

A PEER-REVIEWED ARTICLE

Challenges face clinicians treating HbeAg negative chronic hepatitis B in HIV

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Recent improvements in antiretroviral therapies and medication adherence have resulted in advances in quality of life and decreases in mortality and morbidity rates. In turn, co-morbid infections such as chronic hepatitis B and C have become more prevalent, with co-infection rates of approximately 10% and 30% respectively, representing important aspects of HIV management for caregivers that need to be addressed appropriately to avoid liver complications. Chronic hepatitis B (CHB) is defined as a detectable hepatitis B surface antigen (HBsAg) on two separate checks at least six months apart. Inadequate treatment of both hepatitis B and C can result in liver cirrhosis and hepatocellular carcinoma (HCC), complications rarely seen previously due to high mortality rates from opportunistic infections. Long-term monotherapy or partial treatment of these infections can lead to development of resistance and may require newer therapies to treat chronic hepatitis B.

In the United States, chronic hepatitis is commonly seen in HIV-infected individuals. Chronic hepatitis B co-infection occurs in 7-15% of the HIV-positive population with 1% of HIV positives infected with both hepatitis B and C.^{1,2} Individuals with hepatitis B co-infection tend to have higher hepatitis viral loads, lower rates of spontaneous seroconversion, more severe liver disease, and increased rates of liver related mortality.^{3,5}

The genetic diversity of hepatitis B plays an important role in determining the progression of hepatitis B viral (HBV) infection. Hepatitis B is a hepadnavirus whose genome is composed of four Open Reading Frames (ORF): the “pre c/c” which encodes the hepatitis B e and hepatitis B core antigens (Ag), the “pre s/s” which encodes the hepatitis B s antigen, the “P ORF” (pol) which encodes the viral polymerase, and the “X ORF” which encodes a protein involved in host and viral gene expression. Genetic diversity may be explained by means of selective or non-selective pressure with genotypic diversity occurring due to the absence of selective pressure in the natural course of evolution. Phenotypic diversity can be explained by selective pressure from host immune responses to HBV infection or from antiviral therapies.⁶

Serotypes are classified based on the composition of amino acids of two mutually exclusive epitopes of HbsAg. HIV co-infection has not been found to correlate with differences in serotype expression. Genotypes are divided into ten categories, labeled A to J. A and D are universally found whereas the other serotypes are distributed regionally throughout the world, such as B and C predominantly in Asia, E in Africa, and F and H in Latin America and Pacific regions. Among patients co-infected with HIV/HBV, serotypes A and D predominate while B and C are infrequently observed. The impact of genotypes on liver disease severity has not been extensively studied, though one study showed a strong correlation between degree of liver fibrosis and genotype G after

adjusting for various factors in HIV/HBV co-infected patients.⁷

Generally, the majority of patients with chronic hepatitis B undergo seroconversion with loss of HBeAg and development of anti-HBe antibody, HBV DNA levels < 10⁵ copies/ml, normal ALT levels, and lesser risk of progression to cirrhosis and HCC. However, a small proportion of patients undergoing seroconversion experience return of high HBV DNA levels, have persistently or intermittently elevated ALT levels, demonstrate active inflammation on liver biopsy, and have a higher risk of progressing to cirrhosis and HCC, presumably due to mutations in the pre-core and basal core promoter regions that either prevent or decrease HBeAg expression. These patients generally have a poorer long term prognosis compared to HBeAg positive CHB patients. Thirty to 40% of these patients present with persistently high ALT levels (three to four fold) while 45-65% of patients may present with erratic ALT levels with periods of normal ALT levels interspersed with flares.⁸ Spontaneous lifetime remission occurs in less than 15% of these patients.⁸ The prevalence of HBeAg negative chronic hepatitis B varies geographically and is more common in regions where individuals are infected with non-A genotypes.

Precore, core, and basal core promoter (BCP) mutations are mainly found to affect pre-c/c regions and are more commonly found in HBeAg negative CHB patients. In the United States, the prevalence of precore and basal core mutations are 27% and 44% respectively.⁹ Pre C mutations are found to completely abolish HbeAg expression and are linked to genotype and to BCP mutations. Patients with advanced age and infected with BCP mutants tend to have increased risk for the development of liver cirrhosis and HCC. Although BCP mutations were more common in genotype C than genotype B in Taiwan, there was no difference in genotype B to genotype C ratio in HBeAg negative CHB patients with liver cirrhosis and HCC.¹⁰

MANAGEMENT

Therapy in HBeAg positive patients is indicated when serum HBV DNA levels are above 2 x 10⁴ copies/ml in addition to other factors such as likelihood of response, severity of disease, and likelihood of adverse reactions. However, anti-HBV therapy in HBeAg negative chronic hepatitis B patients is indicated when serum HBV DNA levels are above 2 x 10³ copies/ml and is initiated earlier in co-infected patients due to faster progression. Baseline liver biopsies may be indicated when serum HBV DNA levels of ≥ 10⁵ copies/mL exist. Patients with HBeAg negative CHB have fluctuating HBV DNA levels and may drop down below 10⁴ copies/ml. Hence, patients presenting with HBV DNA levels ≤ 10⁴ copies/ml with normal ALT levels are generally presumed to be either HBeAg negative CHB patients in a quiescent phase or inactive HBsAg carriers. In these situations, either histologic evaluation of a liver biopsy or serial monitoring for elevated ALT or HBV DNA levels is warranted to determine need to initiate therapy. Patients with mono-infection with HBeAg negative CHB generally have lower response rates, experience longer duration of therapy, and have higher relapse rates than HBeAg positive CHB patients. In addition, treatment endpoint for HBeAg negative CHB is not clearly defined since there is no seroconversion from HBeAg positivity to HBeAg negativity and hence has

to be based on suppression of HBV DNA and normalization of ALT levels with or without histological improvement.¹¹

In the HIV/HBV co-infected patient, for those needing treatment for the CHB it is not recommended that treatment should be given only aimed at the hepatitis B by agents that have activity for HIV also. Instead three-drug highly active antiretroviral therapy containing one or two active agents against both HIV and hepatitis B should be started regardless of CD4 count to prevent the development of resistance by the HIV to the agents.

(1) Adefovir

Adefovir dipivoxil is an analogue of adenosine monophosphate and its active metabolite, adefovir diphosphate, inhibits hepatitis B DNA polymerase. At low doses, adefovir suppresses hepatitis B virus replication and is associated with lower rate of resistance compared to lamivudine. Since adefovir is nephrotoxic, especially at the levels needed for HIV suppression, low doses are typically used to suppress HBV levels. Benhamou *et al.* showed that after 144 weeks of adding adefovir to lamivudine, 45% of patients experienced a decrease in serum HBV-DNA levels while 5-10% of CHB patients did not respond to ADV either due to cross-resistance, genetic polymorphisms, or low dose therapy.¹² Resistance mutations to adefovir have been described, such as substitution of asparagine with threonine (N236T) and alanine to valine or threonine A181V/T. There is also concern about the K65R mutation developing in co-infected patients not taking antiretroviral drugs although this has not been shown in recent studies; the K65R mutation influences the HIV sensitivity to reverse transcriptase inhibitors such as tenofovir, abacavir, and didanosine. In a trial comprising a total of 184 patients, fifty-five and seventy patients with HBeAg negative chronic hepatitis B treated for four and five years showed undetectable levels of HBV DNA in 65% and 67%. Addition of adefovir to lamivudine in the presence of lamivudine resistance did not confer any additional benefit according to the Gilead 461 trial, though experts recommend administration of at least three months of combined therapy before discontinuing lamivudine after adefovir has achieved HBV suppression.

(2) Tenofovir

Tenofovir disoproxil fumarate is also a nucleotide analogue, similar to adefovir. Tenofovir is one of the few drugs that demonstrates potent activity against HBV in patients with and without lamivudine resistance and has also proven superior to adefovir. Although tenofovir is similar to adefovir, the incidence of nephrotoxicity is lower with tenofovir than with adefovir at the levels used for HIV treatment and hence the dose of tenofovir can be raised to 300mg/day. Few studies have detected selection of A194T mutation wherein there was ten fold loss in susceptibility, though others have not confirmed this as a source of tenofovir resistance. Snow-Lampart *et al.* showed that after four years of treatment, 93% of HBeAg negative patients and 76% of HBeAg positive patients achieved complete viral load suppression (\leq 400 copies/mL).¹³ At week 144, no

participants developed amino acid substitutions (mutations) known to be associated with resistance to tenofovir. There have also been other prospective studies showing higher efficacy of tenofovir compared to adefovir. Rare side effects include Fanconi's syndrome, renal insufficiency, and osteopenia due to hyperphosphaturia.

(3) Lamivudine

Lamivudine is an oral cytosine analogue with both anti-HIV and anti-HBV activities. In treating co-infected patients, the recommended dose of lamivudine is 300 mg/day and the drug should always be given with at least two other anti-HIV agents. HBV resistance mutations can be recognized in 70% of HBV viremic patients with HIV infection who have received lamivudine for over four years. One of the main concerns with lamivudine treatment is the development of YMDD mutations where methionine is substituted for valine or isoleucine in the tyrosine-methionine-aspartate-aspartate (YMDD) motif and is usually accompanied by leucine to methionine substitution in an upstream region. This resistance can be detected in about 14-32% after one year of treatment and significantly increases to 60-70% after about four to five years of treatment and develops more rapidly in co-infected patients, appearing in about 50% patients after two years of lamivudine therapy and rising to 90% after four years of therapy.¹⁴ In HbeAg negative CHB, lamivudine was shown to suppress HBV DNA in 60-70% of patients, but the majority relapsed. An increase in duration of therapy led to a progressive increase in the development of YMDD mutations. Also, there is no known treatment endpoint for HbeAg negative CHB with lamivudine treatment. Hence, lamivudine is not typically used as first line therapy for HbeAg negative chronic hepatitis B.

(4) Emtricitabine

Emtricitabine is a cytosine analogue with antiviral activity against both HBV and HIV. Emtricitabine should not be used as monotherapy in co-infected persons due to an increased risk of developing M184V resistance in HIV. In a study conducted by Lim *et al.* (2006), HbeAg seroconversion rates were found to be similar in treatment and placebo groups. The recommended dose for emtricitabine is 200 mg/day and follows the same dosing regimen as for HIV therapy.¹⁵ Emtricitabine should not be prescribed after lamivudine failure due to cross-resistance between the two drugs but both drugs can be interchanged if necessary. They are mainly recommended in patients already on HAART therapy and in HbeAg negative chronic hepatitis B where longer duration of therapy is generally required. Emtricitabine does not have an FDA-approved indication for use in the treatment of hepatitis B.

(5) Entecavir

Entecavir (ETV) is a guanosine analogue that inhibits HBV replication at priming, reverse transcriptase, and positive strand synthesis. In a phase II trial, at 48 weeks, entecavir was found to have significantly higher response rates than lamivudine in HbeAg negative chronic hepatitis B patients. In addition, entecavir was found to be effective in

suppressing lamivudine-resistant and adefovir-resistant HBV mutants. Entecavir was found to suppress HIV RNA in co-infected patients but can lead to development of M184V resistance so entecavir is never to be used in the absence of initiation of antiretroviral therapy in co-infected patients and is to be used with caution with other drugs such as abacavir.¹⁶

(6) Telbivudine

Telbivudine is a thymidine L-analogue with greater efficacy than lamivudine or adefovir but has no activity against HIV. Telbivudine selects for mutation M204I and has cross-resistance with lamivudine and hence cannot be used following lamivudine resistance. In addition, patients treated with telbivudine alone were found to have greater seroconversion rates and a higher proportion of patients reported normalization of transaminase levels compared to patients treated with both telbivudine and lamivudine. There has been no evidence of activity and efficacy of telbivudine in co-infected patients.

(7) Interferon-alpha

Pegylated-interferon-alpha is the key component of treatment for hepatitis C but has been shown to have less activity than the previously described oral agents against CHB. Therefore this article will not review its use for CHB therapy at this time.

In summary, none of the reviewed medications except telbivudine are to be used as monotherapy in co-infected patients due to possible development of resistance. Tenofovir and adefovir are effective in patients with lamivudine-resistant virus. Tenofovir and emtricitabine are frequently used for treatment of CHB in HIV-infected patients, although emtricitabine is not FDA-approved for treatment of CHB. When a co-infected patient requires therapy for the CHB, a HAART regimen should be identified containing agents active against both diseases and monotherapy or dual-therapy against CHB should not be used to prevent resistance development by HIV towards the agents. In addition, when HAART regimens are altered, drugs that are effective against HBV should not be discontinued without substituting another drug that has activity against HBV, unless there is evidence of HBeAg seroconversion and an adequate course of consolidation treatment has been completed. In the event that the hepatitis B medicines are discontinued, patient may experience acute flares of hepatitis, more likely when seroconversion has not occurred, and hence have to be immediately put back on therapy.❖

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