Chronic infection with hepatitis B virus (HBV) affects about 5% of the world population (1). In Western Europe, Australia and the USA prevalence of chronic carriers of hepatitis B surface antigen (HBsAg) is less than 1% of the population. Among human immunodeficiency virus (HIV) infected individuals this prevalence is approximately 10 fold higher (2). Until recently, studies on HBV infection in HIV seropositive patients have not been emphasized. The natural history of chronic HBV infection is modified by co-infection with HIV. After initial HBV infection, both development and persistence of chronic HBV infection are greater in patients with prior HIV infection (3, 4). Among chronic hepatitis B surface antigen (HBsAg) carriers a high level of HBV replication or the presence of hepatitis B e antigen (HBeAg) are common in HIV/HBV co-infected individuals (3, 4). These 2 conditions may be predictive of poor survival. However, studies performed prior to the era of highly active antiretroviral therapy (HAART) (prior to 1997), found mild necroinflammatory liver lesions associated with low serum transaminases in deeply immunosuppressed HIV/HBV co-infected patients (5-8). More recent studies, conducted in HAART era, have reported a higher incidence rate of liver related cirrhosis and mortality in HIV/HBV co-infected patients compared to HIV mono-infected persons (9, 10). Factors impacting progression to cirrhosis in HIV/HBV co-infected patients remain unknown. HAART-related immune restoration may have switched the immune reaction to HBV from a tolerance to an intolerance phase, leading in some cases to the complete control of HBV replication or in a majority of patients to an exacerbation of chronic hepatitis. HAART-related hepatotoxicity could also have contributed to worsening of liver damage. On the other hand, improvement of liver lesions may be observed in patients receiving antiretroviral regimens containing lamivudine. Finally, the effect of HIV infection on the natural history of chronic hepatitis B (CHB) could also have been modified by a longer life expectancy, which may allow greater time for cirrhosis to develop. Studies of the natural history of CHB are needed to identify which patients may have the greater benefit from anti-HBV therapy, and to assess when to treat. Therefore, due to the complex potent interactions between these two viruses, the immune system and antiretroviral therapy, the strategy and management of anti-HBV therapy in HIV-infected persons must take into consideration both virus infections.

Therapy of CHB in HIV positive patients has been insufficiently studied. Most of the reported trials were non-randomized, included a small sample size of patients and were performed in the pre-HAART period. In addition, these studies did not consider liver histology as an end point. Interferon Alfa-2 (IFN-α2) and lamivudine (LAM) were the most studied drugs and recently adefovir dipivoxil has been tested for the treatment of LAM-resistant HBV. Additionally, preliminary reports of tenofovir disoproxil fumarate (TDF) activity against HBV in HIV-infected persons were presented in February 2002 at the retrovirus conference in Seattle, Washington and at the EASL 2002 conference in Madrid.

**Interferon Alfa**

Almost all of the studies conducted in HIV/HBV co-infected patients concluded that there is a reduced response to IFN-α2 compared to HBV mono-infected patients (11-16). However, end-points were heterogeneous and the number of patients studied were small. Furthermore, these studies were performed in immuno-suppressed patients not receiving potent anti-HIV therapy.

Only 2 of the reported trials with IFN-α2 were randomized (11, 12). In a dose ranging study of IFN-α2a, 41 patients (14 HIV-positive) with documented chronic wild-type HBV infection were treated with either 2.5 mU/m2 (3 HIV-positive, 6 HIV-negative), 5 mU/m2 (5 HIV-positive, 4 HIV-negative) or 10 mU/m2 (5 HIV-negative).
positive, 4 HIV-negative) three times weekly for 3 (6 patients) or 6 months (26 patients) (16). Nine patients were not treated. None of the HIV-positive patients treated with IFN-α2 became HBV DNA negative (measured by molecular hybridization) or became HBeAg negative. This finding was confirmed later in another randomized, controlled study using IFN-α2a (5 MU/m then increased to 10 MU/m three times per week for 1 and 12 weeks, respectively) in 50 chronically infected patients (13). Twenty-five of the patients were HIV positive with no acquired immunodeficiency syndrome (AIDS) or AIDS-related complex. Only one of the 12 (8.3%) HIV-positive treated patients and none of the 13 HIV-positive controls seroconverted to anti-HBe with negative serum HBV DNA. In comparison, 5 of the 13 (38.5%) HIV-negative treated patients responded compared to 1 of 12 (8.3%) HIV-negative control patients. IFN-α2 in HIV/HBV co-infected patients untreated for HIV appears to have the same tolerance profile as reported in non-HIV patients, although one trial showed a higher rate of side effects and treatment discontinuation in the HIV-positive treatment group compared to the HIV-negative treatment group (16).

No information regarding IFN-α2 activity in HIV-positive patients with pre-core mutant HBV is available.

In summary, it is impossible with the limited amount of published data to propose strong recommendations for the treatment of HBV with IFN-α2 monotherapy in HIV co-infected patients. Although, putting altogether these results suggest that IFN-α2 was inadequately effective for the treatment of wild-type HBV in HIV-infected patients. HIV/HBV co-infected individuals treated after 1996 are most likely immunologically different from patients included in these early published trials, with the major difference being due to the significant use of HAART therapy in industrialized countries. HAART-treated patients have an improved immunity. Large trials in patients receiving HAART are needed to assess safety and efficacy of IFN-α2 (or pegylated IFN) in co-infected patients. Serological, virological and histological end-points should be considered in these studies.

Lamivudine

Lamivudine (LAM) is effective against both HIV and HBV replication. Among HIV/HBV co-infected patients, LAM (150 mg bid) given for HIV infection as a mono-therapy or as anti-retroviral containing regimens promptly inhibits HBV replication (17, 18). Anti-HBV LAM activity was first assessed in a prospective open-label study in 40 patients with advanced HIV-infection (17). After one year of treatment 96.3% of patients had an undetectable serum HBV DNA (less than 5 pg/mL, by molecular hybridization). Anti-HBe seroconversion and HBeAg seronegativity were observed in 11% and 18.5% of the cases, respectively. In patients with HBV DNA higher than 5 pg/mL, increases in serum alanine aminotransferase (ALT) were observed 2 to 8 weeks after LAM initiation. Subsequently, at week 52 of treatment, ALT significantly decreased compared to baseline. A retrospective analysis of HIV/HBV co-infected patients prospectively enrolled within the CAESAR trial has been reported (18). This was a randomized, double blind, placebo-controlled trial of LAM (150 mg bid) or LAM plus loviride added to zidovudine-containing regimens for patients with advanced HIV infection (19). Among patients included in the CAESAR study, 122 were co-infected with HBV (97 in the LAM arm and 25 in the placebo arm). Although randomization was not based on HBV infection, there was no difference between LAM arm and placebo-treated patients with respect to baseline demographic characteristics, HIV disease, serum ALT and HBV virological status. Main virological and biological results are summarized in figure 1. At week 52, the median serum HBV DNA reduction was 2.7 log10 copies/mL measured by PCR (Amplicor Roche, quantification range 2.6–7.6 log10 copies/mL) in the LAM-treatment arm compared with no reduction in the placebo-treated patients. Using a sensitive method, serum HBV DNA was undetectable in 40% of LAM-treated patients at week 52. Finally, LAM (150 mg bid) showed an excellent tolerance profile in both HIV infected patients and in HIV/HBV co-infected patients.

However, no information regarding the underlying liver disease was available in either study. Specific studies with LAM in HIV/HBV co-infected patients in an HBV pre-core mutant population have never been addressed. HIV resistance to LAM is well recognized, and encoded within the YMDD motif around the catalytic site of the reverse transcriptase (RT) (20). The key mutation, M184V, occurs in almost all treated individuals and confers high-level phenotypic resistance. M184V also confers a “fitness deficit” on the virus, at least in part due to reduced processivity of the RT (21). This may explain observations that the presence of M184V may not compromise HIV viral load reduction by LAM-containing regimens (22). HBV polymerase contains a
homologous YMDD motif, also around the catalytic site. Mutations in the YMDD motif of the DNA polymerase confer resistance to LAM. Two major types of mutation have been identified, namely M550V together with L526M, and M550I alone (methionine at codon 550 is homologous to codon 184 within the HIV RT) (23, 24).

A recent retrospective cohort study of HIV/HBV co-infected persons reported an incidence of 50% and 90% of HBV resistance to LAM after 2 and 4 years of therapy, respectively (25). Resistance was associated with mutations located at the YM550DD motif of HBV DNA polymerase in all cases, and the substitution of a Val at position 550 was always associated with a Leu to Met mutation at position 526 (25, 26). CD4 count decrease, body mass index and duration of lamivudine therapy have all been associated with an increased risk of the emergence of HBV resistance. Emergence of resistance is characterized by a rise in serum HBV DNA and a moderate increased in serum ALT (25, 27). At breakthrough, serum HBV DNA is lower than the pre-LAM level. However, serum HBV DNA returns to pre-treatment levels in 6 to 12 months (25). The clinical consequences of HBV resistance in HIV-positive patients is unknown. However, as observed in HBV mono-infected patients, cases of CHB exacerbation and liver failure have been reported in HIV/LAM-resistant HBV co-infected individuals (28-30).

Thus, progression of liver damage related to chronic LAM-resistant HBV is expected in patients who remain untreated.

LAM used as an anti-HIV drug, 150 mg twice daily, is effective and well tolerated for the control of HBV replication in HIV co-infected individuals, although there is no documented improvement of liver lesions in patients with HBV suppression, and the anti-HBe seroconversion rate is low. Rebound in serum HBV DNA occurs rapidly after LAM discontinuation and is associated in some cases with CHB exacerbation (25, 31). Therefore, the duration of LAM therapy in patients who do not seroconvert to anti-HBe is unknown. On the other hand, durability of the response on LAM therapy is limited by the emergence of HBV resistant strain with an approximate incidence rate of 15%-20% per year.

**Adefovir dipivoxil**

Adefovir dipivoxil (ADV) is the prodrug of adefovir, a phosphonate nucleotide analogue of adenosine monophosphate. Intracellularly, adefovir is phosphorylated to the active adefovir diphosphate, which selectively and potently inhibits viral DNA polymerases. ADV demonstrated in vitro and in vivo efficacy in wild-type and pre-core HBV replication in HBV infected only patients (32-35). Among HIV/HBV co-infected patients ADV was tested for the treatment of LAM-resistant HBV (36).

In an ongoing, open-label pilot study conducted in 35 HIV/HBV co-infected subjects with LAM-resistant HBV and controlled HIV infection, ADV 10 mg was administered once daily concurrently with lamivudine 150 mg bid (36). Mean decreases in serum HBV DNA concentrations from baseline (log10 8.64 copies/mL) were -3.40 log10 copies/mL at week 24 (n=31) and -4.01 log10 copies/mL at week 48 (n=29; p<0.0001). Two patients underwent hepatitis anti-HBe seroconversion, at weeks 32 and 36, respectively. ADV interruption was followed by a rebound in serum HBV DNA. A transient increase in serum ALT concentrations was observed in 15 patients by week 8 to week 24. By week 60, serum ALT became significantly lower than baseline levels (37). There was no rebound in serum HBV DNA on ADV through week 48 and no mutations on HBV DNA polymerase and HIV RNA reverse transcriptase were identified through week 48 in all patients. A significant decreased in necroinflammatory lesions was observed in the 15 patients who had baseline and week 48 liver biopsies (37). No significant changes in either HIV RNA or CD4 cell count were observed. ADV was generally well tolerated. No change in renal function tests was observed through week 48. Additional data presented recently at the EASL meeting 2002 in Madrid, showed that serum HBV DNA continue to decline with a mean decrease of -4.80 ±1.15 log10 copies/mL at week 72 with no viral rebound in any patient on ADV (37).

In summary, ADV 10 mg once daily is the only extensively studied therapeutic alternative for lamivudine-resistant HBV infection in HIV co-infected patients. It is important for physicians to note that ADV therapy in HIV/HBV co-infected patients, can be associated with a transient increase in serum ALT but is not related to drug toxicity. Another important point is that ADV at the 10 mg once daily dose seems to have no influence on HIV replication for 2 years (37). The impact of LAM discontinuation in HIV/HBV co-infected patients
treated with ADV is unknown, however it is anticipated that HBV replication would remain controlled with continued ADV even with the discontinuation of LAM (38).

**Tenofovir disoproxil fumarate**

Tenofovir disoproxil fumarate (TDF) has recently been shown to have significant activity in HIV/HBV co-infected patients. TDF is a nucleotide reverse transcriptase inhibitor and has been shown to have potent in vitro activity against both wild-type and lamivudine resistant HBV (39). TDF is the orally bioavailable prodrug of tenofovir (PMPA), has a durable activity against nucleoside resistant HIV and is approved for treatment of HIV-1 infection as a once daily 300 mg tablet. TDF anti-HBV activity was reported this year in two separate studies (40, 41). The first study was a non-comparative, open label pilot study performed in 12 HIV positive patients with LAM-resistant HBV (40). TDF (300 mg once daily) was added to the pre-existing antiretroviral regimen. The mean decreased in serum HBV DNA from baseline (8.10 ± 1.41 log10 copies/mL) was -3.82 ± 0.38 log10 copies/mL at week 24 (p=0.03). A retrospective analysis of HIV/HBV co-infected patients prospectively enrolled within the pivotal TDF trial has been reported (41). Of the 550 patients enrolled 14 were HBsAg positive. At week 24, the mean decreased in serum HBV DNA in the 4 patients with wild-type infection was –5.39 log10 copies/mL and –4.58 log10 copies/mL in the 7 patients with LAM-resistant HBV. No change was observed in the 2 patients who received placebo. No change in serum ALT was observed.

TDF 300 mg once daily significantly suppresses lamivudine-resistant HBV replication in HIV/HBV co-infected patients. However, a larger patient population and a longer treatment period is necessary to assess the extent and durability of HBV suppression, as well as long term tolerance, potential emergence of resistance to TDF, and HBeAg seroconversion rates.

Highly active antiretroviral therapy in HIV/HBV co-infected patients

HBsAg seropositivity has been identified as an independent predictor of HAART-related hepatotoxicity in HIV positive patients (42-45). However, hepatotoxicity was defined as an heterogeneous increased in serum ALT after the onset of HAART. History of HBV serology and serum HBV DNA were unknown. It was also unknown if LAM therapy was included in the supposed hepatotoxic HAART regimen. Furthermore, one third of the patients had decline of serum ALT despite continuation of HAART (42). Finally, the underlying liver disease was not studied. On the other hand, immune restoration related to HAART initiation may induce anti-HBe seroconversion (46). Specific studies of the natural history of chronic hepatitis B in HIV-positive patients receiving HAART are needed in order to assess the respective role of immune restoration, anti-HBV activity of LAM or TDF and hepatotoxicity.

Anti-HBV therapy is indicated in HIV/HBV co-infected patients with evidence of liver disease i.e. necroinflammatory lesions and fibrosis at liver biopsy. LAM, TDF and ADV have demonstrated anti-HBV activity in co-infected patients. However, because both LAM and TDF also have anti-HIV activity, anti-HBV strategies must consider both viruses.

In immunocompetent patients who do not require anti-HIV therapy, monotherapy with LAM (150 mg bid) has demonstrated both efficacy and safety (17). TDF monotherapy has never been evaluated in HIV/HBV co-infected patients untreated for HIV infection. In absence of published data it is impossible to recommend LAM or TDF monotherapy in HIV/HBV co-infected patients who are not receiving anti-retroviral combination therapy. ADV monotherapy may be an alternative in these patients since ADV shows efficacy against HBV wild-type and pre-core mutant HBV. In addition, to date there has been no emergence of HIV or HBV resistance in patients with controlled HIV replication (36).

In HIV/HBV co-infected patients who require anti-HIV therapy, lamivudine should be considered in the antiretroviral regimen. Although, in early results, TDF showed substantial efficacy against HBV wild type or pre core mutant HBV. In LAM-treated patients interruption of therapy may be associated with CHB exacerbation and subsequently progression in liver disease (31). Co-infected patients treated with LAM monotherapy are exposed to resistance. Emergence of resistance can be suspected in patients with a rise in ALT and serum HBV DNA. In some cases, severe hepatitis can be observed with liver insufficiency, particularly in cirrhotic patients. In patients treated with LAM monotherapy careful monitoring of serum ALTs and HBV DNA is warranted. In patients with LAM-resistant HBV, ADV 10 mg/d should be added to pre-
existing antiretroviral regimen, although early TDF reports show that short term treatment with TDF also has strong activity against LAM-resistant HBV. In patients receiving ADV, increased in ALT in the first weeks of treatment may be predictive of efficacy rather than hepatotoxicity.

Finally, trials of combination anti-HBV therapies with pegylated interferon, LAM, ADV or TDF must be assessed in co-infected patients to improve anti-HBe seroconversion rates and to prevent long term resistance.

**Conclusion**

Treatment of CHB in HIV co-infected patients has not been extensively studied. Because of the dual antiviral activity of LAM and TDF, both HIV and HBV infections must be considered when treatment is discussed. LAM used as part of the antiretroviral therapy has shown its efficacy and safety for the control of HBV replication. However, HBV resistance may occur with an incidence rate of 15% to 20%. Preliminary reports of anti-HBV activity of TDF containing-HAART showed encouraging results for the treatment of both wild-type and lamivudine-resistant HBV. ADV has demonstrated efficacy and safety in lamivudine-resistant HBV. Activity of pegylated interferon and combination therapies must also be studied in this population.

**Figure 1:** HBV responses after one year of lamivudine therapy (150 mg bid) in 122 HIV/HBV co-infected patients enrolled in the CAESAR trial (18, 19)

* LAM (n=79) vs placebo (n=19), p=0.018.

**REFERENCES**


