prevalence of HBV infection was expressed as proportion of those who tested HBsAg positive in the total pop-

ulation recruited. Comparison of liver panel among the co-infected and HIV mono-infected patients was performed at bivariate levels Variables with p-values of <0.05 were considered significant.

Results

In the months of May and June 2013, three hundred patients were recruited in the study, composed mainly of young patients with a median age of 36.5 years, most of whom (74.7) were of female gender as seen in table 1. Twenty of 300 patients (6.7%) tested positive for HBsAg while 41% were exposed to hepatitis B (anti-HBcAb positive). All patients were on ART of whom 188 (62.7%) were on lamivudine as the only drug active on HBV in the ART combination and 110 (36.7%) were on a combination of lamivudine plus tenofovir. Overall, patients had been on ART for a median duration of 2 years (IQR 1-5) and their mean CD4+ cell count was 317 cells/ µL (SD 197-482).

Table 1. Baseline characteristics of HIV infected patients on ART attending Gulu Regional referral hospital Infectious Diseases Clinic, 2013 (N=300)

Parameters	
Age; years (median)	36.5 (10.6)
Gender; Female n (%)	224 (74.7)
ART regimen distribution*	
Lamivudine (%)	188 (62.7)
Tenofovir (%)	2 (0.6)
Lamivudine+Tenofovir, n (%)	110 (36.7)
Tenofovir +Emtricitabine (Truvada™), n (%)	0 (0))
Duration on ART median(IQR) years	2 (1 - 5)
CD4 count (mean) cells/ µL	317 (197-482)
HBsAg +, n (%)	20 (6.7)
HBcAb, n (%)	118 (41.0)

*This lists only drugs active against HBV in the ART regimen. Patients were on complete ART combinations

Table 2 describes demographic, clinical and laboratory characteristics of the 20 patients who were co-infected with HBV. Most of these patients, 11/20 (55%) were on lamivudine only ART and they had been on ART for a median duration of 1.5 years. Nineteen (95%) of these patients had undetectable HBV viral loads over this median duration of treatment. Seventeen (85%) patients had the hepatitis B e antigen negative chronic HBV type. In general, the mean CD4+ cell count of the 20 patients was 327 cells/ µL (SD 255-557) and liver enzymes (ALT, AST) were within normal limits.

Table 2 Demographic, clinical and laboratory characteristics of HBV HIV infected patients attending the Gulu HIV clinic 2013, (N=20)

Parameters	No	Percent
Age; median (IQR)	30.5 (27.5- 39)	
Gender; Female	19	95
ART regimen distribution*		
Lamivudine	11	55
Tenofovir	0	0
Lamivudine+Tenofovir	9	45
Tenofovir+Emtricitabine	0	0
Median duration on ART, years (IQR)	1.5 (0.75-5.0)	
Mean CD4 cell count/ µL (SD)	327 (255-557)	
HBeAg negative	17 (85.0)	
HBV DNA detected	1	5
Mean ALT, U/L (SD)	26.3 (20.6)	
Mean AST, U/L (SD)	28.0 (12.9)	

*This lists only drugs active against HBV in the ART regimen. Patients were on complete ART combinations

Comparing liver panel between HBsAg-positive and HBsAg-negative revealed no statistical difference in the two arms, except for a trend to higher total Bilirubin in the HBsAg negative individuals and this is shown on Table 3.

Table 3. Comparison of liver panel among HIV infected patients with (HBsAg+) and without (HBsAg-) Hepatitis B infection in Gulu HIV clinic, 2013

Variable	HBsAg-	HBsAg+	P-value
Albumin: mean(SD), g/l	42 (0.46)	43 (4.1)	0.4419
ALP: median (IQR), U/L	83 (68-99)	92 (76-109)	0.2015
GGT: median (IQR), U/L	33 (24-56)	45 (29-84)	0.1265
Bilirubin: mean (SD) µL	85.0 (56.1)	57.8 (18.7)	0.0560
Protein: mean (SD) g/L	74 (0.81)	73 (7.3)	0.7404
CD4 cell count: median (IQR) /µL	316 (190-481)	327 (255-557)	0.2945

Discussion

Our study has demonstrated that most patients in this clinic have been on lamivudine as the only active drug against hepatitis B in HIV infected patients. This has been the trend previously in most clinics in sub-Saharan Africa where most ART combinations were composed either of zidovudine plus lamivudine, or stavudine and lamivudine in addition to either nevirapine or efavirenz.[13-15] In most patients these treatment regimens were taken without routine screening for hepatitis B and most regimens did not therefore take HBV into consideration.

In this study we have shown that chronic hepatitis B occurred in 6.7% of the patients with a level of exposure measured at 41%. These figures are lower than what has been shown in the general population in this Northern Ugandan region. Bwogi et al, in a study conducted as part of National sero-survey in the year 2004 in Uganda demonstrated a general population prevalence of 21% in the North Central districts of Uganda where Gulu is located.[1] Another study conducted in 2009 by Ochola et al in Gulu Municipality in 2009 showed a prevalence of 17% in the Municipality.[16] It is not clear whether this is a result of general awareness of the population

on HBV and the fact that many people have resorted to HBV vaccination in addition to the early childhood vaccination which was initiated in Uganda in 2002.

Despite the 6.7% prevalence of HBV and the fact that most patients were on lamivudine as the only drug active against HBV in the ART combination we have shown that 93.7% had undetectable viral loads over an average treatment period of 1.5 years. However one patient had detectable viral loads. This was a female patient who was HBeAg negative and had HBV viral loads of 2,464,000 IU/mL at nine years of lamivudine plus zidovudine combination. The liver enzymes were actually elevated with an ALT level of 95.9 U/L. These findings show that lamivudine-only ART therapy was adequate in suppressing HBV virus in the short run. As treatment duration increases there is likely to be an increasing number of patients presenting with increased viral loads as has been seen in the one patient described above. Although in this study resistance testing was not done, it is likely that this patient already had breakthrough infection with HBV resistance and this could lead to worsening of liver disease. In this patient the elevation of the liver enzymes noted in the study already shows liver cell injury which if not treated adequately would lead to cirrhosis and its complications. We recommended HIV viral loads be performed for this patient and the treatment be changed to include tenofovir. .

Limitations

This study had several limitations. First, because of the cross-sectional nature of the study we could not tell what the HBV viral loads were at initiation of ART. The low HBV viral loads observed in these patients especially in those on lamivudine-only ART could be a result of low viral loads at initiation. Lamivudine is able to cause significant viral suppression in situation of low viral loads at antiviral therapy initiation with limited chance of accumulation of resistance strains.[1] The possibility of low viral loads at initiation could also be entertained by the fact that most patients were HBeAg negative. We cannot however also tell if the observed HBeAg status was a result of seroconversion. This is however unlikely since sero-conversion is not a common occurrence especially considering the average duration of therapy and the fact that this HBV is occurring in combination with HIV.[4,17,18] Also, a previous study in the same location in Northern Uganda showed that even in the general population most patients are infected with the HBeAg negative HBV with low viral loads.[16] Secondly, we were not able to perform sequencing thus making it difficult to know if the high HBV viral loads seen in the one patient were a result viral mutations. In the HIV infected populations resistance rates to lamivudine of up to 90% has been shown by 5 years of treatment.[9] It is possible that as more patients continue to be on the treatment with lamivudine-only ART more patients may be seen with HBV high viral loads. Thirdly, we did not assess adherence in the patients and were not able to perform HIV viral load testing. Suppression of both HIV and HBV viral loads would have helped to define possibility of good adherence. It is important to note that the number of patients on ART containing tenofovir seem to be high in the later years and this could reduce the risk of resistance and virologic breakthroughs since it is a very effective drug with limited resistance.[4,10]

Finally, there was no statistical difference in the liver enzymes among those who were HBsAg positive and those who were HBV uninfected. This could also mean that within the mean duration studied, the HBV suppression was adequate.

Conclusion

The prevalence of co-infection was 6.7% and most of these patients were on lamivudine- only antiretroviral therapy combination. Although most patients were suppressed within a short duration of treatment, prolonged treatment with lamivudine could lead to resurfacing of HBV which could lead to worsening of liver disease progression and outcome as seen in the one patient. Treatment with tenofovir in combination with either lamivudine or emtricitabine is recommended to avoid this outcome

Conflict of Interest:

The authors do not have any conflict of interest to declare

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