

Five-Year Review of HIV-Hepatitis B Virus (HBV) Co-Infected Patients in a New York City AIDS Center

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Received: 1 February 2012
Accepted: 28 March 2012

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A retrospective review of 4,721 human immunodeficiency virus (HIV)-infected patients, followed at St. Luke's Roosevelt Hospital Center, New York City, was conducted from January 1, 2005 to December 31, 2009. HIV-Hepatitis B virus (HBV) co-infection rate was 218/4,721, 4.6%. Among co-infected patients, 19 patients (19/218, 8.7%) died; 13 patients (13/19, 68.4%) died from non-acquired immune deficiency syndrome (AIDS) defining including 2 patients with liver failure. More non-survivors (5 patients, 5/19, 26.3%) had liver cirrhosis than those who survived (8 patients, 8/199, 4.0%; $P = 0.002$). There were more patients with positive HBV e antigen (HBeAg) among non-survivors, (12 patients, 12/19, 63.2%) than among survivors (74 patients, 74/199, 37.2%; $P = 0.047$). HIV-HBV co-infection is associated with increased overall mortality. Therefore, use of dual active antiretrovirals, particularly, tenofovir (TDF) based regimen for optimal suppression of HIV-HBV and immune restoration with prevention of high risk behaviors may contribute to improved outcomes.

Key Words: HIV; Hepatitis B Virus; Mortality

Chronic hepatitis B virus (HBV) infection is recognized in 5%-16% of human immunodeficiency virus (HIV)-infected patients in Western Europe and the United States (1, 2). HIV-HBV co-infection poses an increased risk for liver related morbidity and mortality from impact of HIV on progression of HBV leading to greater levels of HBV viremia and increased rate of liver cirrhosis (3, 4). Also lower incidences of spontaneous loss of HBV surface antigen (HBsAg) have been observed because of HIV-induced impairment of host innate and adaptive immunity (5). Few, however, have examined the outcome of HIV-HBV co-infected patients. Therefore, we investigated treatment experience of HIV-HBV co-infected patients in our center.

A retrospective chart review of 4,721 HIV-infected patients, followed at the Center for Comprehensive Care at St. Luke's Roosevelt Hospital Center, New York City, was conducted from January 1, 2005 to December 31, 2009. Co-infection with HBV by positive HBsAg was identified in 218 patients. We analyzed demographic data, laboratory data including CD4 T cell count, HIV viral load, alanine transaminase (ALT), HBV viral load, HBsAg, HBV surface antibody (HBsAb), HBV e antigen (HBeAg), hepatitis C virus (HCV) antibody as well as abdominal imaging (either ultrasound sonography [US] or computed tomography [CT]), liver biopsies, anti-HBV medications, and documented treatment outcomes. HCV co-infection was defined by having

presence of HCV antibody and liver cirrhosis was defined by either abdominal imaging or liver biopsy.

We conducted a descriptive analysis. Then, comparison analysis was performed between patients who survived with those who died. Dichotomous variables and continuous variables were compared using two-sided Fisher's exact test, Mann-Whitney test, respectively. SPSS Version 18.0 for Windows (SPSS) was used for the analysis. P values of less than 0.05 were considered to indicate statistical significance. This study protocols were approved by the institutional review board (IRB) of the St. Luke's Roosevelt Hospital Center (#09-081X).

Our HIV-HBV co-infection rate was 218/4721 (4.6%). The mean age of the HIV-HBV co-infected cohort was 46 yr (interquartile range [IQR]: 41-51 yr). Men were 173 patients (173/218, 79.4%). Blacks were 139 patients (139/218, 63.8%). Hispanics and Whites were 19.3%, 16.1%, respectively. The following HIV risk factors were identified; male sex male (MSM) was noted in the 45.4% of the patients; heterosexual contacts and intravenous drug abuse (IDU) were noted in the 40.8%, 11.0% of the patients, respectively. HIV-HBV-HCV co-infection was noted in 15.6% of the patients (34 patients, 34/218).

At the end of observation period (median follow-up of 2.9 yr, IQR: 1.7-4.0 yr), the following were observed. Median CD4 T cell count was 287 cells/ μ L, and median \log_{10} HIV viral load (copies/

mL) was 3.00. Median ALT was 39 U/L. Radiographic evidence for liver cirrhosis was noted in 13 patients (13/218, 6.0%). Undetectable HBV viral load was seen in 83 patients (83/218, 38.1%). HBV genotype was done in 19 patients and majority of genotype was A (11/19, 57.9%) and G (7/19, 36.8%) with lamivudine resistance in 5 patients. Positive HBeAg was noted in 86 patients (86/218, 39.4%). Loss of HBsAg was noted in 11 patients (11/218, 5.0%) and seroconversion of positive HBsAb occurred in 7 patients. There were 183 patients (183/218, 83.9%) who received anti-HBV treatment with or without part of highly active anti-retroviral therapy (HAART) for HIV treatment. The combination treatment of tenofovir (TDF)/emtricitabine (FTC) was the most commonly used regimen and overall TDF based regimen was observed in majority of patients on anti-HBV treatment (149/183, 81.4%). Of interest, among 83 patients who had undetectable HBV DNA viral load, 63 patients (63/83, 75.9%) were on TDF based anti-HBV treatment regimen. Also 7 patients (7/11, 64%) of those who lost HBsAg were noted to be on TDF based regimen.

Total of 19 patients (19/218, 8.7%) died during observation period, 3.1 deaths/100 person-years; 6 patients (6/19, 31.6%) died from acquired immune deficiency syndrome (AIDS) defining illness (1.0 deaths/100 person-years) including lymphoma (3 patients), Kaposi's sarcoma (2 patients), and disseminated *Mycobacterium avium* complex (1 patient). There were 13 patients (13/19, 68.4%) who died from non-AIDS defining illness (2.1 deaths/100 person-years) including 2 patients with liver

failure (2/19, 10.5%, 0.3 deaths/100 person-years) and others with rectal cancer (n = 2), sepsis (n = 6), bacterial pneumonia (n = 1), drug over dose (n = 1), and suicide (n = 1). We categorized the patients into two groups, 199 survivors (199/218, 91.3%) and 19 non-survivors (19/218, 8.7%) for further analysis. Presence of liver cirrhosis was significantly different in these two groups. More non-survivors (n = 5, 5/19, 26.3%) had liver cirrhosis than those who survived (n = 8, 8/199, 4.0%; $P = 0.002$). Of note, 3 of 8 liver cirrhosis patients who survived were diagnosed by liver biopsies. Causes of death in these 5 liver cirrhosis patients were liver failure (n = 2), sepsis, Kaposi's sarcoma, and bacterial pneumonia. There were more patients with positive HBeAg among non-survivors, (n = 12, 12/19, 63.2%) than among survivors (n = 74, 74/199, 37.2%; $P = 0.047$). No significant differences were found among other variables between two groups including ALT levels, undetectable HBV viral load, CD4 T cell count, HIV viral load, presence of HCV co-infection, and anti-HBV treatment. These are shown in Table 1.

In accordance with previous studies (1, 2), our study showed that the HIV-HBV co-infection rate was 4.6%, reflecting current epidemic of HIV-HBV co-infection in the United States. Although HBV genotype was not checked for our entire HIV-HBV co-infected patients, majority of available HBV genotype was A followed by G. These results correspond with the results of earlier studies (6, 7), which reported prevalence of HBV genotype A and G in the United States.

In the HAART era, deaths from AIDS-related causes decreased

Table 1. Comparison of survivors and non-survivors in HIV-Hepatitis B virus (HBV) co-infected patients

Parameters	Survivors n (199/218, 91.3%)	Non-survivors n (19/218, 8.7%)	P value
Age (yr) (median, IQR)	46 (41-51)	47 (40-55)	0.494
Sex			0.376
Male (%)	156 (78.4)	17 (89.5)	
Female (%)	43 (21.6)	2 (10.5)	
Race			
White (%)	33 (16.6)	2 (10.5)	0.745
Black (%)	124 (62.3)	15 (78.9)	0.212
Hispanic (%)	40 (20.1)	2 (10.5)	0.541
Asian (%)	2 (1.0)	0 (0.0)	1.000
HIV risk factors			
Hetero (%)	82 (41.2)	7 (36.8)	0.810
MSM (%)	91 (45.7)	8 (42.1)	0.814
IDU (%)	20 (10.1)	4 (21.1)	0.140
Other (%)	6 (3.0)	0 (0.0)	1.000
Presence of HCV (%)	30 (15.1)	4 (21.1)	0.508
ALT (median, IQR)	36 (23-61)	50 (39-63)	0.208
Presence of cirrhosis (%)	8 (4.0)	5 (26.3)	0.002
Positive HBV e antigen (%)	74 (37.2)	12 (63.2)	0.047
Undetectable HBV viral load (%)	79 (39.7)	4 (21.1)	0.140
CD4 count (median, IQR)	288 (125-463)	215 (94-395)	0.285
HIV viral load (Log ₁₀ median, IQR)	2.92 (1.87-4.61)	4.08 (2.60-4.80)	0.135
Treatment			
No treatment (%)	32 (16.1)	3 (15.8)	1.000
TDF-based treatment (%)	138 (69.3)	11 (57.9)	0.311
Non-TDF-based treatment (%)	29 (14.6)	5 (26.3)	0.188

IQR, interquartile range; MSM, male sex male; IDU, intravenous drug use; HCV, hepatitis C virus; ALT, alanine transaminase; TDF, tenofovir.

significantly, however, non-AIDS mortality in HIV-infected patients increased (8, 9). Results of the present study correspond with the results of earlier studies which reported decreasing trend of AIDS-related deaths. Death rate in our cohort of HIV-HBV co-infected patients was 3.1 deaths/100 person-years, which was higher than that of recent study (1.3 deaths/100 persons-years in 2004) conducted for overall HIV-infected patients in the multiple United States cities (8), suggesting vulnerability of HIV-HBV co-infected patients to all-cause mortality as evidenced from a recent meta-analysis (10).

The increased overall mortality rate in HIV-HBV co-infected patients has been attributed to liver disease (11). And our results of liver cirrhosis presence and HBeAg reactivity as significant factors for all-cause mortality for both AIDS-related and non AIDS-related mortality including liver-related mortality would support this assumption from the previous study to some extent. However, an important finding in our study was that majority of mortality was due to non-liver related mortality. A recent meta-analysis (10) showed that the summary estimate of HIV-HBV co-infection studies performed after 1997 implied a lower risk of death due to liver-related causes in the HAART era.

Currently, liver-related mortality may have diminished in HIV-HBV co-infected patients with increased use of agents with dual activity against HIV and HBV, particularly TDF, which has been associated with highly suppressive HBV serological and/or virological outcomes with decrease in liver fibrosis score (12) without significant development of resistance (13). Also our data demonstrated that majority of patients who achieved loss of HBsAg and undetectable HBV viral load were on TDF based regimen with low incidence of overall liver cirrhosis and liver-related mortality, which further supports the use of TDF in the HIV-HBV co-infected patients.

The exact mechanisms for excess mortality risk in HIV-HBV co-infected patients is not completely understood, especially in the age of potent combinations of dual active antiretrovirals such as TDF/FTC. There are several possible reasons. First, both direct effects from chronic HBV infection manifested as liver cirrhosis/failure/carcinoma and indirect effects from chronic HBV infection on the host's immune system manifested as weak and narrowly focused immune response with T cell dysfunction (14, 15) need to be considered. Particularly, our study demonstrated HBeAg as a significant factor associated with all-cause mortality. Presence of HBeAg was associated with downregulation of Toll-like receptor 2 expression on hepatocytes and monocytes leading to decreased cytokine expression (16), suggesting a significant interaction between HBV infection with positive HBeAg and innate immune response. In addition, further immunomodulatory effects from HIV infection can lead to increased susceptibility to other diseases. Second, high-risk behaviors associated with HIV-HBV co-infection may place these patients at an increased risk for mortality (14, 17), as our study showed that

MSM and IDU were noted in the 45.4%, 11.0% of the patients, respectively, with including mortality of suicide and drug over dose.

Our study has limitations, however, mostly stemming from its small sample size and its retrospective nature. Although factors such as older age, low CD4 T cell count, detectable HIV viral load were shown to be associated with mortality in HIV-infected patients with compensated liver cirrhosis in the HAART era (18), our study did not show significant association between these factors and overall mortality in HIV-HBV co-infected patients. This might reflect one of limitations based on small sample size due to retrospective nature, not true absence of association. Nonetheless, our cohort of patients might well represent current urban HIV-HBV co-infected patients in the United States or other developed country with access to HIV care. Therefore, this study results should be of assistance to manage HIV-HBV co-infected patients.

In summary, HIV-HBV co-infection continues to be substantial clinical challenges in urban HIV clinic in the United States. HIV-HBV co-infection is associated with increased overall mortality. Therefore, use of dual active antiretrovirals, particularly, TDF based HAART regimen for optimal suppression of HIV-HBV and immune restoration with prevention of high risk behaviors may contribute to improved outcomes in the management of HIV-HBV co-infected patients.

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