

# BHIVA guidelines on HIV and chronic hepatitis: coinfection with HIV and hepatitis B virus infection (2005)

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## 1.0 Key recommendations

Levels of evidence:

- I = Meta-analysis or RCT
- II = Other good-quality trial
- III = Observational studies/case reports
- IV = Expert opinion

### 1.1 Assessment of all HIV-positive patients

- (1) All HIV-positive patients should have serum markers for hepatitis B checked (HBsAg, anti-HBc and/or anti-HBs) tests within a month of diagnosis [II].
- (2) All those negative for hepatitis B markers should be immunized and anti-HBs checked at 12 weeks. Patients failing to respond to a conventional course of 20 µg vaccine should receive booster doses and/or a repeat vaccination cycle with the 40 µg dose. Response to vaccine may be reduced if the CD4 count is less than 500 cells/mm<sup>3</sup> [I].
- (3) Those patients with a CD4 count < 200 cells/mm<sup>3</sup> not on ART should receive combination therapy first and with immune recovery, subsequent immunization.
- (4) Following successful immunization, anti-HB levels should be checked yearly and booster doses of vaccine should be given to those with an anti-HB level < 100 iµ/L [IV].
- (5) Persons who fail to seroconvert to HBV vaccine and are at continuing risk of HBV infection should have annual HBV markers performed (HBsAg and anti-HBc) [IV].
- (6) All patients who are anti-HBc positive but HBsAg negative are at risk of HBV reactivation. HBV markers including HBV-DNA should be rechecked annually or if the liver function tests (AST/ALT) become abnormal [II].

- (7) All HIV-infected persons should have serum markers for HBV checked before antiretroviral (ARV) therapy is commenced and then reassessed at least once a year. Decisions on appropriate ART combinations can then be made [IV].

### 1.2 Assessment and management of HIV/HBV coinfecting patients

- (8) All HIV/HBV coinfecting patients should have an assessment of disease status and risk of progression which includes a clinical history, examination and blood tests including liver function test (LFT), clotting studies, full HBV profile (including HBV-DNA) and HCV status [IV].
- (9) Liver biopsy should be considered, unless contraindicated (e.g. haemophilia), for all those with HBV replication (HBsAg positive or HBV-DNA ≥ 10<sup>4</sup> copies/mL) especially if:
  - history or signs suggestive of cirrhosis or a history of decompensated liver disease,
  - HDV or HCV (PCR-positive) coinfection,
  - deranged LFTs of uncertain aetiology.
- (10) For patients with HBV-DNA levels < 10<sup>4</sup> copies/mL and normal ALT, a liver biopsy is not necessary but regular clinical monitoring should be performed [III].
- (11) Consider other causes of liver disease if LFT is out of proportion to the HBV disease [IV].
- (12) All persons without serum anti-HAV IgG should receive two doses of hepatitis A vaccine 6–12 months apart, although the response to vaccine may be reduced if the CD4 count is less than 500 cells/mm<sup>3</sup> [III].
- (13) Patients should be counselled about the dangers of alcohol consumption. Abstinence or only limited use of alcohol is recommended for those with abnormal liver function tests [III].

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- (14) Carriers should be counselled regarding prevention of transmission of HBV and acquisition of HCV/HDV [I].
- (15) Sexual and household contacts should be tested for HBV markers and receive HBV immunization if susceptible [II].
- (16) Newborns of coinfecting mothers should receive HBIG and HBV vaccine at delivery, in addition to postnatal HIV prophylaxis, and complete the recommended vaccination programme [I]. This requires optimal liaison between hospital and community staff.
- (17) Screening for hepatocellular carcinoma (HCC) should occur in patients with established cirrhosis by 6-monthly  $\alpha$ -FP and USS scans [III].
- (18) There should be close liaison between the HIV physician and a local hepatology team with links to a transplant centre to ensure optimal care [IV].

### 1.3 Anti-HBV therapy in HIV/HBV coinfection

- (19) The optimal time for initiating anti-HBV therapy in coinfecting patients has not been established, but HBV-specific treatment should be considered for all patients who are HBeAg positive, or are HBeAg negative but with an abnormal LFT (ALT > 1.5  $\times$  upper limit of normal) and HBV-DNA  $\geq 10^4$  copies/mL [I].
- (20) Interferon is the preferred option for HBeAg-positive patients and adefovir in HBeAg-negative patients with an HBV-DNA  $\geq 10^4$  copies/mL not on antiretroviral therapy with a high CD4 count [I]. Early results suggest that adefovir does not select resistance in HIV and therefore compromise future use of tenofovir. Pegylated interferon is likely to prove to be more effective than interferon in the future.
- (21) Treatments with antiretroviral activity must only be given as part of, or in addition to, an effective antiretroviral regime [III].
- (22) Tenofovir can be given as the sole anti-HBV agent [III]. 3TC/FTC should not be used without also giving tenofovir because of the likelihood of the development of resistance in HBV [III].
- (23) In HbsAg-positive patients who have HBV-DNA levels <  $10^4$  copies/mL, and who need antiretroviral therapy, inclusion of tenofovir and 3TC/FTC in the ART regimen may be considered in order to prevent HBV relapse but there is no evidence for the value of such therapy [IV].
- (24) If there is a need to change the ART in coinfecting patients on FTC/lamivudine and/or tenofovir who have shown an HBV response, these agents should be continued in addition to the new regimen irrespective of any resistant HIV with the exception of a switch from 3TC/FTC to tenofovir [III].

- (25) New therapies can be considered, which normally should only be used under clinical trial conditions, including entecavir, clevudine (L-FMAU), LdT and pegylated interferon [IV].
- (26) There is no evidence supporting the use of antiviral therapy in acute HBV infection [III].

## 2.0 Audit standards

- (1) All HIV + patients should be screened for HBV markers.
- (2) All HBV nonimmune patients at continuing risk should be vaccinated.
- (3) All patients with abnormal ALT/AST levels who are anti-HBc-positive should have a serum HBV-DNA level measured irrespective of the HBsAg/HBeAg status.
- (4) All patients should have their HBV status measured before commencement of antiretroviral therapy.
- (5) All HBV-infected patients should be vaccinated against hepatitis A if non-immune.
- (6) All HBV-infected patients should have documented evidence in their case notes of a discussion on alcohol avoidance and how to reduce the risks of transmission.
- (7) Case notes should contain clear evidence of an attempt to contact household and sexual contacts and offer vaccination to those who are non-immune.
- (8) All patients who are HBsAg-positive with abnormal LFTs should have a clear management plan written in their notes.

## 3.0 Background

### 3.1 Prevalence

- There are approximately 350 million hepatitis B carriers and almost 40 million HIV-infected people worldwide [1,2]. As the routes of transmission for these infections are similar, there is a significant rate of coinfection in patients. Underlying HIV infection increases the chance of HBV chronicity [3]. There are no comprehensive data from the UK defining HIV/HBV coinfection rates. However, data from the EuroSIDA study [4] showed a 9% prevalence of HBsAg coinfection in participating centres.
- A study in 631 HIV-positive people, most of whom were gay men, in London showed a dual HIV/HBV infection rate of 6% [5].
- In many parts of Africa, HIV/HBV coinfection is common, as seen in Malawi (13%) or the Ivory Coast (10%) [6,7]. Recent immigrants from Africa represent the largest group of newly diagnosed HIV-positive people in the UK [8] and therefore high coinfection rates

are to be expected. A survey of 165 consecutive HIV-positive patients of African origin showed a HBV carriage rate of 5.5% (MG Brook, 2002, unpublished data).

- Very high rates of hepatitis B infection are seen in intravenous drug users (IVDUs) and therefore HIV/HBV is common; one study in Germany found that 8% of an HIV clinic cohort, over half of whom were IVDUs, were chronically infected with HBV [9].

### 3.2 Natural history

- Hepatitis B virus is immunopathic (the immune response to the virus causes most of the liver damage) and, therefore, in HIV infection there is often a decrease in the serum aminotransferase values and a decrease in the histological inflammatory indices [10,11]. However, at very high levels of viral replication the virus may have a direct cytopathic effect. Coinfection with HIV is generally accompanied by an increase in HBV replication [10,11] and there is evidence for an increased rate of progression to cirrhosis and death [4,11].
- Since the introduction of combination antiretroviral therapy and the dramatic improvement in the prognosis of people with HIV, liver disease due to chronic viral hepatitis has become an important cause of morbidity and mortality in coinfecting patients [4,12,13].
- The natural history of HIV infection does not seem to be influenced by hepatitis B [3,4,10], although there is an increased rate of antiretroviral-related hepatotoxicity and possibly a poorer immunological outcome [14,15].
- HBV re-activation and re-infection can also occur, and patients who appeared to have cleared HBV infection can present with a further episode of acute or, more commonly, be found to have abnormal liver function tests and chronic hepatitis [16,17]. The risk of reactivation is higher in patients who are positive for anti-HBc antibody but negative for other markers of HBV infection (including HBV-DNA). In one long-term follow-up study of anti-HBc-antibody-positive, HIV-positive patients, transient HBsAg-positivity developed in 24%, HBV-DNA became positive in 60% and about a third of these had active liver disease [18].
- There is also a reduction in the rate of natural clearance of HBeAg by about 60% in coinfecting patients compared to HIV-negative patients [10,19]. However, there are reports of patients clearing chronic HBV infection with recovery of CD4 count responses following antiretroviral therapy [20].

### 3.3 Immunization

- Hepatitis B is preventable by vaccination. However, HIV-positive patients respond less well to the vaccine, and the response rate varies with the CD4 count with best response (approximately 80%) at >500 cells/mL and worse response (approximately 25%) with counts <200 cells/mL [21]. Protective antibodies are lost more quickly [22].
- All newly diagnosed HIV patients should have an anti-HBc test and additionally an anti-HB test if they have previously been immunized. If negative for both, they should receive a course of vaccination and subsequent boosters up to a further three doses until they have detectable serum anti-HB antibodies, ideally greater than 100 iu/L [22].
- It is not known if the ultra-rapid (0, 1, 3 week, 12 month) schedule is effective in HIV-positive patients but the 0,1,2,12 month schedule is effective [22]. Double-dose vaccine may improve response rates. Subsequently, anti-HB levels should be checked yearly and booster doses given if the anti-HB level falls below 100 iu/L [23].
- Persons who fail to seroconvert to HBV vaccine [24] should have repeat vaccination courses once the CD4 count rises to >500 cells/mL or after significant immune recovery, and whilst non-immune should have annual HBV markers performed (HBsAg and anti-HBc).

### 3.4 Delta hepatitis (hepatitis D virus)

- This virus can only replicate in the presence of HBV as it requires the HBV surface protein for its own structure. HDV is seen mainly in IVDUs and their sexual partners in the UK although it can be found in other HBV-positive patients.
- It is not clear if HIV coinfection influences the course of HBV/HDV disease but there is some evidence that it leads to a more rapidly progressive form of hepatitis and fulminant liver failure [25].

## 4.0 Assessment and investigations

HBV-related liver disease is mostly confined to patients with evidence of ongoing viral replication, usually with HBeAg-positivity and high HBV-DNA levels detectable by PCR or a comparable nucleic acid amplification test.

## 4.1 Assessment

The initial evaluation should include history and clinical examination [26].

- History should include enquiring about injection drug use (current and remote), past immunization for hepatitis A/B, episodes of jaundice, travel abroad and potential risk activity there (blood transfusion, IDU, sexual), alcohol use (current and past), family history of HBV infection, liver disease or HCC, and previous investigation for hepatitis.
- Clinical examination for evidence of chronic liver disease (peripheral stigmata, portal hypertension, decompensation).
- Patients should be counselled about the significance of coinfection, lifestyle modifications that may be necessary (alcohol, injection drug use and safer sex), modes and prevention of transmission, and treatment options. The development of ESLD in HBV infection occurs at a younger age in heavy drinkers [27].

## 4.2 Investigations

### 4.2.1 Initial work-up

Initial work-up for an HBsAg-positive individual should include tests for:

- liver disease – full biochemical profile including bilirubin, albumin and liver enzymes; prothrombin time and full blood count;
- HBV replication – HBeAg, anti-HBe and HBV-DNA;
- exclusion of other viral liver disease – anti-HCVAb and anti-HDV Ab if at particular risk;
- HAV immunity – anti-HAV IgG Ab.

### 4.2.2 Additional tests

Additional tests may be indicated depending on these results:

- Liver biopsy: consider for those with HBV replication (HBeAg positive or HBV-DNA positive [ $\geq 10^4$  copies/mL]) and likely ESLD, HDV or HCV (PCR-positive) coinfection, or with deranged LFTs of uncertain aetiology. For patients with HBV-DNA levels  $< 10^4$  and normal ALT, a liver biopsy is not necessary but regular monitoring should be performed.
- AFP and USS (USS on all HBeAg-positive patients and all anti-HBe-positive who have abnormal liver function tests), especially for patients with suspected advanced liver disease. An OGD to exclude varices is indicated if portal hypertension is suggested on USS or cirrhosis on

liver biopsy or if there has been an episode of haematemesis.

- Autoimmune screen, copper/caeruloplasmin and iron/ferritin if other features consistent with autoimmune hepatitis, Wilson's Disease or haemochromatosis (plus HFE gene test if subsequently indicated).
- Lamivudine (3TC): resistance may be useful for patients with 3TC exposure and detectable HBV-DNA but is not widely available and its utility remains to be determined.
- HBV genotyping: the significance of genotype with regard to risk of progressive liver disease, development of HCC, and response to treatment is being explored. Currently, there is no indication to perform an HBV genotype.

### 4.2.3 Follow-up tests

- All persons should have a regular full biochemical profile including bilirubin, albumin and liver enzymes, and full blood count performed a minimum of every 6 months. Repeat prothrombin time if clinical or biochemical evidence of progression.
- Patients who have an unexpected rise in ALT should be re-screened for HBV replication (HBeAg and HBV-DNA) and other causes of hepatitis [HAV, HCV, HDV if at risk].
- All patients with cirrhosis should be screened for HCC with 6 monthly ultrasounds and alpha fetoprotein ( $\alpha$ FP). Physicians and patients need to be aware, however, that even with more frequent screening the chance of detecting a treatable HCC is small [28,29].

### 4.2.4 Test interpretation

- Abnormal LFTs indicate liver inflammation and/or dysfunction. In coinfecting patients, they may result from several causes:
  - Reactivation of HBV related to worsening immune function.
  - Improved immune response directed against HBV as a result of HAART.
  - Hepatitis flare on withdrawal of 3TC, emtricitabine (FTC) or tenofovir as part of HAART associated with WT virus repopulation.
  - Hepatotoxicity as a result of ARV agents or other drugs. Coinfecting patients have more ARV-related liver toxicity.
  - Inflammation as a result of other hepatotropic virus infections (HCV, HDV, HAV) or HBV re-infection.
  - Development of 3TC/FTC resistance after initial suppression.

- HBeAg or HBsAg seroconversion.
- HBV-DNA is a reliable marker of active HBV replication.
- Detection and quantification can be achieved by signal amplification or target amplification methods. Units of measurement have now been defined. Minor variations (up to half a log) exist between assays and as a result of the intrinsic variability of the test and can be ignored. It is advisable that the same assay is used for patient monitoring. Sensitivity of assays is down to 200–400 copies/mL. Nested PCRs can increase sensitivity but there can be difficulties in accurate quantification [30,31].
- The HBV-DNA cut-off level in HIV-negative HBV-infected patients that is associated with progressive liver disease is unknown although a threshold of  $10^4$  copies/mL is now generally accepted. Most patients with inactive liver disease (HbeAg-negative, anti-HbeAb-positive and normal ALT) have levels below this cut-off. In coinfecting patients, HBV-DNA levels are higher and may change with immune function [32,33].
- Histological examination of the liver remains the most sensitive tool for assessing the severity of liver disease and thereby establishing prognosis and the need or urgency for treatment. It also excludes other aetiologies of liver disease in a patient with HBV infection.
- Several numerical scoring systems exist (Ishak, METAVIR, Knodell) that grade the degree of necroinflammatory activity and stage/extent of fibrosis. Concordance between the different scoring systems is good [34–37].
- On the basis of histology (scored by Ishak), the liver damage can be categorized as mild when the necroinflammatory score is  $\leq 3/18$  and the fibrosis stage is  $\leq 2/6$ . In these circumstances, treatment may not be indicated. Higher scores may indicate the need for treatment (see later).
- 3TC resistance mutations can be identified by either direct sequencing or line probe assay although this is only a research tool at the moment [38].
- HIV/HBV coinfecting patients treated with 3TC accumulate resistance mutations at 20–25% per year. This is conferred by a mutation in the YMDD motif in the HBV DNA polymerase gene [39,40].
- At present, laboratory testing for 3TC resistance is unlikely to influence patient management. Any patient who has detectable (or rising after an initial fall) HBV-DNA levels while taking 3TC/FTC can be

assumed to have 3TC resistance. The place of resistance testing is likely to become more important as newer agents are developed and therapeutic options increase.

#### 4.2.5 Networks

- There should be close liaison with the local hepatology team (gastroenterologist specializing in hepatology or hepatologist), virologist, and established contacts with the regional transplant centre. It is expected that in the developing HIV service networks, protocols detailing clear referral pathways will be developed so that all patients with HIV/HBV coinfection will have equity of access to specialist care by a team of doctors and nurse specialists, irrespective of their main site of HIV care.

## 5.0 Management

### 5.1 Hepatitis A vaccination

- All persons not immune to hepatitis A (HAV-IgG negative) should receive two doses of hepatitis A vaccine 6–12 months apart [41]. However, response is CD4-dependent, being approximately 80% at CD4 > 500 cells/mL and falling to 8% at CD4 < 50 cells/mL [42], vaccination should be repeated once the CD4 has risen significantly or above 500 on ART.

### 5.2 Transmission advice

- Carriers should be counselled regarding prevention of transmission of HBV in terms of safer sex, avoidance of transmission through blood, partner vaccination and neonatal vaccination as appropriate [43]. Contacts of patients with chronic HBV at risk of infection, which includes sexual partners, household contacts and people at risk from parenteral exposure, should be offered testing for HBV and vaccination if non-immune.

### 5.3 General principles of hepatitis B therapy

Treatment is aimed at suppressing viral replication and improving liver histology. If treatment is associated with HBeAg to anti-HBe seroconversion there may be a durable treatment effect and HBV treatment may be withdrawn. This occurs in 10–40% of HIV-negative patients, depending on the agent used and the type of patient treated, but is lower in HIV-positive patients. Once initiated, long-term suppressive treatment will be required in most patients. The approach to treatment depends on the following factors:

- Markers of HBV replication – candidates for treatment are usually HBeAg-positive (see below).

- The activity and stage of liver disease—patients with normal or near-normal liver function tests are less likely ever to develop clinically significant liver disease, and are less likely to respond to treatment.
- Stage of HIV disease – for those with advanced HIV disease, treatment of chronic hepatitis may not be a priority, and a sustained response is very unlikely to be achievable, but viral suppression and improvement in liver function is achievable even in late-stage disease.
- HIV treatment status – whether someone is on antiretroviral treatment affects the choice of HBV treatments available (see below).

### 5.3.1 Who to treat

- Patients with normal or near-normal liver function tests (ALT/AST < 1.5 times the upper limit of normal) and who are HBeAg-negative with an HBV-DNA  $\leq 10^4$  copies/mL are unlikely to have active liver disease or viral replication and should be treated conservatively. Regular monitoring should be continued to detect reactivation of viral replication (usually accompanied by reappearance of HBeAg) or of liver disease (rise in transaminase levels). A liver biopsy may be helpful to confirm that the liver disease is not advanced, as cases of cirrhosis in HIV/HBV-infected men with normal LFTs has been reported [44].
- Patients who are HBeAg-positive have higher levels of viral replication and are at greater risk of progressive liver disease and are more infectious. They are the principal candidates for treatment. Higher LFTs or more active inflammation on liver biopsy increase the probability of a treatment response.
- Treatment should be considered for HBeAg-negative patients with abnormal liver function tests and in whom other possible causes of the abnormal LFTs have been excluded. These patients are likely to be infected with a mutant virus that prevents the expression of HBeAg but is still replication competent. Plasma viral load provides a measure of viral replication but levels are lower than in HBeAg-positive patients. Recent evidence suggests that in HIV-positive, HBeAg-negative patients, HBV-DNA levels  $> 10^4$  copies/mL (or  $> 10^3$  copies/mL if they have decompensated cirrhosis) should be the indicators for therapy [45]. In some patients it may also be appropriate to treat in order to reduce infectivity at any HBV-DNA level.

### 5.3.2 When to start treatment

- The treatment options for chronic HBV infection are limited, but improving. HBV treatments can be categor-

ized according to whether or not they have anti-HIV activity as well. If they have anti-HIV activity, they must be used in conjunction with an effective antiretroviral regimen in order to prevent the emergence of HIV-drug resistance. Drugs with HBV activity may either form part of an antiretroviral regimen, or be in addition. When patients have to change anti-HIV treatments, because of intolerance or lack of efficacy, the anti-HBV component should be continued (unless switching from 3TC/FTC to tenofovir), even if it is not part of the subsequent anti-HIV regimen.

- The optimal time to initiate anti-HBV treatment in HIV coinfecting patients is not known. Response rates may be higher with treatment given earlier, when the CD4 count is well preserved, but the options are limited and long-term antiviral treatment is likely to be needed.

### 5.3.3 What to treat with (also see treatment algorithm Fig. 1) – current treatment options

**5.3.3.1 Alpha-interferon.** Alpha-interferon can be used in patients with coinfection, whether or not they are on antiretroviral therapy; it has some anti-HIV effect but this is not clinically significant.

Side effects (most commonly ‘flu-like symptoms, malaise, weight loss) are common, and the response rate for HBeAg to anti-HBe seroconversion is low. Because interferon may lower CD4 counts, few physicians use interferon-alpha in this setting.

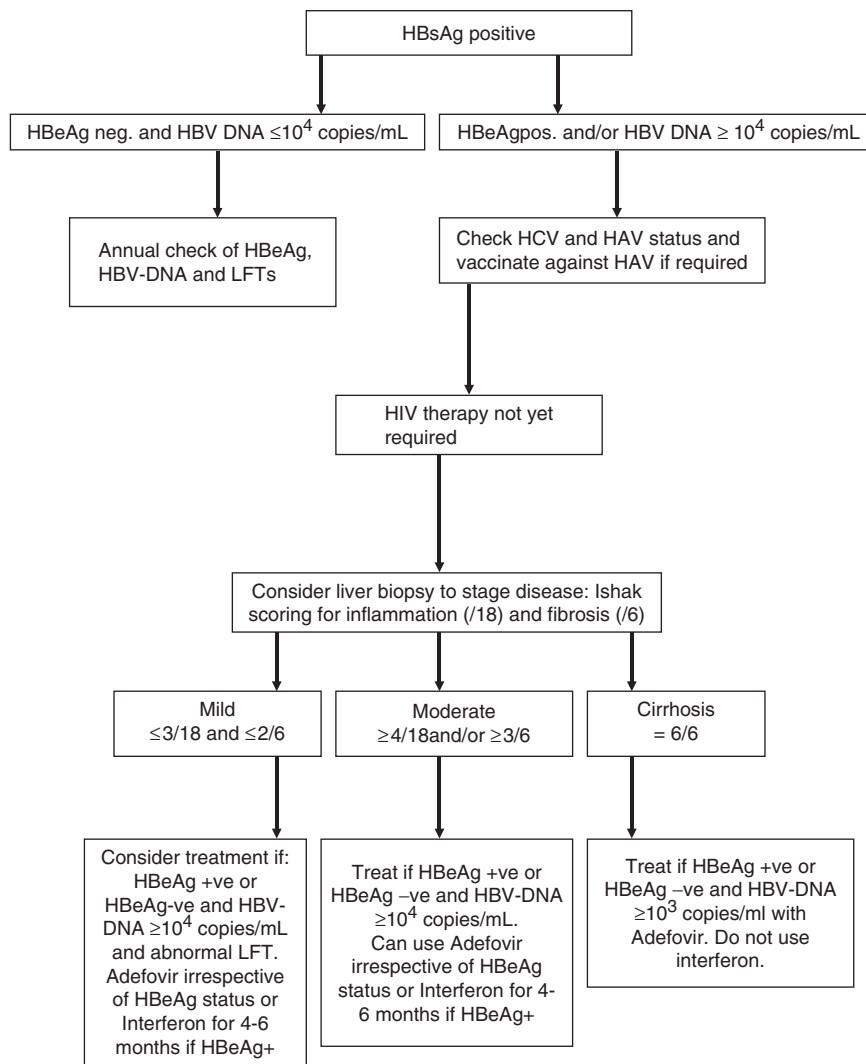
In HIV-negative patients the HBeAg to anti-HBe seroconversion rate is 5–10%, but up to 40% in those with raised transaminase levels and low HBV-DNA levels. The data in HIV-positive patients are limited, with most evidence suggesting a lower response rate [46–48].

Treatment is not recommended in patients with cirrhosis or a history of decompensated liver disease because of the risk of further decompensation (excluding advanced liver disease is the strongest indication for liver biopsy in this setting).

Recent evidence suggests that pegylated interferon may prove to be more effective [48].

**5.3.3.2 3TC.** 3TC is licensed for the treatment of chronic hepatitis B in patients who are HBeAg-positive with evidence of active liver disease. The effective dose for hepatitis B treatment is 100 mg daily, a dose at which it also has inadequately suppressive anti-HIV activity but sufficient to select 3TC-resistance and should not be used except in combination with effective combination antiretroviral therapy and then at a higher dose of 300 mg (daily or split bd).

In both HIV-negative and coinfecting patients, 3TC treatment is associated with viral suppression and improvement in liver function tests [49–52]. However,



**Fig. 1** Management algorithm for HIV-positive patients with HBV infection and high CD4 count not requiring HIV therapy.

mutations in the polymerase YMDD motif, analogous to that in HIV, results in antiviral resistance in up to 69% after 5 of years treatment [50]. This develops more rapidly in coinfecting patients with up to half of all patients showing resistance after 2 years [51,53–55]. With relapse of viral replication, liver disease activity increases [55,56].

Withdrawal of 3TC may result in an acute exacerbation of hepatitis that may be sufficient to precipitate liver decompensation [56,57]. Use of 3TC in coinfecting patients may, therefore, more appropriately be reserved for those patients with evidence of progressive liver disease.

The value of treating anti-HBe-positive carriers with normal liver function and low or undetectable viral load preemptively, to prevent reactivation, has not been established.

In HIV-negative patients who are anti-HBe/HBV-DNA-positive, 3TC suppresses viral replication and improves LFTs, but this effect is not durable [58].

**5.3.3.3 Adefovir.** Adefovir, a nucleotide analogue, is licensed in the USA and Europe. At a dose of 10 mg once daily, adefovir has been shown to suppress HBV replication and improve histology in chronic HBV carriers who are both HBeAg-positive and anti-HBe-positive [59,60].

Adefovir has no significant antiretroviral effect at this dose (although it does at higher doses) and therefore could be given to HIV-coinfecting patients not on antiretroviral therapy [61]. Although there is a theoretical danger of inducing HIV resistance, a recent study of 35 coinfecting patients treated for 144 weeks showed LFT normalization

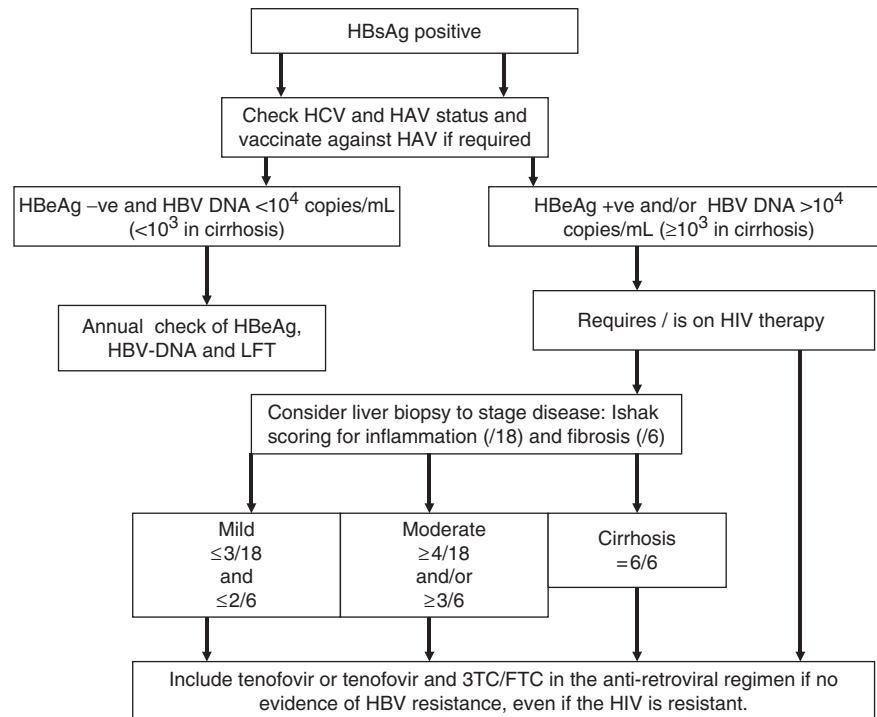


Fig. 2 Management algorithm for patients with HBV infection requiring HIV-therapy.

in most, and no cases of acquired HIV or HBV resistance, although all patients were receiving ART with an undetectable viral load [62].

Adefovir could also be used in HIV-coinfected patients receiving antiretroviral therapy if tenofovir is not being used (there is no rationale for combining them). There is very limited clinical trial data in HIV-coinfected patients [63], although they were included in the first clinical trial in HBV carriers [64] in whom viral suppression was similar in both HIV-positive and HIV-negative patients.

Adefovir is active against lamivudine-resistant strains of HBV [65,66]. In HIV-negative patients it has been shown that treatment can be switched safely from 3TC to adefovir in 3TC-resistant cases; there is no benefit in continuing the lamivudine as well [67].

Whether there is any advantage of combining adefovir with 3TC is unknown for either HIV-coinfected or HIV-negative patients.

**5.3.3.4 Tenofovir.** Tenofovir is a nucleotide analogue similar to adefovir. Although there are no randomized trials in chronic hepatitis B, there is evidence that it suppresses HBV replication [68].

Open-label studies of six and 20 tenofovir-treated coinfecting patients, most of whom were 3TC-experienced, showed a reduction in HBV-DNA viral load (of 4 log<sub>10</sub>), fall in ALT levels and loss of HBeAg (25%) [69,70].

Another retrospective analysis of 40 coinfecting patients on tenofovir, 60% of whom had 3TC-resistant HBV, showed 70% with undetectable HBV-DNA at 96 weeks and 23% had lost HBeAg [71].

**5.3.3.5 Combination therapy.** 3TC/tenofovir can be used in combination for coinfecting patients as part of, or in addition to an effective antiretroviral regimen. Retrospective analysis of the Gilead 903 trial showed that 11 patients had dual HBV/HIV infection, of whom five had received 3TC alone and six received both tenofovir and 3TC [72]. At 144 weeks the patients receiving both tenofovir and 3TC had a 2.6 log<sub>10</sub> greater fall in HBV-DNA compared to 3TC alone. Furthermore, all five patients on 3TC alone developed resistant HBV, which only occurred in one of the six on dual therapy. Another recent study also showed durable HBV-DNA suppression in coinfecting patients on tenofovir/3TC at 96 weeks [73].

Patients should be encouraged to join clinical trials.

**5.3.3.6 Emtricitabine (FTC).** Early studies show significant and prolonged anti-HBV activity in HIV-negative patients. *In vitro* evidence suggest that there will be cross-resistance between lamivudine and FTC [74–76], and, therefore, these agents should not be used together. They should not be exchanged in the face of HBV resistance.



**Table 1** Modified Ishak Score of Liver Histology [81]

Liver damage	Inflammatory score*	Fibrosis score**
Mild	1–3	1–2
Moderate	4–18	3–5
Cirrhosis		6

\*Portal/Periportal Inflammation Graded 1–18.

\*\*Fibrosis Graded 1–6.

#### 5.4 Future treatment options

- Other nucleoside analogue therapies are currently in clinical trials, including entecavir, clevudine (L-FMAU) and telbivudine (l-dT), which is the beta-L configuration of the natural nucleoside thymidine [77].
- Entecavir has anti-HBV activity [78]. Phase III trials in chronic hepatitis B are in progress. *In vitro* studies suggest that there will be no cross-resistance with 3TC [79].
- In HIV-negative patients, pegylated interferon is associated with an improved response rate compared with conventional interferon, as has been demonstrated in chronic hepatitis C. How this agent may be used in HIV coinfection remains to be determined although it seems likely that it will replace conventional interferon [48].
- Famciclovir has anti-HBV activity but only at high doses and is not recommended treatment outside clinical trials. Adding famciclovir in patients with lamivudine-resistant infection is of no value [80].
- Other experimental therapies have included ribavirin and thymosin alpha but there is no place for these therapies outside of clinical trials.

#### 5.5 Summary of treatment

- In patients with a high CD4 count not requiring HIV therapy, but requiring HBV therapy, HBV therapy should be with agents that have no anti-HIV activity at the doses used. Interferon alpha for 4–6 months is suitable in non-cirrhotic HBeAg-positive patients and an abnormal LFT or alternatively, long-term adefovir in any patient. Pegylated interferon may replace interferon in the future.
- In patients requiring HIV therapy who are HBsAg-positive, therapy would normally include tenofovir or a combination of tenofovir with either 3TC or FTC as part of, or in addition to, their antiretroviral regimen.

#### 5.6 Acute hepatitis B

Even in HIV-positive patients, most cases of acute hepatitis B resolve spontaneously and without complications. No

specific therapy has been shown to improve the outcome or reduce the risk of developing chronic infection. Treatment is supportive. Antiretroviral treatment may have to be interrupted if there is marked LFT elevation.

#### Written on behalf of the British HIV Association.

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