

BHIVA GUIDELINES - HIV AND CHRONIC HEPATITIS: CO-INFECTION WITH HIV AND HEPATITIS B VIRUS INFECTION, Updated October 2004

BHIVA Hepatitis Coinfection Guideline Committee on behalf of the British HIV Association.

Contents

1.0 Key recommendations	2
1.1 Assessment of all HIV+ patients	2
1.2 Assessment and management of HIV/HBV co-infected patients	2
1.3 Anti-HBV therapy in HIV/HBV co-infection	3
2.0 Audit standards	4
3.0 Background	4
3.1 Prevalence	4
3.2 Natural history	4
3.3 Immunisation	5
3.4 Delta virus	5
4.0 Assessment and investigations	6
4.1 Assessment	6
4.2 Investigations	6
4.2.1 Initial work-up	6
4.2.2 Additional tests	6
4.2.3 Follow-up tests	6
4.2.4 Test interpretation	6
4.2.5 Networks	7
5.0 Management	8
5.1 Hepatitis A vaccination	8
5.2 Transmission advice	8
5.3 General principles of hepatitis B therapy	9
5.3.1 Who to treat	9
5.3.2 When to start treatment	9
5.3.3 What to start with - current treatment options	9
5.3.3.1 Alpha Interferon	9
5.3.3.2 Lamivudine	9
5.3.3.3 Adefovir	10
5.3.3.4 Tenofovir	10
5.3.3.5 Combination therapy	11
5.3.3.6 Emtricitabine (FTC)	11
5.4 Future treatment options	11
5.5 Summary of treatment	11
5.6 Acute Hepatitis C	13
6.0 References	13
7.0 Figures and Tables	16
Table 1: Modified Ishak Score of Liver Histology	16
Fig 1&2 : Management algorithms for HIV-positive patients with HBV infection	17&18

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+ 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 [I]
2. All those negative for hepatitis B markers should be immunised and anti-HBs checked at 12 weeks. Patients failing to respond to a conventional course of 20_g vaccine should receive booster doses and/or a repeat vaccination cycle with the 40_g dose. Response to vaccine may be reduced if the CD4 count is less than 500 cells/mm³ [I]
3. Those patients with a CD4 count <200 cells/mm³ not on ART should receive combination therapy first and with immune recovery, subsequent immunisation.
4. Following successful immunisation, anti-HBs levels should be checked yearly and booster doses of vaccine should be given to those with an anti-HBs level < 100 iu/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 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 co-infected patients

8. All HIV/HBV co-infected patients should have an assessment of disease status and risk of progression which includes a clinical history, examination and blood tests including 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 (HBeAg positive or HBV-DNA $\geq 10^4$ copies/ml especially if:
 - History or signs suggestive of cirrhosis or a history of decompensated liver disease,
 - HDV or HCV (PCR-positive) co-infection,
 - deranged LFTs of uncertain aetiology.
10. For patients with HBV-DNA levels <10⁴ 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 out of proportion to the HBV-disease [IV].
12. All persons without serum anti-HAV IgG should receive 2 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/mm³ [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].
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 immunisation if susceptible [II].
16. Newborns of co-infected mothers should receive HBIG and HBV vaccine at delivery, in addition to post-natal HIV prophylaxis, and complete the recommended vaccination programme [I]. This requires optimal liaison between hospital and community staff.
17. Screening for HCC should occur in patients with established cirrhosis by 6-monthly α -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 co-infection

19. The optimal time for initiating anti-HBV therapy in co-infected 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 > 1.5x Upper Limit of Normal) and HBV-DNA $\geq 10^4$ copies/ml. [I].
20. Interferon is the preferred option for HBeAg +ve patients and adefovir in HBeAg -ve 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. [II].
22. Tenofovir can be given as the sole anti-HBV agent (II). 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 +ve 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 co-infected 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, include entecavir, clevudine (L-FMAU), L-dT 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 non-immune 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 anti-retroviral 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 co-infection in patients. Underlying HIV infection increases the chance HBV chronicity [3]. There is no comprehensive data from the UK defining HIV/HBV co-infection rates. However, data from the EuroSIDA study [4] showed a 9% prevalence of HBsAg co-infection 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 co-infection 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 co-infection 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 and therefore HIV/HBV is common – one study in Germany found 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. Co-infection 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 co-infected 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 reactivation and reinfection 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 co-infected 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 anti-retroviral therapy [20].

3.3 Immunisation

- 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 (c.80%) at >500 cells/ul and least response (c.25%) with counts <200 cells/ul [21]. Protective antibodies are lost more quickly [22].
- All newly diagnosed HIV patients should have an anti-HBc test and additionally an anti-HBs test if they have previously been immunised. If negative for both they should receive a course of vaccination and subsequent boosters up to a further 3 doses until they have detectable serum anti-HBs antibodies, ideally greater than 100i.u./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-HBs levels should be checked yearly and booster doses given if the anti-HBs level falls below 100 i.u./l [23]
- Persons who fail to seroconvert to HBV vaccine [24] should have repeat vaccination courses once the CD4 count rises to >500 cells/ul 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 co-infection 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 immunisation 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 co-infection, 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 younger age in heavy drinkers. [27]

4.2 Investigations

4.2.1 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 particular risk.
- HAV immunity – anti-HAV IgG Ab.

4.2.2 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) co-infection, 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 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)
- 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 regular full biochemical profile including bilirubin, albumin and liver enzymes; and full blood count performed a minimum of every six 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 AFP. 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 co-infected 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, FTC or tenofovir as part of HAART associated with WT virus repopulation
 - Hepatotoxicity as a result of ARV agents or other drugs. Co-infected patients have more ARV-related liver toxicity.
 - Inflammation as a result of other hepatotropic virus infections (HCV, HDV, HAV) or HBV reinfection
 - 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 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 co-infected 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) which 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 categorised 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 co-infected 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.

4.25 Networks:

- There should be close liaison with the local hepatology team (gastroenterologist specialising 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 co-infection 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 –ve) should receive 2 doses of hepatitis A vaccine 6-12 months apart [41]. However, response is CD4-dependant, being c.80% at CD4 >500 cells/ul and falling to 8% at CD4 <50 cells/ul [42]. In all patients with a CD4 <500 cells/ul, 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+, 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 categorised 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 co-infected 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.

5.3.4 What to Treat With (Also See Treatment Algorithm Fig 1)

Current Treatment Options

5.3.4.1 Alpha-interferon can be used in patients with co-infection, 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 therefore 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 is 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].

5.3.4.2 Lamivudine (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 100mg 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 300mg (daily or split bd).

- In both HIV-negative and co-infected patients, lamivudine treatment is associated with viral suppression and improvement in liver function tests [49-51]. However mutations in the polymerase YMDD motif, analogous to that in HIV, results in antiviral resistance in up to 69% after 5 years treatment [50]. This develops more rapidly in co-infected 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 lamivudine may result in an acute exacerbation of hepatitis that may be sufficient to precipitate liver decompensation [56,57]. Use of lamivudine in co-infected 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 pre-emptively, to prevent reactivation, has not been established.
- In HIV-negative patients who are anti-HBe/HBV-DNA-positive, lamivudine suppresses viral replication and improves LFTs, but this effect is not durable [58].

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

- Adefovir has no significant antiretroviral effect at this dose (although it does at higher dose) and therefore could be given to HIV co-infected patients not on antiretroviral therapy [61]. Although there is a theoretical danger of inducing HIV resistance, a recent study of 35 co-infected patients treated for 144 weeks showed LFT normalisation 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 co-infected 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 co-infected 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 lamivudine to adefovir in lamivudine-resistant cases; there is no benefit in continuing the lamivudine as well [67].
- Whether there is any advantage of combining adefovir with lamivudine is unknown for either HIV-coinfected or HIV-negative patients

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

- Open-label studies of 6 and 20 tenofovir-treated co-infected patients, most of whom were lamivudine-experienced, showed a reduction in HBV-DNA viral load (of 4 log₁₀), fall in ALT levels and loss of HBeAg (25%) [69, 70].
- Another retrospective analysis of 40 co-infected 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].

5.3.4.5 Combination Therapy

- Lamivudine/tenofovir can be used in combination for co-infected 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 5 had received 3TC alone and 6 received both tenofovir and 3TC [72]. At 144 weeks, patients receiving both tenofovir and 3TC had a 2.6 log₁₀ greater fall in HBV-DNA compared to 3TC alone. Furthermore, all 5 patients on 3TC alone developed resistant HBV, which only occurred in 1 of the 6 on dual therapy. Another recent study also showed durable HBV-DNA suppression in co-infected patients on tenofovir/3TC at 96 weeks [73].
- Patients should be encouraged to join clinical trials.

5.3.4.6 Emtricitabine (FTC)

- Early studies show significant and prolonged anti-HBV activity in HIV negative patients. In vitro evidence suggests that there will be cross-resistance between lamivudine and emtricitabine [74-6] and therefore these agents should not be used together. They should not be exchanged in the face of HBV resistance.

5.4 Future Treatment Options

- Other nucleoside analogue therapies are currently in clinical trial 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 –ve 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 co-infection 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 lamivudine 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.

Principle authors: Dr Gary Brook Central Middlesex Hospital, London, Dr Richard Gilson, Mortimer Market Centre, London. Dr Ed Wilkins, North Manchester Hospital.

Guideline Committee: Dr Gary Brook, Dr Janice Main (Co-Chairs), Mr Paul Bateman, Dr Richard Gilson, Dr Gayle Mathews, Dr Mark Nelson, Prof. Caroline Sabin, Dr Ed Wilkins.

6.0 References

1. WHO. Hepatitis B. Fact sheet WHO/204 Oct 2000. www.who.int/inf-fs/en/fact204.html
2. UNAIDS. 2004 Report of the global HIV/AIDS epidemic. Accessed 20/10/2004. <http://www.unaids.org/bangkok2004/report.html>
3. Sinicco A, Raiteri R, Sciandra M *et al*. Coinfection and superinfection of hepatitis B virus in patients infected with immunodeficiency virus: no evidence for faster progression to AIDS. *Scand J Infect Dis* 1997;29:111-5
4. Rockstroh J, Konopnicki D, Soriano V *et al*. Hepatitis B and Hepatitis C in the EuroSIDA cohort: prevalence and effect on mortality, AIDS progression and response to HAART. 11th Conference on Retroviruses and Opportunistic Infections. San Francisco 2004 Abstract 799.
5. Beck E J, Mandalia S, Leonard K *et al*. Case-control study of sexually transmitted diseases as cofactors for HIV-1 transmission. *Int J STD AIDS* 1996;7:34-8
6. Ahmed SD, Cuevas LE, Brabin BJ *et al*. Seroprevalence of hepatitis B and C and HIV in Malawian pregnant women. *J Infect* 1998 37:248-51
7. Combe P, La Ruche G, Bonard D *et al*. Hepatitis B and C infections, human immunodeficiency virus and other sexually transmitted infections among women of childbearing age in Cote D'Ivoire, West Africa. *Trans Roy Soc Trop Med Hyg* 2001;95:493-6
8. PHLS AIDS Centre and Scottish Centre for Infection. AIDS/HIV quarterly surveillance tables. No. 55: 02/2 July 2002 www.phls.co.uk
9. Opravil M, Hunziker R, Luthy R *et al*. Chronic hepatitis B and C in HIV infected patients. *Deutsche Medizinische Wochenschrift* 1998;123:753-60
10. Gilson RJ, Hawkins AE, Beecham MR *et al*. Interactions between HIV and hepatitis B virus in homosexual men: effects on the natural history of infection. *AIDS* 1997;11:597-606
11. Colin JF, Cazals-Hatem D, Liorot MA *et al*. Influence of human immunodeficiency virus infection on chronic hepatitis B in homosexual men. *Hepatology* 1999;29:1306-10
12. Puoti M, Spinetti A, Ghezzi A *et al*. Mortality for liver disease in patients with HIV infection: a cohort study. *J AIDS* 2000;24:211-7
13. Martin-Carbonero L, Soriano V, Valencia E *et al*. Increased impact of chronic viral hepatitis on hospital admissions and mortality among HIV-infected patients. *AIDS Res & Hum Retrovirol* 2001;17:1467-71
14. Aceti A, Pasquazzi C, Zechini B *et al*. Hepatotoxicity development during antiretroviral therapy containing protease inhibitors in patients with HIV: the role of hepatitis B and C. *JAIDS* 2002;29:41-8
15. Sulkowski MS, Thomas DL, Mehta SH *et al*. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology* 2002;35:182-9
16. Atfield M, Rockstroh JK, Addo M *et al*. Reactivation of hepatitis B in a long-term anti-HBs-positive patient with AIDS following lamivudine withdrawal. *J Hepatology* 1998;29:306-9
17. Manegold C, Hannoun C, Wywiol A *et al*. Reactivation of hepatitis B virus replication accompanied by acute hepatitis in patients receiving highly active antiretroviral therapy. *Clin Infect Dis* 2001;32:144-8
18. Hofer M, Joller-Jemelka HI, Grob PJ *et al*. Frequent chronic hepatitis B virus infection in HIV-infected patients positive for antibody to hepatitis B core antigen only. Swiss cohort study. *Eur J Clin Microbiol Infect Dis*. 1998;17:6-13
19. Mai AL, Yim C, O'Rourke K *et al*. The interaction of human immunodeficiency virus infection and hepatitis B virus infection in homosexual men. *J Clin Gastroenterol* 1996;22:299-304
20. Piroth L, Grappin M, Buisson M *et al*. Hepatitis B seroconversion in HIV-HBV coinfecting patients treated with highly active antiretroviral therapy. *J AIDS & Hum Retrovirol* 2000;23:356-7
21. Veiga APR, Casseb J, Duarte AJS. Efficacy to hepatitis B vaccination and its relationship with T CD45RA+ (naïve) and CD45RO+ (memory) subsets in HIV-1-infected subjects. XV International AIDS Conference, Bangkok, 2004. Abstract B10392
22. Rey D, Krantz V, Partisani M *et al*. Increasing the number of hepatitis B injections augments anti-HBs response rate in HIV-infected patients. Effect on viral load. *Vaccine* 2000;18:1161-5
23. European consensus group on hepatitis B immunity. Are booster immunisations needed for lifelong hepatitis B immunity? *Lancet* 2000;355:561-65
24. Yoon C *et al*. Comparison of the efficacy of hepatitis A and hepatitis B vaccination in HIV infected patients. XIV Int AIDS Conf 2002; abstract MoPeB3156.
25. Toyoda H, Fukuda Y, Nakano I *et al*. Fatal liver failure in haemophiliacs with HIV-induced immunodeficiency: observation of six patients. *Haemophilia* 1999;5:109-14
26. Lok A, McMahon BJ. Practice Guidelines Committee, American Association for the Study of Liver Diseases. Chronic hepatitis B. *Hepatology* 2001; 34: 1225-1239
27. Chevillotte G, Durbec JP, Gerolami A *et al*. Interaction between hepatitis B virus and alcoholic consumption in liver cirrhosis: an epidemiological study. *Gastroenterology* 1983; 85: 141-5
28. McMahon BJ, Bulkow L, Harpster A *et al*. Screening for hepatocellular carcinoma in Alaska Natives infected with chronic hepatitis B: a 16-year population-based study. *Hepatology* 2000; 32: 842-6
29. Sherman M, Peltekian KM, Lee C. Screening for hepatocellular carcinoma in chronic carriers of hepatitis virus B: incidence and prevalence of hepatocellular carcinoma in a North American urban population. *Hepatology* 1995; 22: 432-714.
30. Chu CJ, Lok AS. Clinical utility in quantifying serum HBV DNA levels using PCR assays. *J Hepatology* 2002; 36: 549-551
31. Kao JH, Chen DS. Global control of hepatitis B virus infection. *Lancet Infect Dis* 2002; 2: 395-403
32. Lok AS, Heathcote EJ, Hoofnagle JH. Management of hepatitis B: 2000 - summary of Workshop. *Gastroenterology* 2001; 120: 1828-1853
33. Manesis EK, Papatheodoridis GV, Hadziyannis SJ. Serum HBV DNA levels in inactive hepatitis B carriers. *Gastroenterology* 2002;122:2092-3
34. Knodell RG, Ishak KG, Black WC *et al*. Formulation and application of numerical scoring system for assessing histological activity in asymptomatic chronic hepatitis. *Hepatology* 1981; 1: 431-435
35. Ishak K, Baptista A, Bianchi L *et al*. Histological grading and staging of hepatitis. *J Hepatology* 1995; 22: 696-9
36. The French Metavir Cooperative Study Group. Intraobserver and interobserver variations in liver biopsy interpretation in patients with chronic hepatitis C. *Hepatology* 1994; 20: 15-20
37. Rozario R, Ramakrishna B. Histopathological study of chronic hepatitis B and C: a comparison of two scoring systems. *J Hepatology* 2003;38:223-9
38. Lok AS, Zoulim F, Locarnini S, *et al*. Monitoring drug resistance in chronic hepatitis B virus (HBV)-infected patients during lamivudine therapy: evaluation of performance of INNO-LiPA HBV DR assay. *Journal of Clinical Microbiology*. 2002;40:3729-34,
39. Cooley L *et al*. Hepatitis B virus and HIV co-infection: development of Lamivudine resistance. 9th CROI; abstract 673-M

40. Benhamou Y, Bochet M, Thibault V *et al.* Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus-related patients. *Hepatology* 1999; 30: 1302-6
41. Centers for Disease Control and Prevention. Prevention of hepatitis A through active or passive immunisation: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1996; 45: 1-30
42. Rimland A, Guest JL. Response to hepatitis A vaccine in HIV patients in the HAART era. XV International AIDS Conference, Bangkok, 2004. Abstract MoPeB3299
43. CDC. Hepatitis B virus: a comprehensive strategy for limiting transmission in the United States through universal childhood vaccination. Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR* 1991; 40: 1-25
44. Colin J, Cazals-Hatem D, Liorot M, *et al.* Influence of HIV infection on chronic hepatitis B in homosexual men. *Hepatology* 1999; 29: 1306-1310
45. Keeffe E, Dieterich D, Han SH *et al.* A treatment algorithm for the management of chronic hepatitis B virus infection in the United States. *Clin Gastroenterol Hepatology* 2004; 2: 87-106
46. Wong D K, Yim, C, Naylor C D *et al.* Interferon alfa treatment of chronic hepatitis B: randomized trial in a predominantly homosexual male population. *Gastroenterology* 1995; 108: 165-71
47. Krogsgaard K, Bindslev N, Christensen E *et al.* The treatment effect of alpha interferon in chronic hepatitis B is independent of pre-treatment variables. Results based on individual patient data from 10 clinical controlled trials. European Concerted Action on Viral Hepatitis (Eurohep). *J Hepatol* 1994; 21: 646-55
48. Cooksley W. Treatment with interferons (including pegylated interferons) in patients with chronic hepatitis B. *Semin Liver Dis* 2004; 24 (suppl): 45-53.
49. Zylberberg H, Jiang J, Pialoux G *et al.* Alpha-interferon for chronic active hepatitis B in human immunodeficiency virus-infected patients. *Gastroenterol Clin Biol.* 1996; 20(11): 968-71
50. Dore G J, Cooper D A, Barrett C *et al.* Dual efficacy of lamivudine treatment in human immunodeficiency virus/hepatitis B virus-coinfected persons in a randomized, controlled study (CAESAR). The CAESAR Coordinating Committee. *J Infect Dis.* 1999; 180: 607-13
51. Benhamou Y, Bochet M, Thibault V *et al.* Long-term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus-infected patients. *Hepatology* 1999; 30: 1302-6
52. Hoff J, Bani-Sadr F, Gassin M *et al.* Evaluation of chronic hepatitis B virus (HBV) infection in coinfecting patients receiving lamivudine as a component of anti-human immunodeficiency virus regimens. *Clin Infect Dis* 2001; 32: 963-9
53. Leung N. Treatment of chronic hepatitis B: case selection and duration of therapy. *J Gastroenterol Hepatol* 2002; 17: 409-14
54. Pillay D, Cane P A, Ratcliffe D *et al.* Evolution of lamivudine resistant-hepatitis B virus and HIV-1 in co-infected individuals: an analysis of the CAESAR study. CAESAR co-ordinating committee. *AIDS* 2000; 14: 1111-6
55. Wolters L M M, Niesters H G M, Hansen B E *et al.* Development of hepatitis B virus resistance for lamivudine in chronic hepatitis B patients co-infected with the human immunodeficiency virus in a Dutch cohort. *J Clin Virol* 2002; 24: 173-81.
56. Bessesen M, Ives D, Condreay L *et al.* Chronic active hepatitis B exacerbations in human immunodeficiency virus-infected patients following development of resistance to or withdrawal of lamivudine. *Clin Infect Dis* 1999; 28: 1032-5
57. Bonacini M Kurz A, Locarnini S *et al.* Fulminant hepatitis B due to a lamivudine-resistant mutant of HBV in a patient coinfecting with HIV. *Gastroenterology* 2002; 122: 244-5.
58. Santantonio T, Mazzola, M, Iacovazzi T *et al.* Long-term follow-up of patients with anti-HBe/HBV DNA-positive chronic hepatitis B treated for 12 months with lamivudine. *J Hepatol.* 2000; 32: 300-6
59. Marcellin P, Chang TT, Lim SG, *et al.* GS-98-437: a double-blind, randomized, placebo-controlled study of adefovir dipivoxil (ADV) for the treatment of patients with HBeAg+ chronic hepatitis B infection: 48 week results. *Hepatology* 2001; 34: 340A.
60. Hadziyannis S, Tassopoulos N, Heathcote E, *et al.* GS-98-438: a double-blind, randomized, placebo-controlled study of adefovir dipivoxil (ADV) for presumed precore mutant chronic hepatitis B: 48 week results. 37th Annual Meeting the European Association for the Study of the Liver. Madrid, Spain, 17-21 April, 2002. Abstract 648
61. Delaugerre C, Marcellin, AG, Thibault V *et al.* Human immunodeficiency virus (HIV) Type 1 reverse transcriptase resistance mutations in hepatitis B virus (HBV)-HIV-coinfected patients treated for HBV chronic infection once daily with 10 milligrams of adefovir dipivoxil combined with lamivudine. *Antimicrob Agents Chemother* 2002; 46: 1586-8.
62. Benhamou Y, Thibault V, Vig P, *et al.* Long-term treatment with adefovir dipivoxil 10 mg (ADV) in patients with lamivudine-resistant (LAM-R) HBV and HIV co-infection results in significant and sustained clinical improvement. XV Int Conf AIDS 2004; Bangkok. Abstract WeOrA1329
63. Benhamou, Y, Bochet M, Thibault V *et al.* Safety and efficacy of adefovir dipivoxil in patients co-infected with HIV-1 and lamivudine-resistant hepatitis B virus: an open-label pilot study. *Lancet* 2001; 358: 718-23.
64. Gilson RJC, Chopra KB, Newell AM *et al.* A placebo-controlled phase I/II study of adefovir dipivoxil in patients with chronic hepatitis B virus infection. *J Viral Hep* 1999; 6: 387-395.
65. Xiong X, Flores C, Yang H *et al.* Mutations in hepatitis B DNA polymerase associated with resistance to lamivudine do not confer resistance to adefovir in vitro. *Hepatology* 1998; 28: 1669-73.
66. Perrillo R, Schill E, Yoshida E *et al.* Adefovir dipivoxil for the treatment of lamivudine-resistant hepatitis B mutants. *Hepatology* 2000; 32: 129-34.
67. Peters, M, Hann, HW, Martin, P *et al.* Adefovir dipivoxil (ADV) alone and in combination with lamivudine (LAM) suppresses YMDD mutant hepatitis B virus replication: 48 week preliminary analysis. *Hepatology (AASLD 2002 poster)*
68. Benhamou, Y, Bochet, M, Tubiana, R *et al.* Tenofovir disoproxil fumarate suppresses lamivudine-resistant HBV replication in chronic hepatitis B patients co-infected with HIV/HBV. XIV International AIDS Conference, Barcelona, 2002. Poster 7527.
69. Ristig MB, Crippin J, Aberg JA *et al.* Tenofovir Disoproxil Fumarate therapy for chronic hepatitis B in Human Immunodeficiency Virus/Heptitis B Virus-coinfecting individuals for whom interferon- α and lamivudine therapy have failed. *J Infect Dis* 2002;186:1844-7
70. Nelson M, Portsmouth S, Stebbing J *et al.* An open-label study of tenofovir in HIV-1 and Heptitis B virus co-infected individuals. *AIDS* 2003;17:F7-F10
71. Gilleece Y, Nelson M, Clarke A, *et al.* Tenofovir in the treatment of hepatitis B/HIV coinfecting individuals. XV Int Conf AIDS 2004; Bangkok Abstract MoPeB3298.
72. Dore G, Cooper D, Pozniak A, *et al.* Efficacy of tenofovir disoproxil fumarate in antiretroviral therapy-naive and -experienced patients coinfecting with HIV-1 and hepatitis B virus. *J Infect Dis* 2004; 189: 1185-1192
73. Bani-Sadr F, Palmer P, Scieux C, Molina JM. Ninety-six week efficacy of combination therapy with lamivudine and tenofovir in patients coinfecting with HIV-1 and wild type hepatitis B virus. *Clin Infect Dis* 2004; 39: 1062-1064.
74. Gish R, Leung N, Wright T, Trinh H, Lang W, Kessler H, *et al.* Dose range study of pharmacokinetics, safety, and preliminary antiviral activity of emtricitabine in adults with hepatitis B virus infection. *Antimicrob Agents Chemother* 2002; 46: 1734-1740.

75. Das K, Xiong X, Yang H, Westland C, Gibbs C, Sarafianos S, et al. Molecular modeling and biochemical characterization reveal the mechanism of hepatitis B virus polymerase resistance to lamivudine (3TC) and emtricitabine (FTC). *J Virol* 2001; 75: 4771-4779.
76. Gish R, Leung N, Wang C, Corey L, Sacks S, Fried M, et al. Resistance to emtricitabine may develop less frequently than to lamivudine. 53rd AASLD, Boston 2002 Abstract 838.
77. Papatheodoridis, GV; Dimou, E; Papadimitropoulos, V. Nucleoside analogues for chronic hepatitis B: antiviral efficacy and viral resistance. *Am J Gastroenterol* 2002; 97: 1618-28.
78. de-Man, RA, Wolters, LM; Nevens, F *et al.* Safety and efficacy of oral entecavir given for 28 days in patients with chronic hepatitis B virus infection. *Hepatology* 2001; 43: 578-82.
79. Ono, SK; Kato, N; Shiratori, Y *et al.* The polymerase L528M mutation cooperates with nucleotide binding-site mutations, increasing hepatitis B virus replication and drug resistance. *J Clin Invest* 2001; 107: 449-55
80. Matthews, G V, Pillay, D; Cane, P *et al.* Failure of combination therapy with lamivudine and famciclovir following lamivudine monotherapy for hepatitis B virus infection in patients coinfecting with human immunodeficiency virus-1. *Clin Infect Dis* 2001; 33: 2049-54.
81. Ishak KG. Pathologic features of chronic hepatitis. A review and update. *American Journal of Clinical Pathology*. 2000;113:40-55

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

Fig 1. MANAGEMENT ALGORITHM FOR HIV POSITIVE PATIENTS WITH HBV INFECTION AND HIGH CD4 COUNT NOT REQUIRING HIV-THERAPY

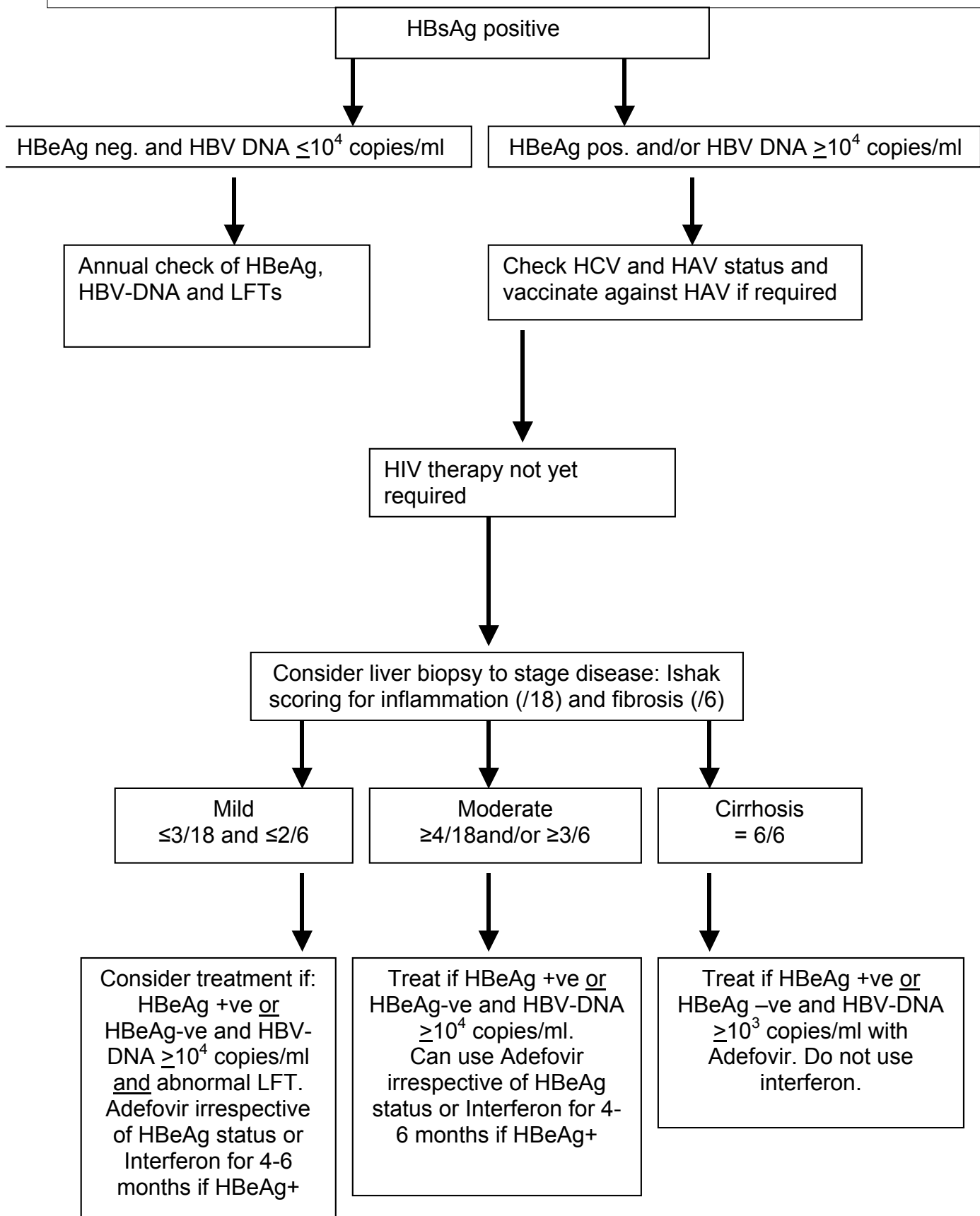


Fig 2. MANAGEMENT ALGORITHM FOR HIV POSITIVE PATIENTS WITH HBV INFECTION REQUIRING HIV-THERAPY

