Published in final edited form as:
Int J STD AIDS. 2008 November ; 19(11): 780–781. doi:10.1258/ijsa.2008.008020.

Alanine aminotransferase levels are not significantly elevated in patients with HIV/HBV co-infection and lamivudine resistance

D Bhattacharya, MD[*,†,‡], **D Katzenstein, MD**[*], **A Wong**[§], **D Israelski, MD**[*,†], **J C Imperial, MD**[†,**], **E B Keeffe, MD**[**], and **R M Donovan, PhD**[§]

[*]Division of Infectious Diseases, Stanford University School of Medicine, Stanford, CA 94305

[†]San Mateo Clinical AIDS Program, San Mateo, CA 94305

[‡]Division of Infectious Diseases, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA 90095, USA

[§]Viral and Rickettsial Diseases Laboratory, Department of Health Services, Richmond, 94804

[**]Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford 94304, USA

Summary

In hepatitis B virus (HBV) monoinfection, alanine aminotransferase (ALT) levels are linearly correlated with HBV DNA levels and lamivudine resistance. In human immunodeficiency virus (HIV)/HBV co-infection, little is known about the association between ALT, HBV DNA, and lamivudine resistance. We assessed HBV DNA, lamivudine resistance and ALT levels in 45 time points in 11 patients with HIV/HBV co-infection during lamivudine-containing antiretroviral therapy. High HBV DNA levels (>10^6 copies/mL) and lamivudine resistance developed in 45% and 91% of patients, respectively. However, ALT levels were not elevated in the setting of high HBV DNA levels (mean ALT, 48 IU/mL) or lamivudine resistance (mean ALT, 44 IU/mL). HBV viraemia and lamivudine resistance during extended lamivudine-containing antiretroviral therapy are common in HIV/HBV co-infection, occurring in the absence of significant ALT elevations. In HIV/HBV co-infection, measurement of HBV DNA and HBV resistance mutations may identify HBV virological failure before biochemical changes and should be routinely used in the management of HIV/HBV co-infection.

Keywords

HIV infection; highly active antiretroviral therapy; hepatitis B infection; hepatitis B drug resistance; lamivudine

INTRODUCTION

Upto 10% of human immunodeficiency virus (HIV)-infected individuals[1] are co-infected with hepatitis B virus (HBV). In resource-limited settings, many HIV/HBV co-infected individuals will receive lamivudine-containing highly active antiretroviral therapy (HAART), resulting in lamivudine monotherapy for hepatitis B infection. Alanine aminotransferase (ALT) values are markers of hepatic inflammation and used as tools in the

Correspondence to: Debika Bhattacharya, Division of Infectious Diseases, David Geffen School of Medicine at UCLA, 10833 Le Conte Avenue, 37-121 CHS, Los Angeles, CA 90095, USA, debikab@mednet.ucla.edu.

management of HBV infection. In HBV monoinfection, there is a linear correlation between serum HBV DNA and ALT levels.2 During lamivudine resistance, hepatitis flares are common; in those with transaminitis at five years of therapy, lamivudine resistance was temporarily associated with hepatic flare in >80% of individuals.3 In HIV/HBV co-infection, both HBV viraemia4 and lamivudine resistance5 are more frequent but little is known about the association between HBV viraemia, lamivudine resistance and ALT levels. In order to study the effects of lamivudine monotherapy for HBV infection in the setting of HAART, we sought to characterize HBV viraemia, lamivudine resistance and serum ALT levels in HIV/HBV co-infected individuals receiving extended lamivudine-containing therapy, in the era before the availability of other anti-HBV active nucleos(t)ide therapy.

METHODS

We evaluated 45 annual serum samples from 11 HIV/HBV co-infected patients who received lamivudine-containing antiretroviral therapy from 1996 to 2004. The mean duration of lamivudine therapy at study entry and termination was 2.4 and 5.6 years, respectively. All were males; 4/11 (36%) were non-white and 5/11 (45%) had hepatitis C virus co-infection. The study was approved by the San Mateo County Medical Center institutional review board.

Serum HBV DNA was determined using a real-time polymerase chain reaction (lower limit of detection 10^2 copies/mL).[6] HBV lamivudine resistance and genotype were identified by INNO-LiPA HBV DR and Genotyping, (Innogenetics). Rebound viraemia was defined as stable then rebounding HBV DNA or persistently elevated HBV DNA levels. An HBV viral load (VL) $\geq 10^6$ copies/mL was defined as a high HBV DNA levels.

RESULTS

At study entry, median HIV VLs and CD4 counts were 3.3 $\log_{10}$ copies/mL and 202 cells/μL, respectively. Ten of 11 patients were infected with HBV genotype A and one with genotype D (Table 1).

After a mean of 5.6 years of lamivudine-containing antiretroviral therapy, 91% (10/11) individuals and 76% (34/45) of samples had detectable HBV DNA (>200 copies/mL). In these patients, 64% (7/11) had rebound HBV viraemia, which was associated with lower mean CD4 counts (174 versus 379 cells/μL; P, < 0.08) and higher mean HIV VLs (4.8 $\log_{10}$ copies/mL versus 2.9 $\log_{10}$ copies/mL, P, < 0.03) at study entry. Rebound HBV viraemia usually occurred after more than four years of lamivudine-containing antiretroviral therapy. Lamivudine resistance was present in 10/11 (91%).

Serum HBV DNA and ALT levels were measured in all patients and in 40/45 samples. Five patients (10 isolates) had HBV VLs ≥ 10^6 copies/mL. Mean ALT values were not different between those with and without HBV VL ≥ 10^6 copies/mL, i.e. 48 and 42 IU/L, respectively (P = 0.65). Only 4/10 (40%) of samples with HBV VL ≥ 10^6 copies/mL had an ALT >51 IU/mL and none of the serum ALT determinations were > 125 IU/mL Mean HBV DNA levels during lamivudine resistance were higher (4.5 $\log_{10}$ versus 3.2 $\log_{10}$, respectively; P, < 0.07), but there was no difference between ALT levels in wild-type HBV viraemia compared with lamivudine-resistant HBV viraemia, 43 versus 44 IU/mL, respectively (P = 0.96). Although ALT levels were slightly higher during lamivudine resistance associated with HBV VL ≥ 10^6 copies/mL (52 versus 37 IU/mL), this difference did not reach statistical significance.

DISCUSSION

As lamivudine resistance is temporarily associated with transaminitis, recommendations for monitoring lamivudine resistance in HIV/HBV co-infection management also include the assessment of aminotransferase levels. However, our observations demonstrate that HIV/HBV co-infected patients do not demonstrate significant ALT elevations with high HBV DNA levels or the emergence of lamivudine resistance, limiting the utility of ALT as a surrogate marker for HBV DNA levels and resistance in this population. A limitation of this study was its small sample size. However, even in larger cohorts of HIV/HBV co-infected patients with lamivudine resistance only mild ALT elevations (<2.5 × ULN)[7,8] have been reported and usually with HBV VLs of > 10^8 copies/mL. These milder ALT elevations are in contrast to the higher ALT elevations seen in HBV monoinfection; in a large study of lamivudine resistance all ALT flares with lamivudine resistance occurred at elevations of 3 × ULN.

In HBV infection, CD4 cells are responsible for recognizing viral antigen and secreting cytokines.[9] In HIV/HBV co-infection, CD4 depletion may abrogate this response. Paradoxically, despite higher levels of HBV DNA and lower ALT values,[10] progression to cirrhosis occurs at a higher rate, reinforcing the need to identify the appropriate markers of disease progression.

In HIV/HBV co-infection, including those in resource-limited settings, HBV DNA levels and HBV resistance testing should be considered in the routine monitoring of HIV/HBV co-infection and the failure of antiviral therapy, as ALT levels may not reliably indicate HBV replication or the emergence of HBV lamivudine resistance.

Acknowledgments

This work was supported by NIH grant T32 AI052073 and a Bristol Myers Squibb Fellowship Award (DB). The authors would also like to acknowledge Innogenetics for supplying the INNO-LiPA HBV DR and Genotyping kits.

REFERENCES

1. Soriano V, Puoti M, Bonacini M, et al. Care of patients with chronic hepatitis B and HIV co-infection: recommendations from an HIV-HBV International Panel. AIDS 2005;19:221–240. [PubMed: 15718833]
2. Mommeja-Marin H, Mondou E, Blum MR, Rousseau F, Serum HBV. DNA as a marker of efficacy during therapy for chronic HBV infection: analysis and review of the literature. Hepatology 2003;37:1309–1319. [PubMed: 12774009]
3. Lok AS, Lai CL, Leung N, et al. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. Gastroenterology 2003;125:1714–1722. [PubMed: 14724824]
4. Hadler SC, Judson FN, O'Malley PM, et al. Outcome of hepatitis B virus infection in homosexual men and its relation to prior human immunodeficiency virus infection. J Infect Dis 1991;163:454–459. [PubMed: 1825315]
5. Benhamou Y, Bochet M, Thibault V, et al. Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus-infected patients. Hepatology 1999;30:1302–1306. [PubMed: 10534354]
6. Pas SD, Fries E, De Man RA, Osterhaus AD, Niesters HG. Development of a quantitative real-time detection assay for hepatitis B virus DNA and comparison with two commercial assays. J Clin Microbiol 2000;38:2897–2901. [PubMed: 10921947]
7. Matthews GV, Bartholomeusz A, Locarnini S, et al. Characteristics of drug resistant HBV in an international collaborative study of HIV-HBV-infected individuals on extended lamivudine therapy. AIDS 2006;20:863–870. [PubMed: 16549970]

8. Cooley L, Ayres A, Bartholomeusz A, et al. Prevalence and characterization of lamivudine-resistant hepatitis B virus mutations in HIV-HBV co-infected individuals. AIDS 2003;17:1649–1657. [PubMed: 12853747]

9. Vierling JM. The immunology of hepatitis B. Clin Liver Dis 2007;11:727–759. [PubMed: 17981227]

10. Rector WG Jr, Govindarajan S, Horsburgh CR Jr, Penley KA, Cohn DL, Judson FN. Hepatic inflammation, hepatitis B replication, and cellular immune function in homosexual males with chronic hepatitis B and antibody to human immunodeficiency virus. Am J Gastroenterol 1988;83:262–266. [PubMed: 3344728]

Table 1

Patient, virological and clinical characteristics

Patient	Age*	HCV†	Genotype	YMDD‡	Lamivudine duration§
1	43	Yes	A	Yes	8
2	48	No	A	Yes	7
3	41	Yes	A	Yes	6
4	43	No	A	Yes	6
5	31	Yes	A	Yes	7
6	51	Yes	A	Yes	2
7	35	No	A	Yes	6
8	44	No	A	Yes	4
9	37	No	A	Yes	4
10	50	Yes	D	No	7
11	38	No	A	Yes	5

*Age at study entry

†HCV = hepatitis C antibody positive

‡YMDD: lamivudine resistance

§Lamivudine duration at study end

Int J STD AIDS. Author manuscript; available in PMC 2010 August 2.