

# Understanding the Pathogenesis and Management of Hepatitis B/HIV and Hepatitis B/Hepatitis C Virus Coinfection

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Hepatitis B virus (HBV) pathogenesis is influenced by a variety of factors including coinfection with other viruses, most notably HIV and hepatitis C virus (HCV). Dual virus infection can modify the epidemiology, including the natural history and the development of complications of the infection. The management of dually infected patients also differs from that of HBV-monoinfected patients. With regard to the effect of HIV on HBV, pivotal changes occurred with the introduction and widespread use of effective antiretroviral therapy (ART) in 1996. This article provides an in-depth discussion of the effects of HIV and HCV on HBV pathogenesis.

HBV is a noncytotoxic virus. It is divided into eight genotypes (A–H) that are geographically distinct and influence disease progression and treatment outcome. Most adult HBV-infected patients demonstrate serologic evidence of immunity toward the virus, indicating prior resolution of the infection. Host T-cell responses in patients who do not resolve the viral infection are directed against epitopes on virus-infected hepatocytes and are

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thought to determine the extent of hepatic injury [1]. During chronic HBV infection, disease manifestations depend on the equilibrium between virus and host immune responses. After entry, intranuclear viral processing produces covalently closed circular DNA that produces a potential reservoir for persistent viral replication (Fig. 1A, B). Cytosolic translation of immunogenic proteins includes HBV surface, core, and e proteins. These antigens and their associated antibodies are meaningful parameters in the assessment of the status of the infection. Viral replication as well as assembly and transport are targets of currently approved anti-HBV therapies [2].

### **Hepatitis B virus/HIV coinfection**

The percentage of patients who have active HBV replication is higher in HIV-infected than in HIV-uninfected individuals. Coinfected patients demonstrate elevated HBV DNA and transaminase levels, hepatocyte injury, and progressive fibrosis. Studies, however, have not shown a greater incidence of hepatocellular carcinoma (HCC) in coinfecting HBV patients than in mono-infected HBV patients. Because the host immune response determines, to a large part, the clinical course of chronic HBV, considerations of the effects of HIV on HBV pathogenesis must include the effects of ART.

#### *Epidemiology*

Worldwide, the prevalence of chronic HBV infection is approximately 370 million [3], whereas the prevalence of HIV infection is approximately 40 million [4]. Among the HIV-infected population, the likelihood of developing chronic HBV after viral exposure is increased three- to sixfold, which translates into a global disease burden of 2 to 4 million HBV/HIV-coinfecting individuals [3,5,6]. Chronic HBV infection has been identified in 6% to 14% of HIV-positive individuals in the United States and in Western Europe. Among high-risk groups, 9% to 17% of men who have sex with men, 4% to 6% of heterosexuals, and 7% to 10% of injection drug users are HBV/HIV coinfecting [3].

The two principal routes of HBV infection, sexual contact and percutaneous exposure to blood, also are the primary routes of HIV transmission. In 2005, 79% of newly acquired HBV cases among adults were associated with high-risk sexual activity or injection drug use. Heterosexual transmission accounted for 39% of new HBV infections, and 24% of new cases were attributed to homosexual transmission [7]. Approximately 15% to 20% of new HBV infections in the United States occur in unvaccinated injection drug users [7] with an annual incidence of 9 to 31 per 100 person-years [8]. An increased risk of HBV transmission is associated with increased frequency of injection and with sharing of drug preparation equipment, such as filters, cottons, and cookers [9].

Recent developments in the treatment of HIV infection have influenced the epidemiology of HBV/HIV-coinfecting patients. As a consequence of

ART, HIV-attributable mortality has declined [10]. During this period, liver-related mortality caused by HBV infection has increased [11–15]. Most studies indicate an inverse relationship between liver-related mortality and CD4+ cell number [11,12,14]. The impact of the introduction of ART on HBV-attributable mortality in HIV infection remains controversial.

### *Pathogenesis*

#### *The effect of HIV on hepatitis B virus*

*Viral replication.* The effect of HIV on HBV replication can be assessed by comparing HBV DNA levels, the rate of spontaneous HBV clearance, or the probability of spontaneous loss of either hepatitis B surface antigen (HBsAg) or hepatitis e antigen (HBeAg) in HBV/HIV-coinfected and HBV-monoinfected patients.

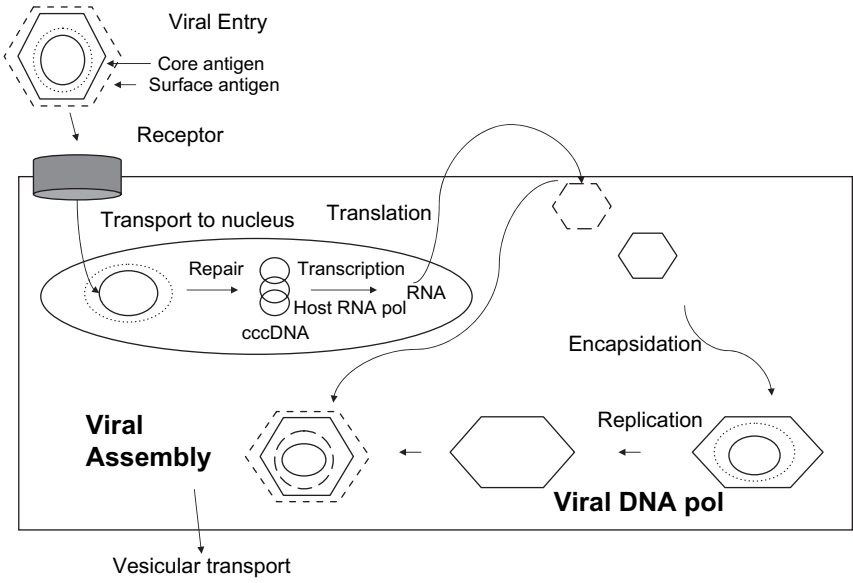
Coinfected patients have significantly elevated serum HBV DNA levels [16,17] as well as other markers of HBV replication, including elevated HBV DNA polymerase activity and HBeAg seropositivity [18,19]. Additionally, HBV/HIV-coinfected individuals are less likely than HBV-monoinfected individuals to clear HBV DNA spontaneously or to lose HBeAg [20].

*Hepatitis B virus–specific immune responses and necroinflammation.* Because the pathogenesis of HBV-induced liver disease is determined to a large extent by the equilibrium between the virus and the host, initiating ART (with activity against both HBV and HIV) early in the HIV disease process can positively impact the course of HBV. ART hastens the restoration of both innate and adaptive anti-HBV immune responses. For example, the number and function of HBV-specific CD4+ and CD8+ cells in coinfecting patients improved on the initiation of ART [21]. Although ART leads to improvements in the cellular immune response, serologic evidence of resolution of the infection, as indicated by HBsAg seroconversion, is an infrequent event that occurred in only 1 of 24 patients in a prospective study [22].

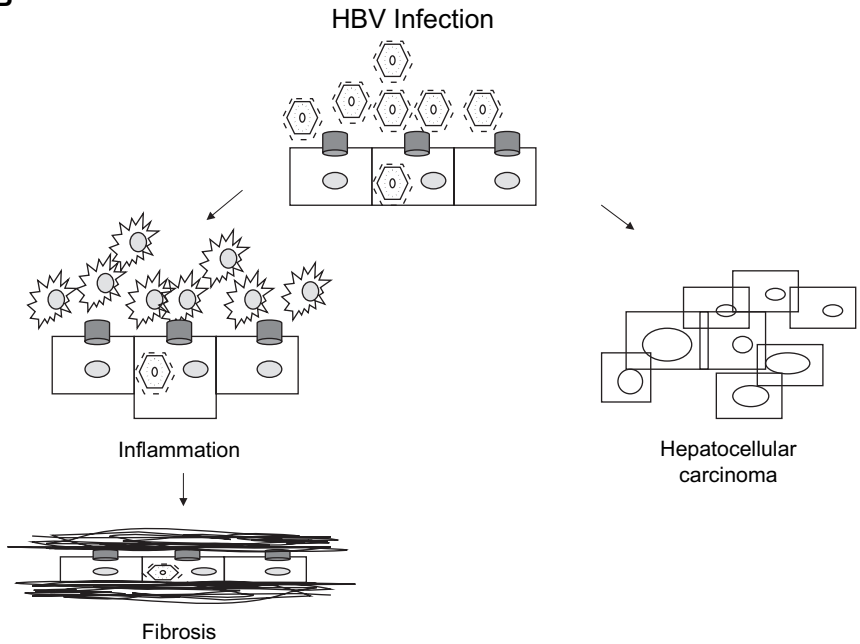
In HBV, the immune response directed against virally infected hepatocytes results in necrosis and transaminase elevation. Because alanine aminotransferase (ALT) levels correlate, at least somewhat, with the degree of necroinflammation, ALT can be a surrogate marker. In two studies, histologic activity and serial ALT measurements did not differ comparing HBV-monoinfected and HBV/HIV-coinfected patients [23,24]. In HBV/HIV-coinfected patients, however, ALT levels have been reported to be lower in patients who have low CD4 cell counts [17].

*Fibrogenesis.* The impact of HIV on fibrogenesis has been controversial, with some studies suggesting accelerated fibrogenesis [16,25], and others suggesting the converse [17,19]. Earlier studies that did not report accelerated fibrogenesis in HBV/HIV-coinfected patients may have included patients who had more profound immunosuppression than those included in

**A**



**B**



more contemporary studies. Furthermore, confounding factors such as concomitant alcohol use, differences in HBV genotypes, and differences in the number of HBeAg-negative subjects also may have been reasons for the lack of an association between coinfection and accelerated fibrogenesis [26]. In more recent studies, immunosuppression has been associated with the development of cirrhosis: coinfecting patients with fewer than 200 CD4+ cells/mm<sup>3</sup> were significantly more likely to be cirrhotic than those with higher CD4+ cell counts [27]. Additionally, hepatic decompensation is accelerated among coinfecting cirrhotic patients in comparison with their monoinfected counterparts [26]. Another factor that affects the progression of fibrosis is HBV genotype. As in HBV-monoinfected patients, HBV genotype G had the strongest influence on fibrosis progression, independent of body mass index, alcohol consumption, gender, or the use of ART, in HBV/HIV-coinfecting patients [28].

*Oncogenesis.* Animal models have suggested that the HIV-1-secreted protein, Tat, induces liver cell dysplasia and facilitates the malignant transformation of liver tumors [29]. To date, however, HBV/HIV-coinfecting patients have not been shown to have accelerated progression to HCC in comparison with HBV-monoinfected patients [26,30].

#### *The effect of hepatitis B virus on HIV*

As opposed to the influence of HIV on HBV pathogenesis, HBV has been shown to have minimal impact on HIV pathogenesis. In vitro, the HBV X protein has been implicated in increasing HIV-1 replication and transcription [31]. In vivo, major effects of HBV on HIV have not been reproduced, as evidenced by data from several epidemiologic studies. For example, the multicenter EuroSIDA cohort study revealed that the incidence of AIDS-defining events, time to reach undetectable HIV RNA (defined as < 400 copies/mL), and improvements in CD4+ cell counts did not differ significantly between HIV-monoinfected and HBV/HIV-coinfecting patients [13]. Consistent with data from the EuroSIDA cohort, which involved 75 centers from predominantly industrialized nations, are the results of similar studies



Fig. 1. (A) Viral lifecycle and host pathogenic response. Hepatitis B virus (HBV) gains entry into the hepatocyte by cell surface binding to a receptor. Viral genome is uncoated and subsequently transported to the nucleus. In the nucleus, the virion DNA is repaired and converted to covalently closed circular (ccc) DNA that then is transcribed into HBV RNA using the host RNA polymerase (pol). In the cytosol, HBV RNA is translated, resulting in virion proteins such as hepatitis B surface (HBsAg) and core (HBcAg) antigens. The core antigen encapsidates the HBV RNA. HBV RNA subsequently serves as a template for HBV DNA using viral DNA polymerase (*bold*), the target for the currently approved oral anti-HBV agents. Virion assembly is completed when HBV DNA is coated with HBsAg, producing intact virions that exit the hepatocyte by budding and vesicle formation. Interferon-based therapies are directed primarily against viral RNA stability and virus assembly (*bold*) [2]. (B) Viral replication is a stimulus for the migration of inflammatory cells to the hepatic parenchyma that promotes fibrogenesis as well as hepatocellular carcinoma.

from developing nations. In a large Thai cohort, HIV RNA decline was equivalent at weeks 4 and 12 for HIV-monoinfected and HBV/HIV-coinfected patients initiating ART. Early (weeks 4 and 8) increases in CD4+ cells were significantly greater in the HIV-monoinfected patients than in the coinfecting group [32], but by week 12 CD4+ cell counts were equivalent in the two groups. Consequently, HBV might have delayed the early improvement in CD4+ cell counts, although the long-term effects are comparable.

#### *Management of disease and treatment of hepatitis B virus/HIV coinfection*

Recent studies in HBV-monoinfected patients suggest that the level of HBV DNA is associated with the likelihood of the development of cirrhosis [33] and HCC [34]. Controversy remains, however, as to the prognostic significance of HBV DNA threshold levels in coinfecting patients. Future investigation is necessary to determine the level below which development of HCC and cirrhosis is unlikely. Until these data are available, the therapeutic goal is maximal HBV DNA suppression.

#### *Assessment of fibrosis in hepatitis B virus/HIV-coinfecting patients*

Because progression of fibrosis may be accelerated in coinfecting patients, the authors of this article believe that all HIV-infected patients with detectable HBV DNA should have necroinflammation and fibrosis assessed by liver biopsy. Simultaneously, the biopsy can provide information related to drug toxicity, hepatic steatosis, or other causes of liver disease [35]. Limitations of the biopsy as a result of its invasive nature, associated morbidity, and sampling error have motivated the development of noninvasive markers of fibrosis including multiparameter indices whose activity can be measured on peripheral blood [36] and ultrasound-based techniques (Fibroscan, Echosens, Paris, France) [37]. Very limited data exist on their use in HBV-monoinfected patients [38], and no data exist on their use in HBV/HIV-coinfecting patients. Because the rate of cirrhosis is increased even among HBV/HIV-coinfecting patients who have normal transaminase levels [16], international panels continue to recommend that biopsies be obtained on all HIV-infected patients with viral hepatitis [39,40].

#### *Treatment of hepatitis B virus/HIV-coinfecting patients*

Guidelines recommend considering ALT and HBV DNA serum levels, HBeAg status, and, possibly, liver histology when deciding whether treatment for HBV infection is indicated [39,41,42]. Given the poorer prognosis of HBV in the setting of HIV infection, therapy may be warranted in all coinfecting patients who have evidence of active HBV replication (Fig. 2).

*Medications.* Six drugs, adefovir, entecavir, telbivudine, lamivudine, standard interferon alfa-2b, and pegylated interferon (PEG-IFN) alfa-2a, have been approved for the treatment of chronic hepatitis B. Two additional

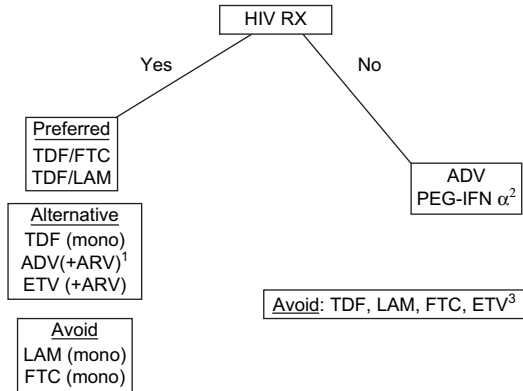


Fig. 2. Proposed treatment algorithm for HBV in HBV/HIV-coinfected patients. <sup>1</sup> Choice of either entecavir (ETV) or adefovir (ADV) depends on lamivudine (LAM) resistance status. <sup>2</sup> Patients with high alanine aminotransferase levels, low HBV DNA, and high CD4+ cell counts are best candidates for interferon therapy. <sup>3</sup> Preliminary findings suggest that entecavir may have anti-HIV activity and select for the HIV M184V mutation [59]. ARV, antiretroviral; FTC, emtricitabine; PEG-IFN, pegylated interferon; TDF, tenofovir.

drugs approved for HIV treatment, tenofovir disoproxil fumarate and emtricitabine, also have anti-HBV activity (Table 1) [43]. The approved oral medications are nucleoside or nucleotide analogues that inhibit HBV DNA polymerase [2]. Lamivudine, emtricitabine, and tenofovir have efficacy against HIV and are frequent components of antiretroviral regimens. Lamivudine, the first drug approved for HBV therapy, results in early HBV DNA suppression in 40% to 87% of subjects [44–46]. Unfortunately, however, the HBV polymerase mutations responsible for lamivudine resistance emerge rapidly in coinfecting patients, with resistance occurring in up to 20% per year [45]. Emtricitabine suppresses HBV DNA [47] similar to the effect of lamivudine in HBV-monoinfected patients, has the same pattern of resistance mutations as lamivudine, and is considered interchangeable with lamivudine for the treatment of HIV [48,49]. Because of the poor resistance profiles and the risk of severe hepatitis B flares with emergent resistance [45,46,50], lamivudine and emtricitabine monotherapy against HBV should be absolutely avoided in HBV/HIV-coinfected patients except where economic or regulatory constraints limit tenofovir's use.

Because the nucleotide analogues adefovir and tenofovir do not exhibit cross-resistance with lamivudine, they have been studied for the treatment of hepatitis B in lamivudine-experienced coinfecting subjects. In small, open-label pilot studies, one group demonstrated that 25% of coinfecting patients achieved HBV DNA suppression (< 200 copies/mL) after 144 weeks of adefovir therapy, and a second group demonstrated that 63% achieved suppression after 48 weeks of tenofovir [51,52]. Additionally, a randomized study of coinfecting patients with high rates of lamivudine resistance showed

Table 1  
Agents used to treat hepatitis B virus (HBV) infection in HIV/HBV-coinfected patients

	Nucleoside and nucleotide analogues						Interferons	
	Lamivudine <sup>a</sup> (LAM, 3TC)	Emtricitabine <sup>a</sup> (FTC)	Telbivudine <sup>a</sup> (TBV, LdT)	Adefovir <sup>b</sup> (ADV)	Tenofovir <sup>b</sup> (TDF)	Entecavir <sup>c</sup> (ETV)	Interferon alfa-2b	Peg-interferon alfa-2a
FDA-approved indication	HIV and HBV (HBeAg+ or HBeAg-)	HIV	HBV (HBeAg+ or HBeAg-)	HBV (HBeAg+ or HBeAg-)	HIV	HBV (HBeAg+ or HBeAg-)	HBV (HBeAg+ or HBeAg-)	HBV (HBeAg+ or HBeAg-)
Year approved	1998	2003	2006	2002	2001	2005	1992	2005
HBV DNA decline in coinfected subjects	2.7 log <sub>10</sub> copies/mL at 52 weeks	No data as monotherapy	No data	3.2 log <sub>10</sub> copies/mL at 48 weeks	4.4 log <sub>10</sub> copies/mL at 48 weeks	4.2 log <sub>10</sub> copies/ mL at 48 weeks	N/A	No data
HBV viral suppression in coinfectd subjects	40% < 400 copies/mL at 52 weeks (10% placebo)			6% < 200 copies/mL at 48 weeks	20%–63% < 200 copies/mL at 48 weeks	8% < 3 00 copies/ mL at 48 weeks (LAM- experienced)	27% < 2 pg/mL 6 months after treatment	
Anti-HIV activity	+++	+++	None	None <sup>d</sup>	+++	Possible <sup>e</sup>	+ <sup>f</sup>	+ <sup>f</sup>
Standard dose in HIV-infected patients	150 mg twice daily or 300 mg daily (dosing for HIV infection)	200 mg daily	600 mg daily	10 mg daily	300 mg daily	lamivudine- experienced: 1 mg daily lamivudine naive: 0.5 mg daily	5 MU daily or 10 MU 3×/week	180 mcg weekly

Available coformulations	Combivir: zidovudine/ lamivudine Epzicom: abacavir/ lamivudine Trizivir: zidovudine/ abacavir/ lamivudine	Truvada: tenofovir/ emtricitabine Atripla: tenofovir/ emtricitabine/ efavirenz			Truvada: tenofovir/ emtricitabine Atripla: tenofovir/ emtricitabine/ efavirenz			
Resistance mutations in HBV or HBV/HIV	L180M A181T/V M204 I/V/S	M204 I/V	L80I/V, L180M, A181T/V M204I/V	A181T/V, I233V, N236T	A194T	180M, T184G, S202I, M204I/ V, M250V <sup>g</sup>	N/A	N/A
Reference	[44]			[43,53]	[52,53]	[62]	[27]	

*Abbreviation:* NA, not available.

<sup>a</sup> Lamivudine, emtricitabine, and telbivudine are L-nucleosides.

<sup>b</sup> Adefovir and tenofovir are acyclic phosphonates.

<sup>c</sup> Entecavir is a cyclopentane.

<sup>d</sup> Limited antiretroviral activity at higher dose but no documented antiretroviral activity or resistance at this dose.

<sup>e</sup> Preliminary report of potential anti-HIV activity of entecavir [60].

<sup>f</sup> Limited anti-HIV activity. No concern of antiretroviral cross-resistance.

<sup>g</sup> Resistance requires the presence of at least three mutations: L180M, M204V/I, and one of the following: T184G, S202I, or M250V.

mean  $\log_{10}$  HBV DNA reductions at 48 weeks of 4.4 and 3.2 in those who received tenofovir or adefovir, respectively. Furthermore, virologic suppression was achieved in 20% and 6% in the respective treatment regimens [53]. These findings suggest that tenofovir has greater activity than adefovir, probably because it can be administered in much higher doses. Although tenofovir resistance has been suggested to occur in isolated cases [54], adefovir resistance has been reported in 15% of HBV-monoinfected subjects at 4 years [55]. Therefore, tenofovir, usually in combination with either emtricitabine or lamivudine, has emerged as the preferred treatment of HBV in coinfected patients requiring concomitant therapy for HIV infection.

Entecavir is the anti-HBV medication with the highest barrier to resistance. In monoinfected patients, entecavir suppresses HBV DNA in 67% of HBeAg-positive and in 90% of HBeAg-negative patients by 48 weeks [56,57]. The cumulative entecavir resistance rate in previously treatment-naive patients is less than 1% after 4 years [58]. Because of entecavir's high efficacy, low incidence of resistance, and apparent lack of antiretroviral activity, recent guidelines recommended using entecavir as the first-line HBV treatment in patients not requiring ART [41]. A recent report, however, describes HIV RNA declines of 1- $\log_{10}$  copies/mL in three patients receiving entecavir monotherapy and the appearance of the HIV M184V mutation, which is associated with lamivudine resistance, in one of these patients [59]. The group further presented evidence that entecavir partially inhibits HIV *in vivo*. Until additional data are available, entecavir monotherapy should not be used in HIV-infected patients who are not receiving ART [60].

The only formally reported entecavir study in coinfection involved patients who had not responded to lamivudine [61,62]. Although adding entecavir (1.0 mg daily) to lamivudine for the treatment of HBV was superior to continuing lamivudine monotherapy, with mean  $\log_{10}$  HBV DNA declines of 3.7 copies/mL and of 4.2 copies/mL after 24 and 48 weeks, respectively, only 8% of subjects achieved undetectable HBV DNA by 48 weeks. The percentage of patients achieving HBV DNA suppression is substantially reduced in comparison with the previously cited studies of tenofovir in lamivudine-experienced HIV-infected subjects [52] and entecavir in treatment-naive HBV-monoinfected patients [56,57]. Lamivudine- and emtricitabine-associated resistance reduces entecavir's antiviral activity and predisposes to the development of additional mutations that also compromise entecavir's efficacy. For this reason, entecavir monotherapy also should be avoided in coinfecting patients who have lamivudine-resistant HBV.

The resistance profile of telbivudine is similar to that of lamivudine but with enhanced potency in suppressing HBV replication [41]. Although this agent has yet to be investigated in coinfecting patients, the American Association for the Study of Liver Diseases recommends against its use in this population, citing the potential emergence of the M204I resistance mutation, which confers cross-resistance to lamivudine in HBV infection [41].

Besides the nucleos(t)ide analogues, the interferons are the only other class of medications approved for the treatment of HBV in the United States. Although the precise mechanism of interferon's antiviral activity in HBV is unknown, it is thought to affect viral RNA stability and assembly [2]. In two large, randomized, controlled trials of HBV-monoinfected patients, 1 year of PEG-IFN was associated with higher rates of sustained HBsAg, HBeAg, and HBV DNA loss than seen with lamivudine. These patients also demonstrated improvements in ALT and liver histology 6 months after cessation of treatment [63,64]. Data in the coinfecting population are limited, however, because studies predate the use of effective ART and have been limited to standard interferon. In one of these studies, interferon seemed to be less effective in HBV/HIV-coinfecting patients than in monoinfected patients [27], and higher baseline CD4+ cell counts were associated with improved treatment outcomes.

Similar to the experience with antiretroviral agents, multiclass drug resistance has been described in patients who received sequential HBV monotherapy [65]. HIV-infected patients may be at an increased risk of developing resistance to agents against HBV, because these patients have enhanced HBV replication that might facilitate the selection of resistant mutations. An unresolved issue is whether administration of newer drugs with higher barriers to resistance or of multiple drug classes simultaneously will improve long-term treatment outcomes by suppressing the emergence of resistant strains. Not surprisingly, given the higher potency and barrier to resistance of tenofovir compared with lamivudine, the combination of tenofovir and lamivudine was superior to lamivudine monotherapy against HBV in HIV-infected patients [66]. Superiority of combination therapy over tenofovir monotherapy against HBV has not yet been established and would require large-scale, prospective studies in HIV-infected patients [67,68]. The use of tenofovir plus emtricitabine (or lamivudine) as part of the first-line antiretroviral regimen in HBV/HIV-coinfecting patients is supported by the proven efficacy of these combinations against HIV [48,49], the availability of convenient coformulations, and the potential for enhanced HBV suppression.

*Factors affecting therapeutic choices.* In HBV/HIV-coinfecting patients, the choice of nucleos(t)ide analogue therapy for HBV treatment must consider (1) the need for concomitant antiretroviral therapy, (2) the presence of lamivudine resistance mutations, and (3) the need for long-term anti-HBV therapy, given the low likelihood of achieving HBeAg seroconversion (see Fig. 2). If HIV treatment is absolutely not indicated, lamivudine, emtricitabine, and tenofovir, agents with activity against HIV, should be avoided. Of the remaining options, adefovir and PEG-IFN, should be considered. Caution is warranted, however, because adefovir may possess some degree of anti-HIV activity. In the late 1990s, adefovir was investigated as an anti-HIV agent at doses of 60 to 120 mg, but at the 10 mg dose it neither has

activity against HIV nor selects for the K65R HIV-resistance mutation [69]. The recent report of possible anti-HIV activity of entecavir [59] highlights the need for additional investigation of entecavir in coinfecting patients before it can be recommended as first-line therapy for patients in whom HIV treatment is not indicated. In patients in whom HIV treatment is indicated, either tenofovir plus emtricitabine, which can be administered as a co-formulation, or tenofovir plus lamivudine is recommended as part of the antiretroviral regimen.

Although consideration of HBV genotype is not part of routine patient management, genotypes may be important predictors of a therapeutic response. Consistent with data from HBV-monoinfected patients, 74% of genotype A HBV/HIV-coinfecting patients demonstrated HBV DNA suppression to less than 2000 copies/mL compared with only 20% of the non-genotype A patients [70]. Additional studies, particularly in coinfecting patients, will be required before consideration of HBV genotypes can be incorporated into routine patient management.

Two important issues that have not been addressed adequately in HBV/HIV-coinfecting patients are treatment duration and combination HBV therapy, particularly when HIV treatment has been deferred. Although HBV-monoinfected patients generally are treated for 6 months following HBe seroconversion (defined as loss of HBeAg and gain of HBe antibody [HBeAb]), HBV/HIV-coinfecting patients probably will need to be treated indefinitely, given their diminished seroconversion rates and need for continued HIV treatment. Because serum HBV DNA levels are increased in HBV/HIV-coinfecting patients [6], combination therapy for HBV may be more effective in these patients despite the absence of evidence supporting its use in monoinfected patients. Studies utilizing dual therapy in HBV/HIV-coinfecting patients will be needed to guide therapy optimally.

*Hepatitis flares.* HBV/HIV-coinfecting patients are more likely than HIV-monoinfected patients to experience hepatic flares (ie, episodic transaminase elevations) when ART is initiated [71]. In HBV/HIV-coinfecting patients, these hepatic flares may be a specific component of the immune reconstitution syndrome or may occur independently. Flares of acute hepatitis B are thought to result from T cells directed toward HBV antigens in the setting of an immunologic change such as withdrawal of corticosteroids or initiation of cancer chemotherapy [72] or ART [71,73]. Increases in HBV-specific CD8+ cells [74] directed toward viral antigens on infected hepatocytes are thought to be the underlying mechanism of elevated transaminase levels when ART is initiated. The same process probably occurs when hepatic flares are a component of the immune reconstitution syndrome, which typically occurs during the first 3 months following initiation of potent ART. ART-induced hepatotoxicity, HBV DNA rebound caused by resistance mutations, natural variations in the ratio of precore to wild-type HBV, and medication discontinuation should be considered in the differential

diagnosis of hepatic flares [21,72,73,75]. Consequently, the United States Food and Drug Administration has placed notifications on HBV medications warning that hepatic flares might occur when these drugs are discontinued prematurely.

## **Hepatitis B/hepatitis C coinfection**

### *Epidemiology*

Because both HBV and HCV are transmitted parenterally, cross-sectional studies have documented that 9% to 30% of HBsAg-positive individuals are also HCV seropositive [76]. In individuals from areas where both viruses are endemic, HCV antibody may be detectable in as many as 50% of hepatitis B core antibody (HBcAb)-positive individuals [77]. Because HBV and HCV infection can arise from trace amounts of residual blood, infection can occur from injection drug use practices or paraphernalia [78–82]. HBV/HCV coinfection also has been documented in 3.7% of dialysis patients [83], 12% of renal transplant patients [84], and 6% of beta-thalassemic patients [85]. The seroprevalence of dual infection with HBV and HCV may be underestimated in various studies because of the exclusion of individuals who had occult HBV infection and studies that utilized older assays with less sensitivity than those used today.

### *Pathogenesis*

#### *Fibrogenesis*

The progression of fibrosis is accelerated in HBV/HCV-coinfected patients [86] resulting in higher percentages of cirrhosis (44% versus 21%) and decompensation (24% versus 6%) in these patients than is seen in patients who have chronic HBV monoinfection [87]. The prevalence of HCC is fourfold higher in HBV/HCV-coinfected patients than in HCV-monoinfected patients [88]. Additionally, a case-control study demonstrated that the risk of HCC is fourfold higher in HCV-seropositive individuals who have serologic markers of HBV infection than in seronegative individuals [89]. Synergism between HBV and HCV as a cause of HCC has been confirmed by several prospective studies [90,91] and meta-analyses [92,93].

#### *Predominance of hepatitis C virus over hepatitis B virus*

Cross-sectional [87] and longitudinal [94] studies indicate that HCV replication more frequently predominates over HBV than vice versa. Dominance of HCV over HBV replication is evidenced by lower serum HBV DNA concentration, a lower frequency of peripheral [95] and intrahepatic [96] HBV DNA positivity, decreased hepatic intracellular concentrations of both HBsAg and HBcAg [97], intrahepatic histology consistent with HCV-induced injury [96], and decreased HBV DNA polymerase activity [87].

The sequence in which these hepatotropic viruses are acquired can influence which virus preferentially replicates over the other. For example, the two viruses can be transmitted together, resulting in simultaneous acute HBV and HCV infection. Acute dual transmission resulted in lower levels of HBsAg and ALT than seen in patients who had acute HBV monoinfection [98]. Either HBV or HCV superinfection can occur in a patient who already has chronic infection with the other virus. In one series, HBV superinfection resulted in hepatic decompensation in 28% of chronic HCV-infected patients as indicated by encephalopathy, ascites, or coagulopathy [99]. HCV superinfection also can result in increased rates of hepatic decompensation (48% versus 34%) and HCC (32% versus 10%) at 20 years in chronic HBV-infected individuals who acquire HCV [100] when compared with HBV-monoinfected patients. Alternatively, HCV superinfection can result in HBeAg seroconversion and HBsAg clearance [101,102]. The annual incidence of HBsAg clearance also is increased in coinfecting compared with monoinfected patients (2.08% versus 0.43%) [103]. These results were confirmed in a subsequent prospective study [104].

In vitro studies have suggested several potential mechanisms of hepatotropic viral predominance. Using in vitro cotransfection systems, HBV replication and viral protein secretion were markedly reduced in the presence of HCV core [105,106] or NS2 proteins [107]. HCV core protein has a suppressive effect on HBV transcription and translation, resulting in marked decreases in HBsAg, HBcAg, and HBeAg [105]. An exhaustive discussion of the potential mechanisms by which HBV or HCV may predominate over the other virus is beyond the scope of this article. The topic recently has been reviewed in detail by Lin and colleagues [108].

### *Management of disease and treatment*

Although guidelines have been developed for the treatment of HBV and HCV in monoinfected patients, limited data exist concerning the optimal treatment strategy for HBV/HCV-coinfecting patients. Virus dominance is the most important consideration in the treatment of these individuals. Most of the existent data have been generated from patients treated with interferon monotherapy because of its long-term use and efficacy against both HBV and HCV [104,109–114]. The largest of these studies (n = 30) reported that 31% versus 0% of individuals achieved HCV RNA negativity 1 year after cessation of treatment with 9 million units (MU) compared with 6 MU of standard interferon alfa monotherapy, administered three times per week for 6 months [111]. All high-dose patients were HBV DNA negative and had improvement in the histologic activity index 1 year after treatment cessation.

More recently, the efficacy of standard interferon in combination with ribavirin has been assessed in HBV/HCV-coinfecting patients [115–117]. In the largest (n = 42) interferon/ribavirin trial, 69% of patients achieved

a sustained virologic response, defined as HCV RNA negativity 6 months after cessation of treatment, 31% became HBV DNA negative, and 14% lost HBsAg [117]. HBV DNA was more likely to rebound in the patients who achieved a sustained virologic response than in those who did not, suggesting a suppressive effect of HCV on HBV. To date, only one published case report of PEG-IFN in combination with ribavirin has demonstrated suppression of both HCV RNA and HBV DNA for at least 2 years after end of treatment. This patient also had HBe seroconversion [118]. Because PEG-IFN is the standard therapy for both HBV [63,119] and HCV [120,121], additional studies using this treatment modality are needed in HBV/HCV-coinfected patients. Because these patients are encountered infrequently in North America, prospective evaluation of PEG-IFN/ ribavirin regimens should be conducted in regions of the world where dual virus infection is endemic. Based on the documented efficacy of PEG-IFN in HBV and HCV monoinfection, the agent is likely to be the preferred treatment for HBV/HCV-coinfected patients.

An alternative strategy is the combination of interferon with anti-HBV therapy. In the only trial of this strategy to date, a study that evaluated standard interferon in combination with lamivudine, four of eight patients (50%) achieved a sustained virologic response, and three of eight (37.5%) cleared HBV DNA [122]. Additional studies utilizing newer anti-HBV agents, such as adefovir and entecavir, are needed also. Interferon-treated HBV/HCV-coinfected patients need to be monitored for viral flares, because HBV [123] or HCV [112] flares have been reported previously.

Until prospective studies are performed to determine the optimal treatment strategy, the treatment of HBV/HCV-coinfected patients should be based on expert opinion with consideration of viral dominance in these patients [40]. Because HCV usually predominates over HBV, most patients will be treated according to recommendations for HCV. Individuals with HBV DNA exceeding  $10^4$  international units/mL and undetectable HCV RNA should be treated for HBV predominance. When both viruses are detectable, PEG-IFN/ ribavirin is the recommended option [40]. Entecavir or adefovir can be added if the HBV DNA response is suboptimal. Given the high frequency of dual HBV/HCV infection in certain geographic regions and the paucity of treatment efficacy data, future studies in this area are warranted.

### **Prevention of hepatitis B virus infection and disease**

Because HBV infection significantly influences morbidity and mortality in both HIV- and HCV-infected individuals, implementation of strategies that prevent the acquisition of the infection and avert its consequences is required. Primary HBV prevention aims to minimize or avoid viral acquisition. Secondary prevention includes methods to delay fibrosis progression and the development of cirrhosis and HCC.

### *Primary prevention of hepatitis B virus*

#### *Prevention of infection among injection drug users*

Among injection drug users, harm-reduction interventions should be invoked to decrease the risk of acquiring HBV. These modalities empower injection drug users to improve their own health while minimizing the adverse effects of continued injection drug use [124]. Interventions include (1) avoiding used syringes and injection paraphernalia, (2) cleaning the site before injection, and (3) washing hands thoroughly before and after injecting. The supply of sterile syringes and the concomitant disposal of used ones can be accomplished at venues such as needle-exchange programs, local pharmacies, and safe-injection facilities. In addition, opiate replacement therapy with methadone or buprenorphine must also be considered to reduce exposure.

#### *Prevention of sexual exposures*

Integrating HBV counseling and screening into already existing sexually transmitted disease clinics may be another effective prevention strategy. In an Indian study, condom distribution and a 6-month educational program significantly decreased the incidence of HBV acquisition among female sex workers [125]. These results were substantiated in a Peruvian study that showed significant reductions in HBV infections among sex workers who consistently used condoms in comparison with those who used them intermittently [126].

#### *Prevention of infection by antiretroviral therapy*

In HIV-infected patients, ART with dual HBV/HIV activity in theory might prevent HBV acquisition. In a large study of more than 16,000 HIV-infected patients, the adjusted incidence of acute HBV acquisition was decreased in patients receiving ART compared to those not receiving ART; however, it did not differ between ART-treated patients using regimens with and without lamivudine [127]. These findings suggest that ART with anti-HBV activity may not prevent HBV acquisition and underscore the need for aggressive HBV vaccination strategies for this patient population.

#### *Prevention of infection by vaccination*

In addition to interventions directed at harm reduction that are coupled with aggressive education and screening, primary vaccination plays a significant role in HBV control as illustrated by the approximately 80% decline in the incidence of acute hepatitis B in the United States between 1990 and 2005 [7]. Adolescents and children were found to have the most dramatic reduction in HBV incidence during this period. Although impressive gains have been achieved, more work is needed to increase the coverage of adults at risk for HBV acquisition. Recommended strategies to achieve universal

HBV protection among adults include vaccination in the following venues: (1) substance abuse treatment programs, (2) correctional facilities, (3) sexually transmitted disease/HIV testing and treatment programs, and (4) facilities providing services to men who have sex with men. Furthermore, regardless of risk factors, all adult patients seen in primary care settings should be offered HBV vaccination [7].

Serology for HBV and hepatitis A virus should be assessed in all HIV-infected individuals. Those who do not show evidence of prior immunity should be vaccinated against both viruses (Fig. 3). Hepatitis B virus surface antibody (HBsAb) titers directly reflect evidence of acquired protection. In the case of advanced immunodeficiency, additional vaccination cycles may be required to induce protective immunity [128], defined as HBsAb greater than 10 mIU/mL [7]. In HIV-infected individuals the immunogenicity of HBV vaccine is compromised, ranging from 7.1% to 87.5%, depending upon CD4+ cell counts and HIV RNA levels [129,130]. In comparison, immunogenicity

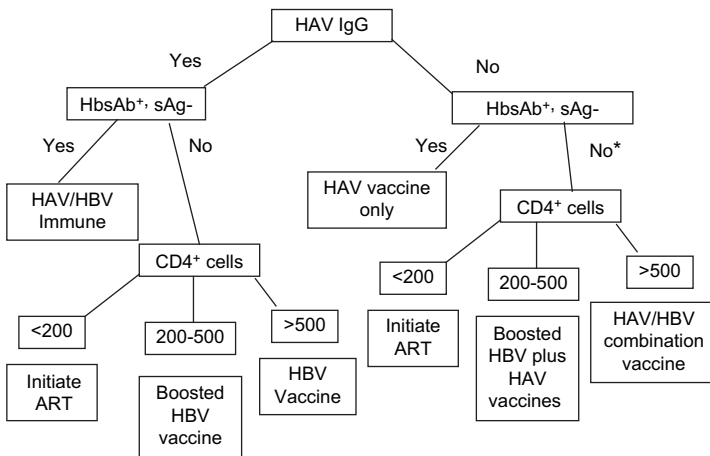


Fig. 3. Vaccination strategy for hepatitis A virus (HAV) and hepatitis B virus (HBV). Nonimmune patients with CD4+ levels higher than 500 cells/mm<sup>3</sup> should receive the conventional vaccination regimen (Recombinavax [Merck & Co., Inc, Whitehouse Station, NJ], 10 mcg or Engerix [GlaxoSmithKline Biologicals, Rixensart, Belgium], 20 mcg at months 0, 1, and 6–12). The boosted HBV vaccination regimen consists of an initial course of 20 mcg at months 0, 1, 2, and 12. If patients do not achieve sufficient immunity (hepatitis B surface antibody [HBsAb] > 10 milli-international units/mL), a second vaccine cycle (40 mcg at months 0, 1, 2, and 6–12) is administered until sufficient immunity is achieved. Anti-HBsAb titers should be assessed 12 weeks after vaccination and every year in high-risk individuals. If evidence of insufficient immunity appears, booster doses or additional vaccination cycles should be administered [39,130]. If the level of CD4+ cells is below 200 cells/mm<sup>3</sup>, use antiretroviral therapy to affect an increase in CD4+ cells. Vaccinate once the level of CD4+ cells is greater than 200 cells/mm<sup>3</sup>, which may require at least 12 months of antiretroviral therapy. If patients are not HAV immune, the same CD4+ cell criteria apply, and the HAV/HBV combination vaccination (Twinrix, GlaxoSmithKline Biologicals, Rixensart, Belgium) should be substituted for the conventional vaccine. ART, antiretroviral; core IgG, core immunoglobulin; sAb, surface antibody; sAg, surface antigen.

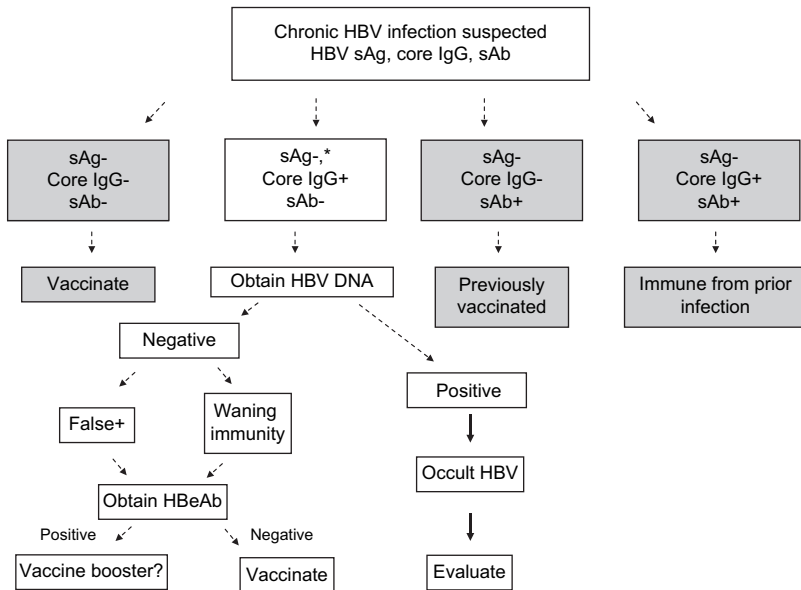


Fig. 4. Serologic screening algorithm for suspected occult hepatitis B virus (HBV) infection in HIV-infected patients. \*If acute infection is suspected, exclude the possibility that patient is in the period between hepatitis B surface antigen (HBsAg) clearance and the appearance of surface antibody (HBsAb). HAV Ig, hepatitis A virus immunoglobulin.

among healthy controls is greater than 70%. Furthermore, HCV seropositivity also may blunt the immune response, because approximately 30% of patients who had chronic hepatitis but only 10% of healthy controls were nonresponders to primary HBV vaccination [131]. Surprisingly, the inability to generate protective immunity did not correlate with HCV RNA levels.

Because HBsAb levels wane over time, HIV-infected patients also are vulnerable to reinfection in the case of exposure [7]. Although most of these infections are asymptomatic and transient, cases of chronic HBV infection have been documented in HIV-infected patients who lost detectable HBsAb [132]. Although data are limited, verification of HBsAb titers yearly may be warranted in high-risk individuals. Although significant adverse reactions to the vaccine have not been reported, immunization can increase HIV RNA levels transiently [129].

#### *Secondary hepatitis B virus prevention: hepatocellular carcinoma*

In contrast to HBV/HCV-coinfected patients, the incidence of HCC is not increased in HBV/HIV-coinfected patients compared to HBV-monoinfected patients. The risk of HCC, however, is increased in patients who have occult HBV [133], defined as the presence of detectable HBV DNA in the absence of HBsAg [134], compared to HBV-monoinfected patients. After controlling for age, gender, and alcohol and tobacco consumption, patients

who have chronic HCV infection who were HBcAb positive were more likely to develop HCC than their HBcAb-negative counterparts [135]. This effect was more pronounced in cirrhotic patients than in those who had only hepatitis. Although occult HBV seems to be a risk factor for HCC in chronic hepatitis C, more studies are needed to demonstrate its role in HIV-infected patients.

All HIV-infected patients should be screened at diagnosis for HBsAg, HBsAb, and HBcAb IgG (Fig. 4). HBcAb may be the only serologic marker of prior HBV infection, present in 42% of HBsAg- and HBsAb-negative HIV-infected individuals [136]. Occult HBV in HIV-infected individuals ranges from 0% to 89.5%. In a study of approximately 700 HBsAg-negative/HBcAb-positive individuals, 10% had occult HBV [137]. Occult HBV infection occurred most commonly in individuals who had HIV RNA levels higher than 1000 copies/mL but was not associated with CD4+ counts below 200 cells/mm<sup>3</sup> or an ART regimen with anti-HBV activity [137]. Another study found that occult HBV was not associated with elevated transaminase levels [138]. Occult HBV infection also has been associated with hepatic flares [139]. Whether occult HBV promotes fibrogenesis in HIV-infected patients is currently unknown.

## Summary

In individuals who have chronic HBV infection, coinfection with either HCV or HIV deserves special attention because of the increased incidence, altered natural history, and worse outcomes. When considering the epidemiology of HBV and HCV, an important difference is that HBV, like HIV, can be transmitted more efficiently than HCV by sexual routes. Important differences exist in the relationship between HBV/HIV and HBV/HCV coinfection and the development of HCC: the incidence of HCC seems to be increased with HBV/HCV coinfection but not with HBV/HIV coinfection in comparison to HBV-monoinfected patients.

Therapeutic decisions in coinfecting patients should be based upon the extent of disease and which virus(es) requires treatment. In the setting of HBV/HCV coinfection, the more replicative virus dictates the therapeutic approach. In HBV/HIV-coinfecting patients, a high potential for the development of lamivudine resistance suggests that lamivudine and emtricitabine monotherapy against HBV should be avoided. In addition to treatment, a high priority must be placed on prevention and screening. High-risk groups for HBV, HCV, and HIV should be screened, and individuals who are susceptible to HBV infection should be vaccinated.

Several issues concerning the evaluation and treatment of HBV-infected patients who also are infected with either HIV or HCV remain to be addressed. For example, what is the threshold HBV DNA level that increases the likelihood of decompensated cirrhosis or HCC? Efficacy studies of combination therapy in these patients are needed also. In the setting of

HBV/HIV, these studies could guide decisions concerning the use of anti-HBV agents in coinfecting individuals in whom anti-HIV therapy is not indicated. In the case of HBV/HCV coinfection, studies are needed to define the optimal management strategy. For both HBV/HIV and HBV/HCV coinfection, investigations of the role of occult HBV are needed.

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