

# Chapter 17: Management of HBV/HIV coinfection

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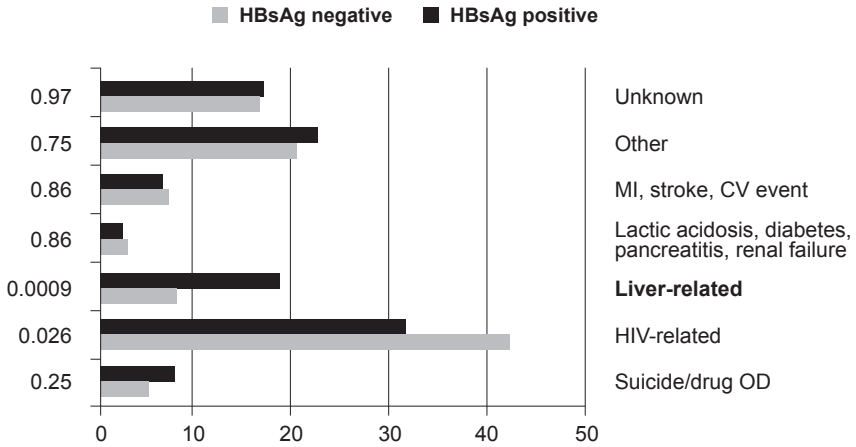
## Introduction

The prevalence and transmission routes of HBV coinfection in the HIV population vary substantially by geographic region (Alter 2006; Konopnicki 2005). In the United States and Europe the majority of homosexual men in the HIV population have evidence of past HBV infection, and 5-10% show persistence of HBs antigen with or without replicative hepatitis B as defined by the presence of HBV DNA (Konopnicki 2005). Overall, rates of HBV/HIV coinfection are slightly lower among intravenous drug users compared to homosexual men and much lower among people infected through heterosexual contact (Núñez 2005).

In endemic regions of Africa and Asia, the majority of HBV infections are transmitted vertically at birth or before the age of 5 years through close contact within households, medical procedures and traditional scarification (Modi 2007). The prevalence in the young population in some Asian countries has substantially decreased since the introduction of vaccination on a nationwide level (Shepard 2006). In Europe vaccination of children and members of risk groups is reimbursed by health care systems in most countries.

The natural history of hepatitis B is altered by simultaneous infection with HIV. Immune control of HBV is negatively affected leading to a reduction of HBs antigen seroconversion. If HBV persists, the HBV DNA levels are generally higher in untreated patients (Bodsworth 1989; Bodsworth 1991; Hadler 1991). In addition, with progression of cellular immune deficiency, reactivation of HBV replication despite previous HBs antigen seroconversion may occur (Soriano 2005). In untreated HIV populations faster progression to liver cirrhosis is reported for HBV/HIV-coinfected patients (Puoti 2006). Moreover, hepatocellular carcinoma may develop at an earlier age and is more aggressive in this population (Puoti 2004; Brau 2007).

Being HBV-coinfected results in increased mortality for HIV-seropositive individuals, even after the introduction of highly active antiretroviral combination therapy (HAART), as demonstrated by an analysis of the EuroSIDA Study, which shows a 3.6-fold higher risk of liver-related deaths among HBsAg-positive patients compared to HBsAg-negative individuals (Konopnicki 2005; Nikolopoulos 2009) (Figure 1). In the Multicentre AIDS Cohort Study, an 8-fold increased risk of liver-related mortality was seen among HBV/HIV-coinfected compared to HIV-monoinfected individuals, particularly among subjects with low CD4 nadir counts (Thio 2002). An independent observation from a large cohort confirming this association is the reduction in mortality for HBV/HIV-coinfected patients treated with lamivudine compared to untreated patients (Puoti 2007). This result is even more remarkable because lamivudine is one of the least effective HBV polymerase inhibitors due to a rather rapid development of resistance.



More than one cause of death allowed per patient; p-values from chi-squared tests

Konopnicki D, for the EuroSIDA group, AIDS 2005

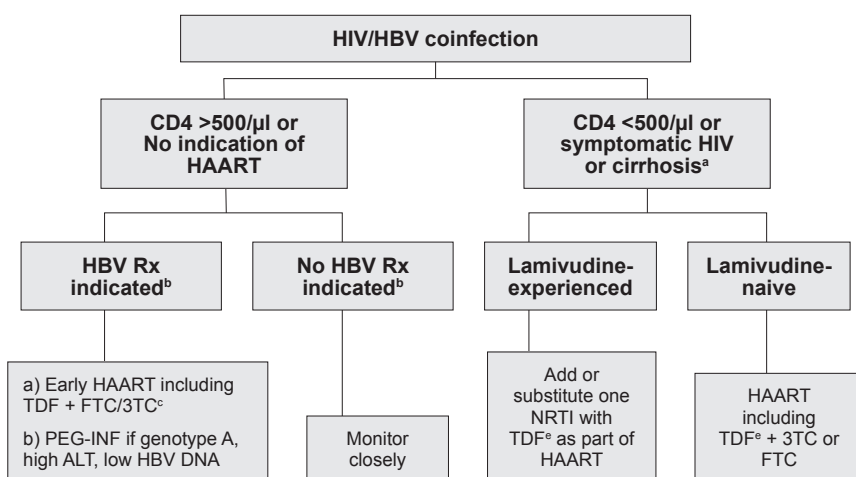
**Figure 1: Association of HBV/HIV coinfection and mortality (Konopnicki 2005).**

These two large cohort studies along with data from HBV mono-infection studies showing a reduction in morbidity and mortality justify treatment of hepatitis B in HBV/HIV-coinfected patients. HBV is often treated simultaneously with HIV, as some nucleoside and nucleotide reverse transcriptase inhibitors are active as HBV polymerase inhibitors as well. Therefore, antiretroviral therapy should be adjusted according to HBV status wherever possible to avoid higher pill burden and additional toxicities. A less frequent but more challenging situation is the initiation of HBV therapy in HIV-coinfected individuals who are not on antiretroviral therapy. Treatment with interferon is one possible therapeutic option in this situation. The main limitation of HBV polymerase inhibitors may be induction of HIV resistance by the anti-HBV agents as they act simultaneously as HIV reverse transcriptase inhibitors.

## HBV therapy in HBV/HIV-coinfected patients without antiretroviral therapy

The recommendations of the updated European AIDS Clinical Society (EACS) for the treatment of chronic hepatitis B in HIV-coinfected patients without antiretroviral therapy are shown in Figure 2 (EACS 2009). Starting hepatitis B therapy depends on the degree of liver fibrosis and the HBV DNA level. Using the level of HBV replication as basis for treatment decisions is an important change of paradigm in HBV therapy. This decision is based on the results of the REVEAL study (Iloeje 2006). REVEAL followed the natural course of chronic hepatitis B without liver cirrhosis in about 3700 Taiwanese patients for more than 10 years. In these HBV-monoinfected patients an HBV DNA of >10,000 copies/ml (i.e., 2000 IU/ml) had a markedly increased risk of developing liver

cirrhosis and hepatocellular carcinoma (Figure 3). This association was even observed in patients with normal ALT levels (Chen 2006) (Figure 4). It should be mentioned that this cohort consisted of Asian patients without HIV coinfection predominantly infected at birth or in early childhood. However, the results were considered too important not to form part of the management of HIV-coinfected patients.



a) Cirrhotic patients should be referred for variceal assessment, have regular HCC monitoring and be referred early for transplant assessment.

b) See Figure 2 for assessment of HBV Rx indication. Some experts strongly think that any HBV-infected patient requiring HAART should receive TDF + 3TC or FTC unless history of TDF intolerance, particularly in HIV/HBV co-infected patients with advanced liver fibrosis (F3/F4).

c) If patient is unwilling to go on early HAART, adefovir and telbivudine may be used as an alternative to control HBV alone. Recently a case report suggested anti-HIV activity of telbivudine. In vitro data using an assay able to demonstrate anti-HIV activity of entecavir failed to detect an influence of telbivudine on the replicative capacity of HIV-1. Treatment duration: in patients not requiring HAART and on treatment with telbivudine +/- adefovir, or those on HAART where nucleoside backbone needs changing, anti-HBV therapy may be stopped cautiously in HBeAg+ patients who have achieved HBe seroconversion or HBs seroconversion for at least six months or, after HBs seroconversion; for at least six months in those who are HBeAg-.

d) Treatment length: 48 weeks for PEG-INF; on-treatment quantification of HBsAg in patients with HBeAg-negative chronic hepatitis B treated with PEG-INF may help identify those likely to be cured by this therapy and optimize treatment strategies.

e) In some cases of tenofovir intolerance (i.e., renal disease), entecavir + adefovir or tenofovir in doses adjusted to renal clearance in combination with effective HAART may be advisable. NRTI substitution should only be performed if feasible and appropriate from the perspective of maintaining HIV suppression. Caution is warranted in switching from a tenofovir-based regimen to drugs with a lower genetic barrier, e.g., FTC/3TC, in particular in lamivudine-pretreated cirrhotic patients, as viral breakthrough due to archived YMDD mutations has been observed. This has also been described in individuals with previous 3TC HBV resistance who have been switched from tenofovir to entecavir.

**Figure 2: Treatment algorithm for therapy of HBV in HIV-coinfected patients (EACS 2009).**

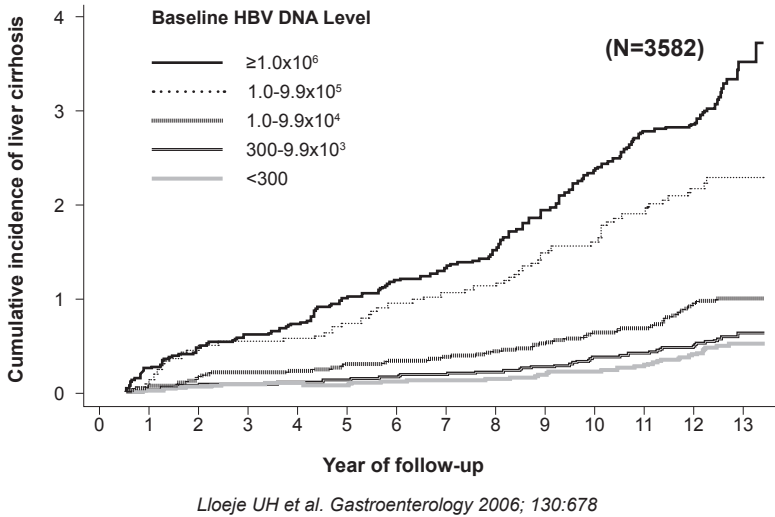
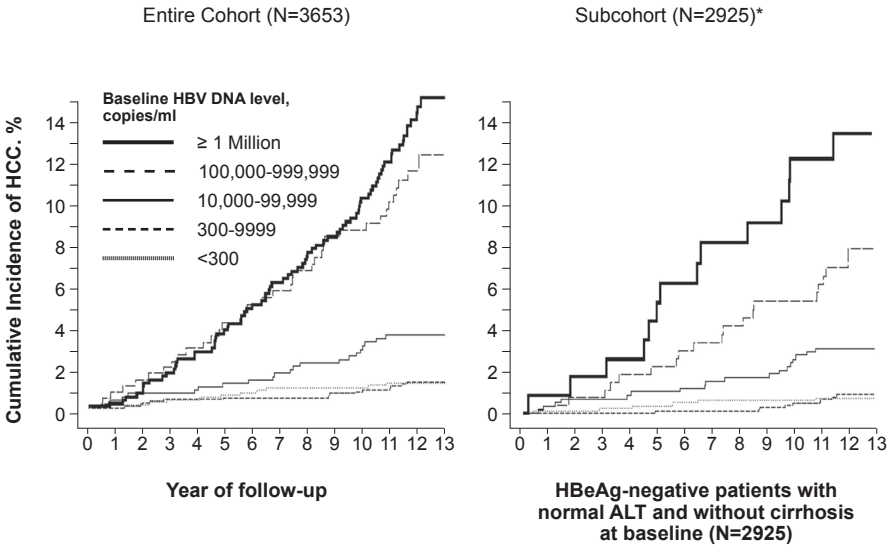


Figure 3: REVEAL Study: Association of HBV DNA level and liver cirrhosis (Iloeje 2006).



*Chen CJ et al. JAMA 2006; 295:65*

Figure 4: REVEAL Study: Association of HBV DNA and the development of hepatocellular carcinoma (Chen 2006).

Usually patients with an HBV DNA of less than 2000 IU/ml have no substantial necroinflammatory activity in the liver and therefore a benign course of fibrosis progression and a low risk for the development of hepatocellular carcinoma. However, especially in patients harbouring HBV precore mutants, fluctuations in HBV DNA and ALT are not rare. Monitoring of the activity of the HBV DNA and ALT accompanied by a sonography every 6-12 months is recommended. In the case of HBV DNA <2000 IU/ml and elevated transaminases and/or signs of advanced liver fibrosis, alternative causes of hepatitis and liver toxicity should be excluded.

For patients with HBV DNA >2000 IU/ml the ALT level is the next decision criterion. Patients with normal ALT should be assessed for liver fibrosis by liver biopsy or elastometry. In case of lack of substantial liver fibrosis (METAVIR stage F0/1) monitoring of the activity of the HBV DNA and ALT accompanied by an ultrasound every 3-6 months is recommended. In the presence of liver fibrosis of METAVIR F2 or higher, hepatitis B treatment should be initiated.

For patients with HBV DNA >2000 IU/ml and increased ALT, treatment for HBV is an option particularly in the presence of relevant liver fibrosis.

In patients not taking antiretroviral therapy, pegylated interferon  $\alpha$ -2a or -2b seems a suitable option. However, data in the literature for HIV-coinfected patients on interferon therapy for HBV infection are limited and not very encouraging (Núñez 2003). For pegylated interferons no data from larger cohorts exist and one study combining pegylated interferon with adefovir did not show encouraging results (Ingiliz 2008). Favourable factors for treatment success with interferon are low HBV DNA, increased ALT, HBV genotype A or infection with HBV wild type.

Alternatively patients can be treated with polymerase inhibitors. However, due to their antiretroviral activity tenofovir, emtricitabine and lamivudine are contraindicated in the absence of effective HIV therapy. In contrast to *in vitro* data reported by the manufacturer, antiretroviral activity and induction of the HIV reverse transcriptase mutation M184V was recently reported for entecavir (MacMahon 2007). Currently only telbivudine and adefovir are considered reasonably safe treatment options. There is limited *in vivo* data for adefovir to support this recommendation (Delaugerre 2002; Sheldon 2005). For telbivudine *in vitro* data are available showing a specific inhibitory activity on the HBV polymerase and no effect on HIV (Avilla 2009). However, in contrast with this, two case reports have suggested antiretroviral activity of telbivudine (Low 2009; Milazzo 2009).

Because of its greater antiviral efficacy, telbivudine is preferred by most experts to adefovir (Chan 2007). Alternatively an add-on strategy of telbivudine to adefovir in the case of not fully suppressive antiviral therapy or primary combination therapy of both drugs can be considered although clinical data are not yet available for this strategy.

As both drugs have limitations in the setting of HBV-monoinfected patients due to considerable development of resistance against telbivudine and the limited antiviral efficacy of adefovir, the initiation of antiretroviral therapy using tenofovir plus lamivudine or emtricitabine should be considered, particularly in HIV-coinfected patients with advanced liver fibrosis.

The treatment duration is determined by HBe antigen seroconversion as in HBV-monoinfected patients. In case of infection with a precore mutant HBs antigen seroconversion is the biological endpoint.

## Antiretroviral treatment of chronic hepatitis B in HBV/HIV-coinfected patients

For patients on antiretroviral therapy a wider choice of polymerase inhibitors is available. In principle the treatment algorithm in Figure 5 is based on the same principles as outlined above (EACS 2009).

For patients with an HBV DNA <2000 IU/ml and no relevant liver fibrosis no specific antiretroviral regimen is recommended. However when choosing an HBV polymerase inhibitor, the complete suppression of HBV DNA is important to avoid the development of HBV resistance mutations. The activity of the HBV infection in these patients should be assessed at least every six months as part of routine monitoring of the HIV infection including an ultrasound due to the slightly increased risk of hepatocellular carcinoma.

When HBV DNA is above 2000 IU/ml in naive patients a combination of tenofovir plus lamivudine/emtricitabine to treat both infections is recommended. Even for patients who harbour lamivudine-resistant HBV due to previous therapies this strategy stands. The recommendation to continue lamivudine/emtricitabine is based on the delay of resistance to adefovir seen when doing so (Lampertico 2007).

For patients with liver cirrhosis a maximally active continuous HBV polymerase inhibitor therapy is important to avoid hepatic decompensation and reduce the risk of developing hepatocellular carcinoma. Tenofovir plus lamivudine/emtricitabine is the treatment of choice. If the results are not fully suppressive, adding entecavir should be considered. At least every six months, assessment of the liver by ultrasound for early detection of hepatocellular carcinoma is necessary. In patients with advanced cirrhosis gastroscopy should be performed as screening for esophageal varices.

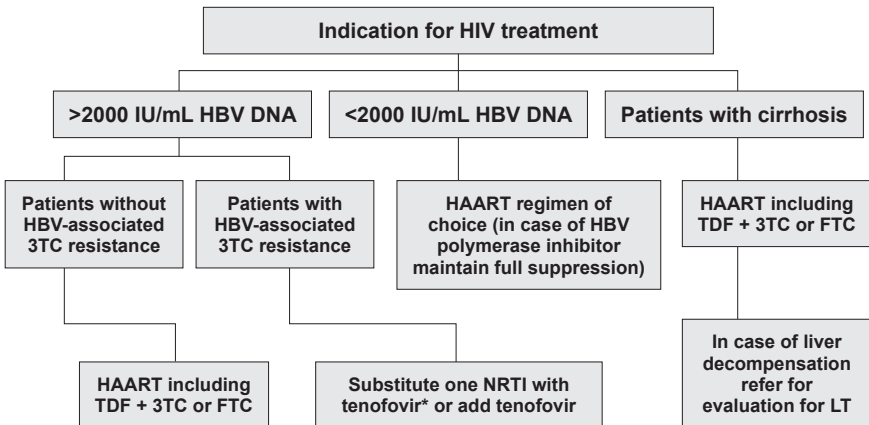


Figure 5. Treatment algorithm for HBV therapy in patients with antiretroviral therapy (EACS 2009).

For patients with hepatic decompensation and full treatment options for HBV and stable HIV infection, liver transplantation should be considered, as life expectancy seems to be the same as for HBV-monoinfected patients (Coffin 2007; Tateo 2009). Patients with hepatocellular carcinoma may be considered liver transplant candidates as well, although according to preliminary observations from small cohorts, the outcome may be worse than for HBV-monoinfected patients with hepatocellular carcinoma (Vibert 2008).

In general tenofovir can be considered the standard of care for HBV in HIV-coinfected patients, because of its efficacy and its strong HBV polymerase activity. Tenofovir has been a long-acting and effective therapy in the vast majority of treated HBV/HIV-coinfected patients (van Bömmel 2004; Mathews 2009). No conclusive pattern of resistance mutations has been identified in studies or cohorts. But resistance is likely to occur in patients with long term therapy as with any other antiviral. In prospective controlled studies tenofovir was clearly superior to adefovir for treatment of HBe antigen positive and HBe antigen negative patients (Heathcote 2007; Marcellin 2007).

The acquisition of adefovir resistance mutations and multiple lamivudine resistance mutations may impair the activity of tenofovir (Fung 2005; Lada 2008; van Bömmel 2010), although even in these situations tenofovir retains activity against HBV (Berg 2008; Petersen 2009).

In lamivudine-resistant HBV the antiviral efficacy of entecavir in HIV-coinfected patients is reduced, as it is in HBV monoinfection (Shermann 2008). Because of this and the property of tenofovir as an approved antiretroviral, tenofovir is the preferred choice in treatment naïve HIV-coinfected patients who have an antiretroviral treatment indication.

The use of entecavir, telbivudine or adefovir as an add-on to tenofovir or other drugs in the case of not fully suppressive antiviral therapy has not been studied in HIV-coinfected patients so far. The decision to do so is made on a case-by-case basis.

It is a general belief that combination therapy with tenofovir plus lamivudine/emtricitabine is superior to monotherapy, in particular in patients with highly replicative HBV infection. However, to date no conclusive studies supporting this are available (Schmutz 2006; Mathews 2008; Mathews 2009).

In the case of development of HIV resistance to tenofovir it is important to remember its HBV activity before switching to another regimen without antiviral activity against HBV. Discontinuation of the HBV polymerase inhibitor without maintaining the antiviral pressure on HBV can lead to necroinflammatory flares which can result in acute liver decompensation in serious cases.

## **Management of resistance to HBV polymerase inhibitors**

Issues concerning the avoidance and management of resistance to HBV polymerase inhibitors are discussed in detail in Chapter 10.

## **Conclusion**

The number of available HBV polymerase inhibitors for chronic hepatitis B has increased substantially over the last few years. In general though, the choice is still limited to two mostly non-cross-resistant classes, the nucleotide and nucleoside com-

pounds. In HIV-coinfected patients where antiretroviral therapy is not indicated the choice is more limited with only adefovir and telbivudine as treatment options. Alternative options in these patients may be interferon therapy or the initiation of full antiretroviral therapy, which is currently preferred by most experts, although both toxicities and costs may increase.

For HBV/HIV-coinfected patients on antiretroviral therapy the treatment of choice is tenofovir in the majority of treatment-naïve or lamivudine-pretreated cases. Due to rapid development of resistance in not fully suppressive HBV therapy lamivudine or emtricitabine monotherapy should never be considered. A combination of tenofovir plus lamivudine or emtricitabine as a primary combination therapy has theoretical advantages, but studies supporting this concept have not been carried out to date.

In general, treatment of HBV as a viral disease follows the same rules as HIV therapy aiming at a full suppression of the replication of the virus to avoid the development of resistance. Successful viral suppression of hepatitis B results in inhibition of necroinflammatory activity, reversion of fibrosis and the ultimate goal of immune control of the infection.

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