

British HIV Association guidelines for the management of coinfection with HIV-1 and chronic hepatitis B or C 2009

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Level of Evidence:

- I = RCT or meta-analysis of several RCTs
- II = Other good quality trial evidence
- III = Observational studies/case reports
- IV = Expert opinion

Audit standards:

1. All new HIV-positive patients should be screened for HBV and HCV markers.
2. All HBV non-immune patients should be vaccinated.
3. All HIV-positive patients should have their HBV and HCV status measured before commencement of antiretroviral therapy.
4. All HBV- and HCV-infected patients should be vaccinated against hepatitis A if non-immune.
5. All HCV-positive patients non-immune to HBV should be vaccinated.
6. All HBV- and HCV-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 of new HBV-positive patients should contain evidence of an attempt to contact household and sexual contacts and offer vaccination if non-immune.
8. Case notes of new HCV-positive patients should contain evidence of an attempt to notify parenteral and sexual contacts and offer them a test.
9. All patients who are HBsAg-positive or HCV-positive should have a clear antiviral treatment plan written in their notes at least once a year.
10. All HCV-RNA-positive patients should have an HCV viral load and genotype performed.
11. All HBV-positive patients should have their 'e' status checked, an HBV DNA viral load and an anti-HDV antibody test.
12. All patients with chronic HBV or HCV should be offered an assessment of liver fibrosis by either liver biopsy, hepatic elastography or other validated non-invasive fibrosis test unless they have a specified contra-indication.
13. All HBV-positive patients with an HBV DNA >2000IU/mL and evidence of liver damage should be offered treatment.
14. All HCV-RNA-positive patients should be offered treatment unless there is a specific contra-indication.
15. All patients with cirrhosis should be jointly treated by a hepatologist and have regular assessments for hepatocellular carcinoma according to risk.

16. All patients with decompensated cirrhosis should be referred for liver transplantation assessment unless specifically contraindicated.

*See Appendix for list of members of the BHIVA Hepatitis B & C Coinfection Guidelines Group.

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1 Introduction

The 2009 guidelines have been updated to incorporate all new relevant information since the previous versions in 2005. The 2005 versions came as separate hepatitis B and C guidelines but for 2009 we have decided to amalgamate them into a single document. This is to avoid duplication, as the general management of chronic liver disease is similar for both infections. The guidelines follow the methodology outlined below and all the peer-reviewed publications and important, potentially treatment-changing abstracts from the last four years have been reviewed.

The translation of data into clinical practice is often difficult, even with the best possible evidence, because of differences in factors such as trial design and inclusion criteria. The recommendations based upon expert opinion have the least good evidence but provide an important reason for writing the guidelines – to produce a consensual opinion about current practice. The Writing Group seeks to provide guidelines that optimize management, but such care needs to be individualized and we have not constructed a document that we would wish to see used as a ‘standard’ for litigation.

The major changes/amendments include:

- Increased discussion on hepatitis screening and prevention;
- Clarification on the role of liver biopsy and non-invasive liver fibrosis assessment;
- More emphasis on screening for delta virus;
- Increased discussion on end-stage liver disease management and HCC screening;
- Molecular diagnostic tests used for the diagnosis and management of HBV and HCV;
- Revised CD4-based guidance on the management of chronic HBV;
- Management of acute HBV;
- Revised guidance on the management of chronic HCV, including ART interactions;
- Management of acute HCV;
- Management of treatment non-responders and relapsers in both chronic HBV and HCV.

2 Methodology

The Writing Group used an evidence-based medicine approach to produce these guidelines. Many important aspects of clinical practice remain to be formally evaluated and many trials have been performed in order to obtain licensing approval for a drug. However, the design of such trials is not ideally suited to addressing questions concerning clinical use. In most cases, the only available data on long-term outcomes are from routine clinical cohorts. While such cohorts are representative of routine clinical populations, the lack of randomization to different regimens means that comparisons between the outcomes of different treatments are susceptible to bias. Expert opinion forms an important part of all consensus guidelines; however, this is the least valuable and robust form of evidence.

3 General section: Prevention of viral hepatitis and management principles for patients with chronic viral hepatitis

There are many prevention and management principles that are common to both hepatitis B and C. We will therefore discuss these before concentrating on issues specific to each type of hepatitis.

3.1 Screening of HIV-positive patients for hepatitis B and hepatitis C

In the disease-specific section of these guidelines we have demonstrated that there is an ongoing epidemic of acute HCV amongst HIV-infected MSM in the UK and Western Europe [1,2] linked with mucosal traumatic sexual practices and co-transmitted with other sexually transmitted infections [3]. Early recognition of acute HCV is therefore important since early treatment offers the best chance of viral clearance [4]. Acute hepatitis B continues to be a problem for HIV-positive patients. We also know that 5–10% of new HIV-positive patients have chronic hepatitis B or C. There is therefore a need to screen newly diagnosed HIV-positive patients on an ongoing basis.

3.1.1 Recommendations

3.1.1.1 Screening for hepatitis in new HIV-positive patients

- All newly diagnosed HIV patients should be screened for coinfection with HBV and HCV as part of their initial work-up (III). These would normally be with the HBsAg, anti-HBc and anti-HCV antibody tests with appropriate further tests if positive. See also sections 4.2 and 5.2.
- Initial screening should also include tests for evidence of protective immunity against hepatitis A (HAV) and HBV (where appropriate) (III).

3.1.1.2 Ongoing hepatitis testing in known HIV-positive patients

- All HCV-negative patients should have an annual anti-HCV antibody screen (III).
- All patients with no natural or vaccine-induced protection against HBV should have an annual anti-HBc or HBsAg test (III).
- Any patient with a recent sexually transmitted infection or having engaged in recent injecting drug use with unexplained rise in serum aminotransferases should be offered an appropriate screening test for acute viral hepatitis (HAV IgM, HBsAg +/- HBV DNA, HCV antibody/RNA) (III).
- Any patient with risk factors for acute HCV (e.g. history of contact with HCV, current or recent IDU, MSM with high risk sexual practices) with an unexplained rise in serum aminotransferases to more than twice upper limit of normal, but negative hepatitis serology, should be offered testing for HCV RNA (III).
- Any HCV antibody-positive/HCV RNA-negative patient (whether previously treated for HCV or not) with an unexplained rise in serum aminotransferases should be offered testing for HCV RNA and annual HCV RNA screening (III).

3.3 Prevention and immunisation

Prevention strategies that work for viral hepatitis include immunisation, education on safer sex for everyone and on harm reduction for injecting drug users. Safer blood and blood products, and medical practices are also important.

3.2.2 Condoms and safer sex

Condoms are an effective means of preventing sexually transmitted hepatitis B [5–7]. A 40% lower prevalence and 66% reduction in incidence of serological evidence of hepatitis B is observed in women reporting consistent condom use for vaginal sex [5]. It would seem likely that given the evidence for condom use and the prevention of many other STIs, then they will be effective for preventing hepatitis C and preventing transmission of hepatitis B and C during other forms of penetrative sex such as penile/anal and penile/oral intercourse. Although hepatitis A is thought to be sexually transmitted in MSM, it is linked to fisting and oro-anal contact [8–10], in which case condoms are unlikely to offer protection.

There is an epidemic of acute HCV amongst HIV-infected MSM in the UK and Western Europe [1,2] linked with mucosal traumatic sexual practices and co-transmitted with other sexually transmitted infections, particularly syphilis and LGV [3]. In many cases this seems to be related to unprotected sex between men who are both HIV-positive. Safer sex education is therefore also important, emphasising the risks for catching HCV and STIs through unprotected anal sex, even if partners are HIV sero-concordant (see also section 5.11).

3.2.3 Harm reduction in injecting drug users

Although needle exchange schemes have been introduced in many parts of the world, the benefit seems to be greater for reducing HIV rather than HBV or HCV [11,12]. One study showed an incidence of new HIV, HBV and HCV of 0, 11 and 26 cases/100 years at risk in IDUs involved in a needle exchange scheme [11]. This reflects the greater infectivity and prevalence of HBV and HCV, but also the fact that sharing of ‘works’ other than the needle or syringe can still lead to transmission. Counselling of IDUs on reducing risk seems to have some effect, but a greater impact on HIV than the hepatitis viruses [12]. However, the challenge in preventative work in IDUs is engaging them in such schemes. Linking vaccination to either monetary inducements or doses of methadone has been successful [13,14].

3.2.4 Recommendations for prevention

- All patients should be counselled about safer sex and the use of condoms for penetrative sex (II).
- In the case of IDUs, potentially effective strategies include counselling on harm reduction to include advice to stop injecting, or safer injecting practices if stopping is not possible (II).
- Access to needle/syringe exchange schemes may also be of value as will incentives to complete vaccination schedules such as linkage to methadone replacement (II).

3.2.5 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/ μ L and with least response (c.25%) at counts <200 cells/ μ L [15]. Protective antibodies may be lost more quickly. Anti-HBs levels of >10 IU/L generally confer some protection, but levels of >100 IU/L are ideal [16,17].

The 0, 1 and 6 months and the 0, 1, and 2 months, with an additional dose at 12 months schedules have both been shown to be efficacious in HIV-infected patients [18,19]. There are very few data on the 0, 7–10 and 21 days, with an additional dose at 12 months schedule in HIV-positive patients, although one small study showed a 51% response after the first three doses and 88% after 6 doses [20]. Given the need to immunise patients at higher risk rapidly, this is a strategy that might be considered. Higher-dose vaccination may enhance anti-HBs response [21].

Patients who are anti-HBc positive, but negative for anti-HBs, anti-HBe and HBe, may either have had previous exposure to HBV and be protected, or may have a false-positive anti-HBc and be vulnerable [22]. These patients will need HBV vaccination.

Patients coinfecting with HBV and/or HCV are also vulnerable to acute HAV, which may lead to decompensation of underlying liver disease [23,24]. For a fuller discourse and further details on viral hepatitis vaccination and post-exposure prophylaxis in HIV-positive patients please refer to the BHIVA immunization guidelines 2008 [25].

3.2.6 Recommendations for immunisation

- 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 (I).
- The 0, 1 and 6 months schedule, or the 0, 1 and 2 months with a subsequent dose at 12 months, are acceptable vaccination schedules (II). The 0, 1 and 3 week schedule can be tried for patients who require rapid immunity (II).
- Anti-HBs levels should be checked at 6–8 weeks post vaccination and up to three further boosters may be given until anti-HBs levels are >100 IU/L (II).
- Subsequently, anti-HBs levels should be checked yearly and booster doses given if the anti-HBs level falls below 100 IU/L (II).
- Higher dose vaccine may improve response rates and may be considered for patients with CD4 counts <200 cells/ μ L (II).
- Persons who fail to seroconvert to HBV vaccine [24] should have repeat vaccination courses once the CD4 count rises to >500 cells/ μ L or after significant immune recovery, and whilst non-immune they should have annual HBV markers performed (anti-HBc/HBsAg) (II).
- Anti-HBc-positive patients should be tested for anti-HBs, anti-HBe and HBsAg. If negative for all, then consider a single dose of HBV vaccine and measure anti-HBs levels 4–6 weeks after. If anti-HBs undetectable consider a full course of vaccination as above (II).
- All HIV and HBV and/or HCV coinfecting patients should be tested for immunity against HAV (HAV-IgG or total antibody) and non-immune

patients should be vaccinated using standard recommended vaccination schedules (II).

- These patients should have booster doses of HAV vaccination every 5 years (II).

3.3 General management/care pathways

3.3.1 Assessment of liver disease

The initial evaluation of all patients with chronic viral hepatitis should include a history and clinical examination [26]. The history should include questions 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 [26,27]. A clinical examination for evidence of chronic liver disease (peripheral stigmata, splenomegaly, ascites) should be performed.

3.3.2 Investigations for liver disease

Blood tests should include a full biochemical profile including bilirubin, albumin, aminotransferases, prothrombin time, alpha fetoprotein and full blood count. A baseline battery of tests to look for alternative causes of chronic liver disease should also be performed. This should include serum ferritin, autoantibodies, serum ceruloplasmin, serum ACE, and alpha 1 anti-trypsin levels. A scan of the liver should be performed using imaging with ultrasound, CT or MRI.

3.3.3 Role of liver biopsy, hepatic elastography and other non-invasive markers of liver fibrosis

Liver biopsy remains the silver standard for the staging of liver disease [28]. Increasingly, some physicians are commencing therapy in individuals without performing liver biopsy [29]. Liver biopsy is an important diagnostic tool in the work-up of patients with liver disease. In those individuals with HIV, who may have other co-factors contributing to liver damage and fibrosis, it remains a useful tool and should always be considered and discussed. Liver biopsy provides utility in the correct staging of liver disease in those considering therapy, in those where disease other than coinfection is being considered and serially for individuals not commencing antihepatitis therapy [30,31]. Unfortunately hepatitis C has been shown to progress rapidly in some individuals, and if serial measurement utilizes liver biopsy rapid changes in liver histology may occur between biopsies [31].

Situations where liver biopsy may not be performed (see also hepatitis B and C sections):

1. Individuals declining this test after appropriate discussion and information.
2. Individuals who will commence therapy for hepatitis C no matter what the liver biopsy shows.
3. Individuals with genotype 2 and 3 requesting antihepatitis C therapy.
4. Individuals with acute hepatitis C.

5. Individuals who meet criteria for the treatment of hepatitis B and are agreeable to therapy.
6. Some physicians prefer not to perform a liver biopsy on men with haemophilia.

When a liver biopsy is not performed, liver fibrosis should still be assessed in all patients to exclude early cirrhosis. Therefore, increasingly, non-invasive methods of staging liver disease have been developed.

The most widely used method is hepatic elastography (FibroScan) [32]. The results of FibroScan give a good correlation with a fibrosis score of less than F2 disease (METAVIR) or with F4 disease (cirrhosis) [33,34] and a recent meta-analysis suggested cut off points of <7.65 kPa for the former and >13 kPa for the latter [34]. In such cases liver biopsy may be avoided. For F2 and F3 disease the correlation is less clear and individuals with readings between 7.65 and 13 kPa should be considered for biopsy when this will alter the treatment of their disease [33,34]. Alternatively a myriad of non invasive tests based on biochemical markers are available [33–36]. In individuals with F2/F3 disease on FibroScan one of these serum biochemical marker tests may be utilized. If the test correlates with the degree of fibrosis suggested by FibroScan then liver biopsy may be avoided [33]. Biochemical markers should not be used as the sole test for fibrosis [33–36].

Individuals requiring a measurement of fibrosis who decline liver biopsy should be referred to a centre offering FibroScan. This test is not NICE approved and there may be a charge for performing such a test. Transient elastography should be repeated every 6–12 months due to the rapid progression of fibrosis in some patients [31], although its utility in this context has not been validated.

3.3.4 Recommendations

- All patients with chronic hepatitis B or C should be offered a liver biopsy for diagnosis and disease staging (I).
- A biopsy is not always necessary for a decision regarding therapy if a patient is willing to start treatment for HCV regardless of histological changes (II).
- It can be appropriate to omit a liver biopsy in certain circumstances such as in patients who will commence treatment for chronic hepatitis B or C irrespective of the histology (II).
- If a biopsy is not performed, a non-invasive technique for liver fibrosis assessment, such as hepatic elastography, can be used instead.(II).

3.4 ART and hepatotoxicity

The use of specific antiretrovirals will be discussed in the HBV and HCV sections. However, when choosing an antiretroviral regimen, the following should also be considered.

All antiretrovirals have the potential to cause acute and long-term hepatotoxicity and this risk is increased two- to threefold in the presence of chronic liver disease such as that due to hepatitis B or C. This increased risk of hepatotoxicity largely disappears if

the hepatitis is successfully treated [37]. Patients should therefore be carefully monitored for hepatotoxicity when HAART is commenced or changed. There is some evidence that the risk of hepatotoxicity with NVP and high dose RTV (1000 mg/day) is relatively higher than with other ARTs [38,39] and NVP may also be linked to increased liver fibrosis [40], although not all studies show this [41]. High-dose RTV is no longer recommended in ART and low-dose RTV (in doses used to boost other PIs) is not associated with significant liver problems.

Didanosine and stavudine have been associated with an increased risk of hepatic steatosis and may potentiate HCV-related liver damage [42,43]. There have been recent reports of portal hypertension and idiopathic liver fibrosis associated with didanosine treatment [44]. The potential for recently developed agents to cause liver damage may only emerge in the post-marketing surveillance phase. For instance, there is some evidence that tipranavir and darunavir may cause hepatotoxicity [45,46] and should be used with caution in patients with HIV/hepatitis coinfection.

3.4.1 Recommendations

- Nevirapine, tipranavir, darunavir, stavudine and didanosine should be used with caution in HIV/hepatitis coinfecting individuals (II).
- Stop ddI in cases of idiopathic portal hypertension/liver fibrosis (II).

3.5 End-stage liver disease and its complications

Combination antiretroviral therapy has vastly improved the prognosis of HIV-positive patients. As mortality from AIDS has fallen, there is increasing recognition of the importance of end-stage liver disease (ESLD) as a cause of significant morbidity and mortality in patients coinfecting with HCV and HBV [47]. As outlined in the following sections, there is now unequivocal evidence that in the context of HIV-infection there is an increased likelihood and a faster progression to ESLD.

Moreover, recent evidence suggests that once cirrhosis is established, the median survival in HIV/HCV coinfecting patients after first decompensation is a mere 13 months [48]. Episodes of decompensation *per se* are associated with a high morbidity and mortality in HIV-infected patients [49]. Many cirrhosis-related complications and episodes of decompensation are avoidable and these patients need to be managed in conjunction with hepatologists or gastroenterologists experienced in the care of patients with ESLD. It is therefore prudent to accurately stage disease and monitor for complications (see section 3.3.3).

Cirrhosis associated with hepatitis viral coinfection, particularly HCV coinfection is a well-recognised risk factor for the development of HCC. Recent studies from Europe and North America suggest a shorter time to HCC development in the context of HIV/HCV coinfection [50,51] and variable survival when compared to an HIV-negative population [52].

Furthermore, it is well recognised that HBV is directly carcinogenic and may promote the development of HCC in the absence of cirrhosis, especially in populations where HBV may have been acquired at birth and in early childhood [53]. It has also become evident that high HBV viral loads may be linked to the development of HCC [54]. It

is probable that a lower CD4 cell count, particularly in the context of HBV coinfection, is associated with a higher risk of HCC [55]. Over recent years there has been an increasing number of treatment options available for patients with HCC that prolong life, including liver transplantation as a curative option in selected patients [56]. Screening programmes utilising serum alpha-feto protein (AFP) measurements together with 6-monthly ultrasound scans (USS) have been demonstrated to improve survival in non-HIV-infected patients [57]. Surveillance for HCC needs to be tailored to specific risk. Some patients may warrant more intensive surveillance with shorter frequency or different modality (such as CT or MR).

Since the advent of HAART, a number of transplant programmes have evaluated liver transplantation in HIV-infected patients. HIV-infection is no longer considered a contra-indication to liver transplantation and a number of guidelines, including BHIVA guidelines, are now in existence [58,59]. The overall success of liver transplantation in this setting has been adequately demonstrated in a number of recent reports [60–65] demonstrating comparable short and medium-term graft and patient survival to non-HIV recipients. There are however, reports of aggressive HCV recurrence and shorter post-transplant survival in HIV/HCV coinfecting patients [62,65–67]. The use and success of post-transplant anti-HCV therapy in this context is currently under evaluation. What is also not clear is the optimal timing of transplantation in this group of patients. Recent data from a multi-centre study suggests increased mortality on transplant waiting lists of HIV-positive patients compared to HIV-negative patients [68]. An important factor in this regard may be late referral for transplantation as evidenced by higher MELD (Model for End Stage Liver Disease) scores at referral, in addition to a faster kinetic of decline. It is therefore imperative that HIV-positive patients with a diagnosis of ESLD are co-managed by hepatologists who have links with transplant units, and are referred early for consideration and assessment for liver transplantation. This should occur no later than after their first decompensation.

3.5.1 Recommendations

- Accurate disease staging is crucial for all patients with HBV and HCV coinfections for the early identification of cirrhosis (II).
- All cirrhotic patients should be managed jointly with hepatologists or gastroenterologists with a special interest in liver disease, such as in specialist coinfection clinics (II).
- Screening for, and prophylaxis and management of complications of cirrhosis and portal hypertension should be done in accordance with local and national guidelines on the management of liver disease (I).
- HCC screening with six-monthly AFP and liver USS should be offered to all cirrhotic patients with HBV and HCV coinfections (II).
- Non-cirrhotic HBV coinfecting patients with high HBV viral loads (>2000 IU/mL), low CD4 counts (<100 cells/ μ L), a family history of HCC and acquisition of HBV in childhood should be considered for HCC screening (II).
- HIV-positive patients with cirrhosis should be referred early, and certainly after first decompensation, for transplant assessment (II).
- Eligibility for transplantation should be assessed at a transplant centre and in accordance with guidelines for transplantation in HIV-positive patients (II).

3. 6 The role of clinical networks

There should be close liaison with the local hepatology team (gastroenterologist specialising in hepatology or hepatologist), a 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 coinfection will have equality of access to specialist care by a team of doctors and nurse specialists, irrespective of their main site of HIV care.

4. Coinfection with HIV and hepatitis B virus

4.1 Background

4.1.1 Prevalence

There are approximately 350 million hepatitis B carriers and about 33 million HIV-infected people worldwide [69,70]. 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 [71]. There is no comprehensive data from the UK defining HIV/HBV coinfection rates. However, data from the EuroSIDA study [72] showed a 9.1% prevalence of HBsAg coinfection in participating northern European centres. A survey of 100 UK clinics in 2004 showed that the dual HIV/HBV infection rate was estimated to be 3–10% of patients in 93% of clinics [73].

In many parts of Africa, HIV/HBV coinfection is common, as seen in South Africa (5%) or Malawi (20%) [74,75]. Recent immigrants from Africa represent the largest group of newly diagnosed HIV-positive people in the UK [76] and therefore high coinfection rates are to be expected. High rates of hepatitis B infection are also seen in injecting drug users and therefore HIV/HBV is relatively common in this group of patients [77]

4.1.2 Natural history

4.1.2.1 The influence of HBV on HIV infection

The natural history of HIV infection does not seem to be influenced by hepatitis B [71,72,78] although there is an increased rate of antiretroviral-related hepatotoxicity, immune-reconstitution hepatitis and possibly a poorer outcome [79–81].

4.1.2.2 The influence of HIV on HBV infection

Although the evidence remains conflicting, acute infection with hepatitis B is more likely to be mild or asymptomatic in HIV-positive patients compared with those who are HIV-negative [82,83]. The rate of hepatitis B clearance is also lower, with up to 20–40% of infected patients progressing to chronic (>6 months) infection [82,83]. Progression to liver cancer is more rapid, with HIV-positive patients with HBV infection developing liver cancer younger than in patients with HBV infection alone [82–84].

Once HBV infection is established, liver damage is immunopathic (the immune response to the virus causes most of the liver damage) so liver disease would be expected to be less severe in HIV-related immunosuppression. However, recent evidence suggests that ALT and liver inflammatory scores in HIV coinfecting patients are no different to HBV mono-infected patients [78]. At very high levels of viral replication, HBV may have a direct cytopathic effect. Coinfection with HIV is generally accompanied by an increase in HBV replication [78] which might explain the evidence for an increased rate of progression to cirrhosis and death [72,78,85,86] when compared to HBV mono-infected patients.

There is also a reduction in the rate of natural clearance of HBeAg by about 60% in coinfecting patients compared to HIV-negative patients [87]. However, there are reports of patients clearing chronic HBV infection with the recovery of CD4 cell count responses following antiretroviral therapy [88,89]. HBV reactivation and re-infection (rare) can also occur and patients who appeared to have cleared HBV infection can present with a further episode of acute hepatitis or chronic hepatitis [88,90]. The risk of reactivation is higher in patients who are positive for anti-HBc antibody but negative for other markers of HBV infection [91]. 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 one-third of these had active liver disease [92].

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 due to cirrhosis and liver cancer [72,75,93].

4.1.2.3 Chronic hepatitis B: Classification

Chronic HBV infection should not be regarded as a single entity, as the severity of the liver disease and prognosis is influenced by the timing of infection (childhood or in later life) and the host immune response. Therefore, in HIV-negative people, four phases of chronic carriage are described (Table 1):

1. Immune Tolerant (HBeAg-positive, normal aminotransferase levels, little or no necro-inflammation on liver biopsy)
2. Immune Active, HBeAg-positive phase (HBeAg-positive, raised aminotransferases, progressive necro-inflammation and fibrosis)
3. Inactive hepatitis B carrier (HBsAg-positive, HBeAg-negative, low levels of HBV DNA and normal aminotransferases)
4. HBeAg-negative chronic active hepatitis (pre-core, core-promoter mutations, eAg-negative, detectable HBV DNA, progressive inflammation and fibrosis).

Type 1 is generally seen in people infected in childhood and type 2 in those infected as older children/adults; types 3 and 4 may follow types 1 or 2 after many years of infection. Types 2 and 4 may progress to cirrhosis and liver cancer, with type 4 generally progressing fastest [94]. The utility of this classification and frequency of each type is not yet known for HIV-positive patients.

Table 1. Classification of chronic hepatitis B

Patient populations in chronic hepatitis B				
Marker	Immune tolerant (type 1)	Immune active (type 2)	Inactive HBsAg carrier (type 3)	HBeAg-negative CHB (precore/core promoter mutant) (type 4)
HBsAg	+	+	+	+
HBeAg	+	+	-	-
Anti-HBe	-	-	+	+
ALT	Normal	↑	Normal	↑
HBV DNA (IU/mL)	> 2x10 ⁴	> 2x10 ⁴	< 2x10 ²	> 2x10 ³
Inflammation on histology	Normal/Mild	Active	Normal	Active

4.2 Assessment and investigations

4.2.1 Diagnosis of HBV infection in HIV-infected individuals

For the indications of when to test for hepatitis B see the general section. The number of hepatitis B tests and their interpretation can be quite complex and they are summarised in Table 2.

Table 2. Interpretation of hepatitis B serology

Stage of infection	Surface antigen (HBsAg)	'e' antigen (HBeAg)	IgM anti-core antibody	IgG anti-core antibody	Hepatitis B virus DNA	Anti-HBe	Anti-HBs	ALT
Acute (early)	+	+	+ ¹	+ ¹	+	-	-	↑↑↑
Acute (resolving)	+	-	+	+	-	+/-	-	↑↑
Chronic (immune tolerant)	+	+	-	+	++	-	-	Normal
Chronic (immune active)	+	+	- ²	+	+	-	-	↑
Chronic (HBeAg-negative)	+	+	-	+	+	-	-	↑
Chronic (inactive HBsAg carrier)	+	-	-	+	-	+	-	Normal
Resolved (immune)	-	-	-	+	-	+/-	+/-	Normal
Successful vaccination	-	-	-	-	-	-	+	Normal

¹ In very early infection the IgM/IgG anti-core can be negative

² In chronic hepatitis B, with raised ALT, anti-core IgM may be weakly reactive

4.2.2 Molecular and serological tests in HBV infection

4.2.2.1 *The use of serum HBV DNA*

There is controversy over the level below which HBV DNA concentrations are indicative of ‘inactive’ disease, and above which treatment should be initiated. High levels of HBV DNA are associated with more rapid hepatic fibrosis and progression to cirrhosis, decompensation and hepatocellular carcinoma (HCC) [93–98]. An arbitrary cut off value of 2×10^4 IU/mL (10^5 copies/mL) has been selected as one of the criteria for identifying patients at risk of progressive liver disease [93–98]. But it must be recognised that some patients with chronic HBV infection, both HBeAg-negative and some HBeAg-positives, can have fluctuating levels of HBV DNA which can fall below 2×10^4 IU/mL intermittently, making its use as a predictor of severity of disease unreliable unless repeated [99,100]. Nonetheless, HBV DNA quantitation is useful in distinguishing replicative from non-replicative chronic HBV infection. HBV DNA levels are also useful in deciding how to treat and for monitoring any response to antiviral therapy. For instance, patients with very high HBV DNA levels ($>7 \log_{10}$ IU/mL) are less likely to respond to treatment with interferon alpha therapy [101]. This has also been observed in patients treated with nucleos(t)ide therapy (lamivudine, adefovir or tenofovir) with reduced rates of eAg seroconversion in patients with a baseline HBV DNA $>7 \log_{10}$ IU/mL [102].

During therapy, HBV DNA testing is used to decide whether to continue or stop interferon treatment (See ‘Therapy’, section 4.3 below) [101]. This also applies to nucleos(t)ide therapy where primary non-response is defined as $<1 \log_{10}$ IU/mL drop in HBV DNA level from baseline at 3 months, and response is defined as an undetectable HBV DNA by real-time PCR assay within 48 weeks of therapy. Partial virological response is defined as $>1 \log_{10}$ IU/mL drop in HBV DNA but detectable HBV DNA by real-time PCR assay [101,102]. In HIV-uninfected patients, a partial virological response should lead to a decision about modifying therapy at 24 weeks of therapy for lamivudine and telbivudine and at 48 weeks for entecavir, adefovir and tenofovir [102]. How this should be applied in coinfecting patients is uncertain. Virological breakthrough on treatment, defined as a confirmed increase of $>1 \log_{10}$ IU/mL above nadir HBV DNA level on therapy, means either non-adherence or resistance [102]. The lower limit of detection of the assays used to monitor HBV DNA should be 10–15 IU/mL and this level should also be the aim of treatment.[103] Measurement of HBV DNA every 6–12 months is sufficient if the patient is not on HBV therapy [104].

4.2.2.2 *Measuring HBV serology during and after therapy*

The ideal outcome of treatment is HBe seroconversion in patients who are HBeAg positive and HBs seroconversion (very rare) in all patients [102]. Once HBV DNA is undetectable, HBeAg and eAb in HBeAg-positive patients and HBsAg in all patients should be tested every 12–24 weeks to pick up seroconversion. It should be noted that there is no HBV DNA level at which seroconversion from HBeAg-positive to negative is completely predictable [105]. Spontaneous or treatment-induced seroconversion from HBsAg-positive to negative is associated with ongoing undetectable HBV DNA but in patients who convert from HBeAg-positive to negative, HBV DNA may still be detectable at low levels [102,106].

4.2.2.3 *HBV resistance testing*

Resistance testing is becoming more widely available and should be considered as a baseline pre-treatment, and a means to inform treatment decisions in those with non-response to treatment, or with virological breakthrough. A line probe assay for the detection of hepatitis B wild-type virus and a drug induced mutation using direct sequencing can identify specific resistance mutations [107,108]. Direct sequencing of the HBV polymerase gene can detect variants that are present in 10–20% of the virus population [109]. Restriction fragment length polymorphism and reverse hybridization using strips coated with oligonucleotide probes (line probes) are the most common methods used for detecting antiviral resistant HBV mutations. They can only detect previously identified mutations, and these methods would need adaptation to detect mutants that confer resistance to a growing list of nucleos(t)ide analogues [110].

4.2.2.4 *HBV genotyping*

Currently, there is no indication for performing this as standard of care, except possibly in patients being considered for interferon therapy. It may be more relevant in the future as information on the differences between genotypes emerges. HBV genotypes have been reported to correlate with spontaneous and interferon-induced HBeAg seroconversion, activity of liver disease, and progression to cirrhosis and hepatocellular carcinoma [101,111,112]. For example, HBV genotypes C and D are more difficult to treat than genotypes A and B [113,114]. There is also some evidence suggesting an increased pathogenicity of genotype C over B, with a greater likelihood of developing hepatocellular carcinoma [115,116].

Much of the current data examining the clinical relevance of HBV genotype should be viewed with caution. Many studies were small and cross-sectional in design, comparing two of the major genotypes with each other, and may be affected by referral bias. The predictive values of genotype in prognosis and treatment response have not been evaluated in prospective trials, and, currently, most clinicians do not base their management decisions on the viral genotype. However, this approach is likely to change as more data becomes available. Further studies are still needed in this area [117].

4.2.3 Screening for hepatocellular carcinoma (see 3.5 General section)

HBV is directly carcinogenic and may promote the development of HCC in the absence of cirrhosis, especially in populations where HBV may have been acquired at birth or in early childhood [53]. High HBV viral loads and low CD4 cell counts may be linked to the development of HCC [54,55]. Screening programmes utilising serum alpha-fetoprotein (AFP) measurements together with 6-monthly ultrasound scans (USS) have been demonstrated to improve survival in non-HIV-infected patients [57].

4.3 Therapy

Treatment decisions should be guided by the algorithms in Figures 1 and 2.

4.3.1 Who to treat?

Central to optimal management is the need for adequate initial assessment of both HBV and HIV status to inform the decision as to whether neither, HBV alone or both viruses require treatment [118]. This includes consideration of the severity of liver disease [119].

In HBV monoinfection, the decision on who to treat is based primarily on the ALT level, liver histology, HBeAg status and HBV DNA level [118–123]. ALT normality should not be used to assume that treatment is not necessary although when raised it often reflects HBV-induced inflammation and the need for treatment.

As significant liver damage may be present without raised liver enzymes, assessment of liver fibrosis by transient elastometry (e.g. FibroScan), serum fibrosis markers, or ideally liver biopsy should be performed in all patients [120,122]. This informs of the need for therapy in patients with high CD4 cell counts and no indication for HAART, as well as the choice of drug treatment and the need for hepatocellular carcinoma (HCC) screening if cirrhosis is present. Liver biopsy may provide additional information on the degree of inflammation and fibrosis and the presence of other pathology (e.g. steatosis) [121]. Assessment of fibrosis is essential before a decision is made to defer HBV and/or HIV treatment. Given the accelerated progression of fibrosis in coinfection, any patient with significant necroinflammation or fibrosis should be treated [120].

The key determinants of who needs treatment for HBV are the HBV DNA level and the CD4 cell count. In HBV mono-infected patients, there is a good correlation between high HBV DNA levels, long-term histological progression to cirrhosis and the rate of HCC. It is presumed that this correlation also exists for coinfecting persons but whether liver disease progresses at a lower HBV DNA level is unknown [123]. The accepted HBV DNA threshold for consideration for treatment is now >2000 IU/mL. In patients who have significant liver damage but low or undetectable HBV DNA levels, the possibility of hepatitis delta virus (HDV) coinfection should be considered. The presence of HBV DNA without HBsAg, with or without HBcAb (occult HBV), is very rare and does not account for significant liver damage [119]. The CD4 cell count is integral to deciding on when to initiate HIV therapy. A threshold of 350 cells/ μ L is recommended by BHIVA and other international guidelines as a level below which antiretrovirals are indicated in HIV-monoinfected persons [124]. Because of the negative effect of immune depletion on HBV progression, the availability of single drugs with high level dual activity, and the increased risk of liver-related deaths in patients with CD4 counts below 500 cells/ μ L, coinfecting patients with CD4 counts between 350–500 cells/ μ L should also be treated with drugs active at suppressing both viruses [119].

4.3.1.2 Recommendations

- ALT elevation is less sensitive as an indicator of disease severity in coinfection and a level below the upper limit of normal should not be used as a reason to defer treatment if otherwise indicated. Normal levels should be considered as 30 IU/L for men and 19 IU/L for women (II).

- HBV DNA measurement is essential in the decision to treat and subsequent monitoring of disease (I).
- Assessment for liver fibrosis, using either liver biopsy or a non-invasive technique, should be performed on all patients to define treatment strategy (I).
- All patients with raised ALT [above the upper limit of normal (ULN)] not fulfilling other criteria for treatment and with no other obvious cause should have a liver biopsy (I).
- In patients with a CD4 count of >500 cells/ μ L, HBV treatment should be commenced using the same criteria (HBeAg, HBV DNA, fibrosis assessment, and ALT) as in an HIV-negative person (III).
- All patients with significant fibrosis (Metavir \geq F3 or Ishak \geq S3 or FibroScan \geq 9kPa) should be treated if HBV DNA is detectable, at any level (I). It should be noted that cut-offs for FibroScan are not as clearly defined for HBV as they are for HCV coinfection.
- All patients with an HBV DNA >2000 IU/ml should be considered for treatment (III). The only exception may be young adults (<20 years old) with a CD4 count of >500 cells/mL, persistently normal liver enzymes, and no evidence of fibrosis who probably have immunotolerant HBV and where careful monitoring may be an alternative (III).
- The presence of significant liver damage but a low or undetectable viral load for HBV should prompt exclusion of hepatitis delta (I).

4.3.2 What to treat with?

There are currently seven drugs that have been, or are soon to be, approved for use against HBV: four have additional HIV activity (3TC, FTC, tenofovir, and entecavir) and three are only active against HBV at licensed doses (interferon, adefovir and telbivudine). The data excluding anti-HIV activity for telbivudine is limited and monitoring of HIV viral load and repeat HIV genotyping pre-HAART initiation is advised. The efficacy of these drugs has been assessed in randomised trials extending out to 5 years in monoinfected patients [118].

The strategy used to treat HBV/HIV depends upon the need for ART determined by the CD4 cell count. Where ART is recommended (all patients with a CD4 count <350 cells/ μ L), agents with HBV activity should be incorporated into the ART regimen. In patients with CD4 cell count 350–500 cells/ μ L, in whom ART is not otherwise recommended, treatment for HBV infection may best be achieved by using a combined ART/HBV regimen. If ART is not required, that is CD4 count >500 cells/ μ L, the optimum strategy may be to use agents with exclusive HBV and no HIV activity so that HIV resistance is not induced, however, earlier initiation of ART should still be considered [118–123]. Awareness of the additive hepatotoxic risks of certain ARV drugs should be considered (e.g. nevirapine).

4.3.2.1 HIV therapy not indicated

If the CD4 count is above 500 cells/ μ L, the HBV DNA is below 2000 IU/L, the ALT is normal, and there is no fibrosis, treatment is not indicated and patients should be monitored on a 3–6-monthly basis.

If the CD4 count is above 500 cells/ μ L and HBV therapy is indicated, the options are to use drugs only active against HBV, alone or in combination, or early introduction of ARVs including tenofovir with FTC.

Limited evidence exists on the use of pegylated interferon in coinfecting persons [125] but it appears less effective and is associated with greater toxicity. However, resistance does not occur and a 12-month course of pegylated interferon is an option in a patient with elevated ALT, low serum HBV DNA, and minimal liver fibrosis, especially if genotype A [119]. Lack of response, as judged by failure to reduce HBV DNA by 1 log₁₀ by week 12 and to <2000 IU/L by week 24, should prompt discontinuation and consideration for antivirals [119,120]. Pegylated interferon should not be used in patients with decompensated cirrhosis [126].

Adefovir has been evaluated in coinfecting persons and is active for both wild-type and 3TC-resistant virus but is less potent than tenofovir [127]. Nevertheless, at the dose used in HBV treatment, it does not affect HIV replication or select resistance mutations that may limit future tenofovir use. It is therefore an option in this situation, unlike tenofovir which must be used only with other ART agents [128,129].

Telbivudine has greater intrinsic activity than adefovir or 3TC but has also not been studied in coinfection. Its efficacy is limited by the development of resistance (25% at 24 months in mono-infected persons), with cross-resistance to 3TC/FTC but not adefovir [118]. Adefovir and telbivudine select for non-overlapping HBV resistance mutations.

Entecavir, although previously thought to be devoid of antiretroviral effect, has been found to possess modest anti-HIV activity and can select for HIV rtM184V [130]. This drug should not be used in the absence of fully suppressive ARV therapy.

4.3.2.2 HIV therapy indicated

A preferred ARV drug regimen should be used, combining a 2NRTI backbone that has additional activity against HBV. The two recommended NRTI options for treatment of naïve patients with wild-type HIV alone are abacavir/3TC and tenofovir/FTC [124].

Although 3TC is a potent anti-HBV agent [131], monotherapy is associated with a high likelihood of HBV resistance in coinfecting persons (M204V develops at a rate of 25%/year) and hence therapy with this drug, or FTC, without a second anti-HBV active drug is not recommended [132,133].

Tenofovir is effective at suppressing HBV DNA and may induce HBeAg seroconversion although, as for other antivirals in coinfection, this is less likely than in an HIV-negative person [127,134–136]. Resistance is rare and combination with 3TC or FTC has been demonstrated to be effective at suppressing HBV DNA and may induce HBeAg seroconversion. Combining 3TC/FTC with tenofovir may reduce the risk of breakthrough [137].

If renal toxicity precludes the use of tenofovir, entecavir is an option that can be used along with a fully active ARV regimen [137].

If genotypic HIV resistance to tenofovir and/or 3TC/FTC is present or develops, but HBV DNA suppression is maintained, tenofovir and 3TC/FTC should be continued in addition to an effective new ARV regimen. The presence of mutations conferring 3TC resistance affects the fitness of both viruses which potentially slows down HBV progression and therefore continuing this drug should be considered [131].

ART may lead to an immune reconstitution flare when commenced, and a viral escape inflammatory flare if drugs with anti-HBV activity are stopped, both of which may be severe, particularly in persons with cirrhosis [138, 139].

4.3.2.3 Recommendations for patients with a CD4 \geq 500 cells/ μ L

- No HBV therapy is recommended for patients who are HBsAg and HBV DNA negative but HBcAb positive (I).
- HBsAg-positive patients with an HBV DNA $<$ 2000 IU/L and no significant degree of fibrosis (Metavir \leq F1 or Ishak \leq S1 or FibroScan \leq 8kPa) or inflammation on biopsy should not be treated and should commence 3–6-monthly sequential monitoring with HBV DNA and ALT (III).
- 12 months' pegylated interferon is an option in a patient who is HBeAg positive, has a raised ALT, low HBV DNA, minimal fibrosis and (if tested) genotype B (I). Lack of HBV DNA response ($<$ 1 \log_{10} reduction at 12 weeks and $>$ 2000 IU/L at 24 weeks) should prompt discontinuation (I).
- After stopping pegylated interferon for HBeAg-positive disease, repeat testing should be performed 3-monthly if seroconversion has occurred (III).
- Adefovir is an option in all patients and does not generate future resistance to tenofovir and is the drug of choice in patients with evidence of significant fibrosis (II).
- Telbivudine should not be used alone because of the high rate of HBV resistance (I).
- Tenofovir, entecavir, 3TC and FTC should not be used without suppressive ARV therapy in order to avoid HIV resistance induced by suboptimal anti-HIV treatment (I).
- Adefovir and telbivudine given together is an option and is likely to reduce risk of resistance to telbivudine (III). The potential for anti-HIV activity in telbivudine is currently unknown.
- Patients started on adefovir, with or without telbivudine, who have suppressed HBV DNA should remain on these drugs until HAART is started (III).
- Early introduction of ARVs, inclusive of tenofovir and FTC, should be considered as an option for naïve patients with wild-type HIV (III).

4.3.2.4 Recommendations for patients with a CD4 $<$ 500 cells/ μ L

- Patients with HBV coinfection who have a CD4 count of $<$ 500 cells/ μ L should commence HAART (II). The only exception to this may be the patient with a CD4 count of 350–500 cells/ μ L, an HBV DNA level of $<$ 2000 IU/ml, with a normal ALT and no evidence of fibrosis or hepatic inflammation: in this situation, close monitoring is essential.
- Tenofovir and FTC should form the backbone of an ARV regimen in naïve patients with wild-type virus and no contraindications to either drug (II).

- If tenofovir is not being given as part of HAART it should be added. If tenofovir is contraindicated, an alternative active anti-HBV agent should be used instead (II).
- 3TC or FTC should not be used as the only active drug against HBV in HAART because of the likelihood of emergent HBV resistance to these agents (I).
- Entecavir is an option when tenofovir has to be discontinued, because of toxicity, if given with a fully active ARV regimen. Where 3TC resistance is possible, entecavir 1.0mg dosage combined with adefovir (unless the severity of renal disease precludes) should be used and the patient monitored carefully for HBV breakthrough and probable entecavir resistance. HBV resistance testing should be undertaken where available (II).
- If patients on suppressive anti-HBV therapy require a switch of their ARVs because of HIV resistance to tenofovir and/or 3TC/FTC, their active HBV therapy (tenofovir with or without 3TC/FTC) should be continued (III) and suitable anti-HIV agents added.

4.3.2.5 Goals of therapy

As in HBV monoinfection, the long-term goal is to prevent cirrhosis and primary hepatoma by sustained suppression of viral replication to the lowest possible level [140].

Seroconversion from HBeAg positive to HBeAg negative and normalisation of ALT are endpoints that indicate success of therapy in monoinfected patients and allow consideration for discontinuation of treatment. However, these indicators cannot be expected in most of those who are coinfecting and a more realistic goal is long-term suppression of HBV replication to undetectable levels, to reduce liver inflammation and to stop or delay progression of hepatic fibrosis [121,122,124,133–135].

If seroconversion does occur, antiviral treatment should be maintained, as relapse is more likely with discontinuation of therapy than in monoinfection. The ultimate serological end-point of HBsAg seroconversion is rarely achieved in coinfecting patients and even then, reactivation on withdrawal of therapy remains a concern [121,122,124,133–135].

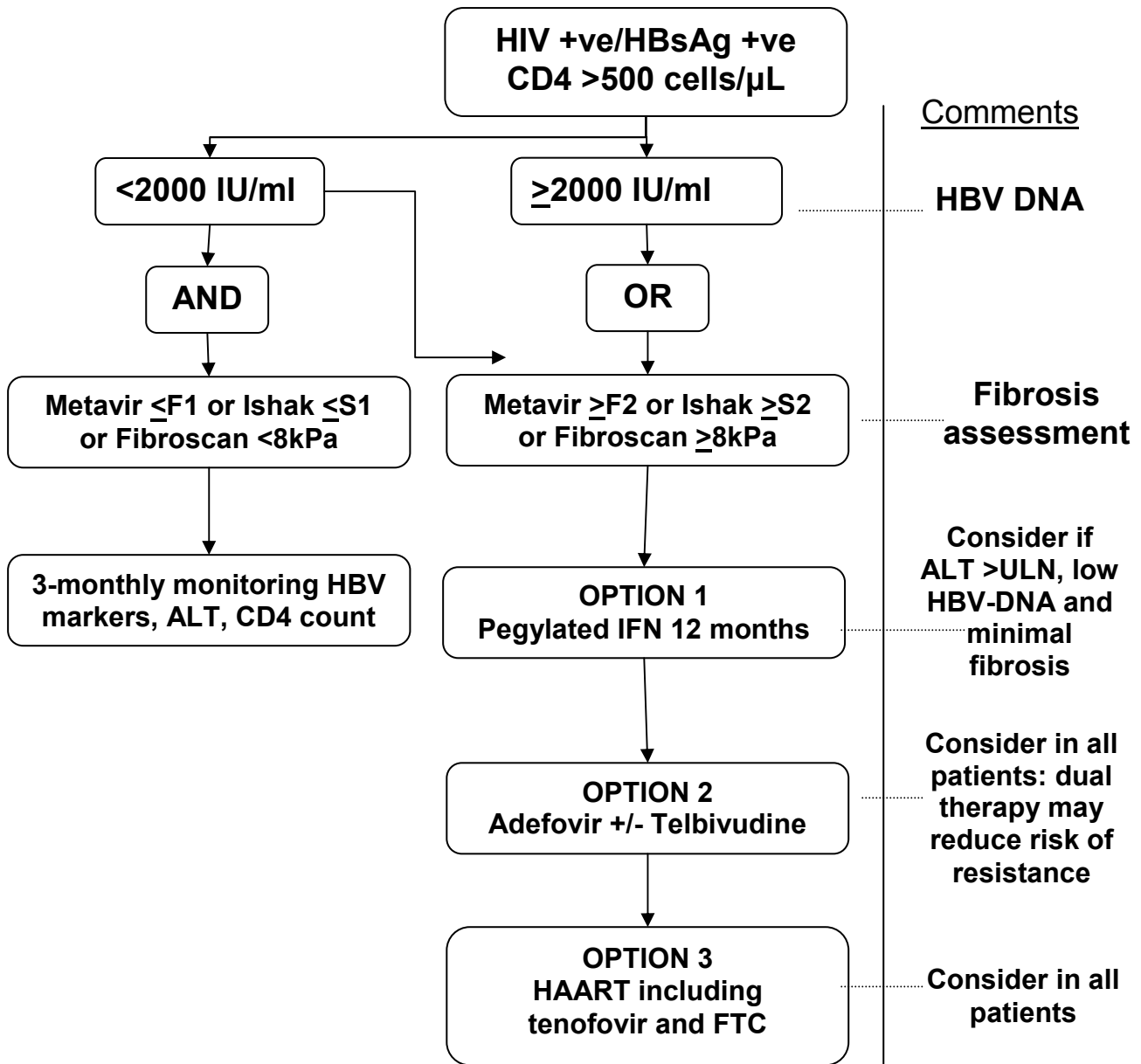


Fig 1. Flow chart: HBV management if CD4 count >500 cells/μL
 IFN, interferon; ULN, upper limit of normal

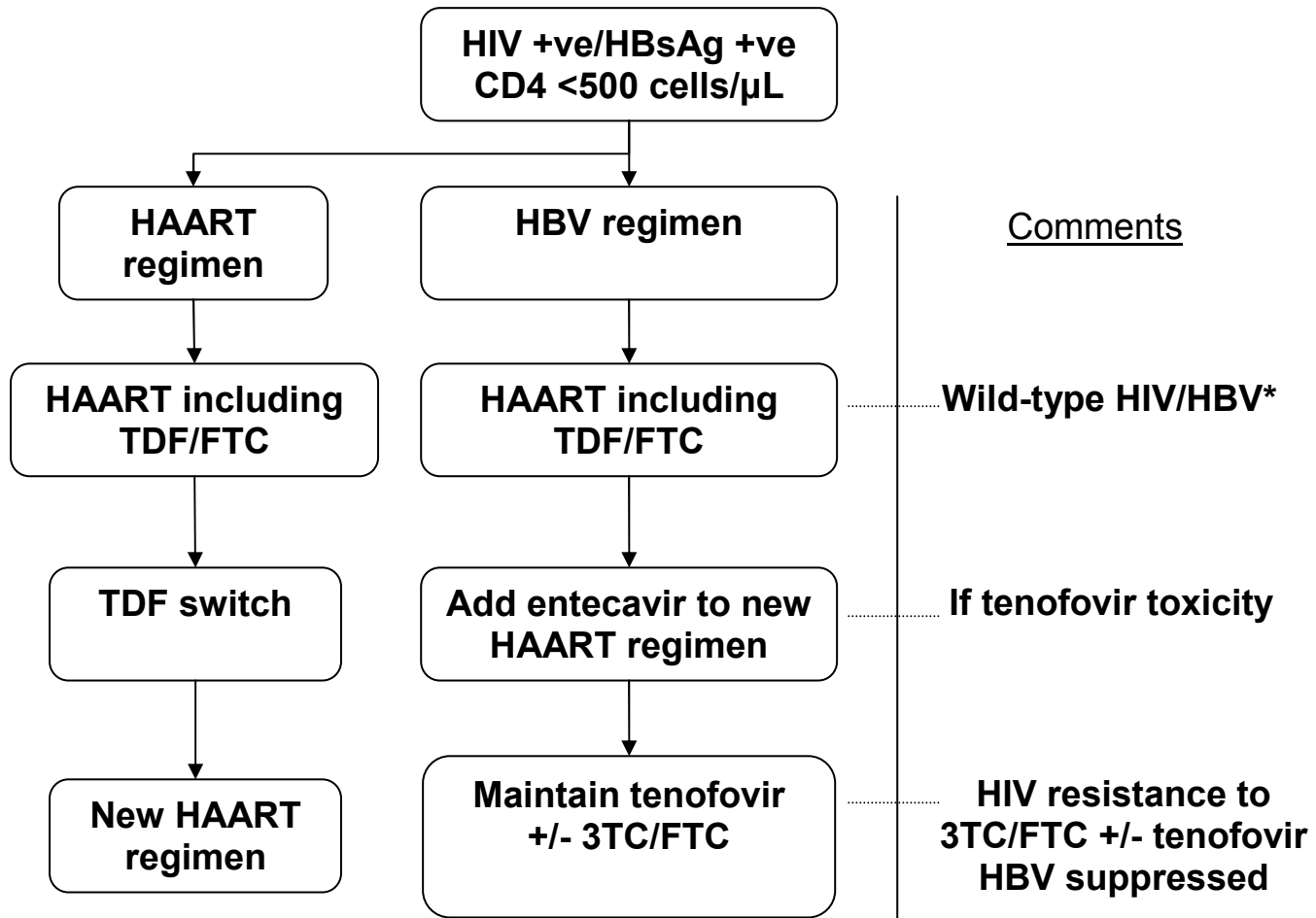


Fig 2. Flow chart: HBV Management if CD4 count <500 cells/μL TDF, tenofovir.

* Consider close monitoring as an alternative strategy in a patient with a CD4 count of 350–500 cells/μL, HBV DNA of <2000 IU/L and no evidence of liver inflammation or fibrosis.

4.3.3 New therapies for hepatitis B

4.3.3.1 Clevudine (*L-FMAU*)

Clevudine is a thymidine analogue which is currently unlicensed. Only limited data have been published, with no data in HIV coinfection. It does not appear to have activity against HIV. In a placebo-controlled trial of 24 weeks' therapy for HBsAg-positive chronic hepatitis B, there was a median 5 log₁₀ fall in HBV VL from baseline, which was sustained in some patients for up to 24 weeks after stopping [141]. Patients with prior lamivudine resistance had a greater risk of breakthrough in a non-randomised study of 48 weeks treatment [142].

4.4 Acute hepatitis B

In monoinfected persons, more than 90% of adults with acute HBV will recover spontaneously and seroconvert to HBsAb without antiviral therapy. However, severe or fulminant liver disease occurs rarely (<0.1%) and is life-threatening. Treatment with antivirals is usually recommended in fulminant disease. Small randomised controlled trials with 3TC have demonstrated a more rapid fall in HBV DNA although no difference in outcome in acute infection [143]. In coinfection, fewer (60–80%) patients with acute HBV clear their infection [82,83]. Data suggests that 3TC as part of HAART does not completely protect against the development of acute HBV infection [144] although it is unknown whether this is also the case with tenofovir with or without 3TC/FTC. Because patients with HIV are more likely to develop chronic HBV infection and the consequences thereof, there is a theoretical argument to consider HBV treatment after acute infection to promote clearance. For patients with acute but non-fulminant disease, the options include not giving antivirals, using drugs only active against HBV, or early introduction of ARVs including tenofovir with FTC. There are no data to support any of these approaches but for the majority of patients no antiviral treatment is indicated. For patients with fulminant disease, where a rapid fall in HBV DNA is desirable, a balance has to be made between the need for antivirals, the potential for drug toxicity, and the risk of selecting HBV and HIV drug resistance. Telbivudine in the short term is safe [145] and, although HBV resistance is likely, probably will not interfere with future ARV therapy.

4.4.1 Recommendations

- Most patients with HIV who acquire acute HBV do not require treatment (III).
- Coinfected patients with fulminant HBV may benefit from telbivudine although its anti-HIV activity and potential for causing HIV ART resistance remains unclear (III).

4.5 Hepatitis delta virus (HDV)

HDV is found as coinfection or superinfection with hepatitis B. It was previously thought to be rare in the UK and seen mostly in injecting drug users and their sexual partners. Recent evidence suggest a rising incidence in some areas of the UK, and in one study in South London 8.5% of all HBsAg-positive patients were HDV-positive, of whom only 27% had evidence of parenteral exposure [146]. Patients with delta virus superinfection are more likely to have severe hepatitis [147]. In HIV-coinfected

patients delta virus may further accelerate the progression of liver disease [148]. For these reasons, patients with delta virus are candidates for treatment. However, evidence of treatment activity has been mostly obtained in HIV-negative patients. Interferon has been shown to be active [149,150]. In one study, 72 weeks of treatment with PEG-IFN alpha-2b is associated with SVR in about 20% of cases, and ribavirin does not add to this benefit [150]. There is a successful case report of the use of pegylated interferon alpha 2b for 72 weeks in a patient with HIV coinfection on HAART with undetectable HIV RNA [151]. In an earlier study, where standard interferon was used in 16 HIV-infected patients with HDV, the results were poor [152]. There is early efficacy data on tenofovir use [153].

4.5.1 Recommendations

- Test for delta virus in all patients with hepatitis B (III).
- Repeat the test for delta virus in all patients with hepatitis B yearly and if they develop an unexpected rise in ALT (II).
- All delta virus-infected patients should be considered for early treatment by a physician with experience in this problem (II).

5. Coinfection with HIV and Hepatitis C Virus

5.1 Background

5.1.1 Prevalence

There is now widespread recognition of the potential morbidity and mortality associated with HIV and hepatitis C coinfection. Overall, the prevalence of HCV in the general UK population is estimated to be approximately 0.44% [154] but the rate varies by area and population and should be considered as a minimum. The highest risk groups for HCV infection are injecting drug users and people with bleeding disorders such as haemophilia [154]. Other risk groups include sexual partners of injectors, prisoners, sex workers and children of HCV-infected mothers. There may also be an increased rate in people who have had treatment abroad and healthcare workers subject to sharps injury [154].

Although heterosexual transmission of HCV is uncommon, the higher levels of HCV RNA seen in the setting of HIV infection may facilitate transmission [154,155], particularly in the presence of other sexually transmitted infections such as infectious syphilis. This is of particular concern in the light of the recent rise of syphilis cases within the HIV community [1,3,156–161]. There have been reports from several European countries, Australia and the USA of hepatitis C transmission within the homosexual HIV community linked to possible sexual transmission and/or use of non-injecting recreational drugs, particularly snorting cocaine.

The prevalence of HCV infection in HIV-positive individuals is higher than in the general population but varies between clinics according to risk factors for HIV acquisition.

5.1.2 Natural history

5.1.2.1 The influence of HCV on HIV infection

HCV may have a deleterious effect on HIV progression. The Swiss HIV Cohort study and others have demonstrated that HCV infection was independently associated with an increased risk of progression to AIDS or death, despite a similar use of antiretroviral therapies within the coinfecting group as those with HIV alone [162–164]. A Swiss study also suggested that those patients with dual infection may be less likely to achieve a CD4 count rise of at least 50 cells/ μ L within 1 year of starting HAART than those with mono-infection. The HIV viral load response to therapy was similar, however, in patients with and without HCV. This deleterious effect is confirmed in some, but not all other studies [165–167].

5.1.2.2 The influence of HIV on HCV infection

Only 20–30% of immunocompetent individuals with HCV will progress to cirrhosis over an average of 15–30 years. Evidence suggests that in HIV-positive individuals progression is likely to occur more frequently and at a faster rate [31,168–171]. One study estimated the median time to cirrhosis as 32 years and 23 years from time of acquisition in HCV and HCV/HIV-coinfecting individuals respectively. This is now manifest as a proportional increase in deaths from end-stage liver disease (ESLD) throughout the HIV-infected population such that HCV infection is one of the major causes of death in people with HIV [31,168–173].

In contrast, studies that have considered absolute numbers of deaths (rather than proportions of deaths due to different causes) have often reported no increase in the number of deaths from liver failure [174], although one study in the HAART era which compensated for competing risks still showed a small increase in liver-related mortality [175]. It is therefore uncertain if there has been a true increase in deaths from liver failure, or whether the apparent increase is simply a consequence of the longer HIV survival. It should also be noted that men with haemophilia and injecting drug users, in whom many of these studies have been carried out, have generally been infected with HCV for some time before becoming infected with HIV. The impact of HCV seroconversion after HIV seroconversion is unclear.

Coinfecting patients have comparably higher levels of HCV viraemia and HCV in other body fluids [176] and these are inversely correlated with the CD4 cell count and degree of immunosuppression present.

Several studies show that liver-related mortality rates are higher in those with a low CD4 cell count, irrespective of ART use [86,177]. Other variables that negatively influence HCV progression have been shown to be alcohol, increasing age at acquisition and the presence of hepatitis B infection [170–178]. Hepatocellular carcinoma (HCC) is estimated to occur at a rate of 1–4% per annum in patients with HCV-related cirrhosis; in patients who also have HIV infection it tends to occur at a younger age and within a shorter time period [50].

5. 2 Assessment and investigations

5.2.1 Diagnosis of HCV infection in HIV-infected individuals

The majority of individuals (75–85%) who become infected with HCV become chronic carriers with detectable HCV RNA in the blood indicating viraemia. The remainder (15–25%) clear virus spontaneously, usually within 6 months of becoming infected [179–182]. Diagnosis of chronic infection is usually made on the basis of a positive anti-HCV antibody test (ELISA +/- RIBA), confirmed by a positive HCV RNA (RT-PCR) test. However, a proportion of patients will have normal liver enzymes or a negative antibody test in the presence of chronic HCV viraemia [183–187].

Individuals with past resolved infection have positive anti-HCV antibody tests (usually by two different assays) with repeatedly negative HCV RNA tests and would be expected to have normal liver enzymes, in the absence of other causes of liver disease. Over time, anti-HCV antibody levels decline such that it can be difficult to differentiate infection in the distant past from non-specific false positivity [183–187]. RNA levels may be transiently undetectable during acute infection so it is particularly important to repeat HCV RNA levels in patients if the time at which they were initially infected is unknown [183–187].

With current assays, false negative antibody tests are rare in chronic infection but may be a problem in early acute infection [183–187]. Consideration should be given to HCV RNA testing of HCV antibody-negative HIV-positive individuals where:

- acute infection is suspected;
- there are unexplained abnormal liver function tests (rare).

(For the general principles of management, liver assessment and networks see the General section.)

5.3 Therapy

5.3.1 The coadministration of anti-HCV and anti-HIV treatment agents

Patients should ideally be started on anti-HIV therapy when their CD4 count falls to 350 cells/ μ L or less (see General section). Prior to initiation of anti-HCV therapy, potential interactions and/or overlapping toxicities with anti-HIV therapies need to be considered. Where possible, anti-HIV therapies should be adjusted to enable optimal administration of anti-HCV therapy, although this should never compromise anti-HIV drug efficacy. Consideration needs to be given to which anti-retroviral agents should be coadministered with interferon and ribavirin therapy due to:

- drug interactions which may lower antiretroviral drug levels, thereby raising concerns of reduced efficacy;
- drug interactions which may increase antiretroviral drug levels, with a risk of increased toxicity;
- overlapping toxicity profiles which may cause increased morbidity/mortality and reduced completion of treatment.

The increasing availability of newer antiretroviral agents with improved safety profiles usually enables us to avoid such difficulties, but this may be less possible in heavily antiretroviral-pretreated patients. The key potential coadministration issues

are summarised in Table 3. Whilst there currently appear to be no theoretical problems with coadministration of interferon or ribavirin with the newer classes of antiretroviral therapy (integrase inhibitors, CCR5 blockers, and second-generation NNRTIs), clinical data to confirm this are awaited.

5.3.2 Recommendations

- When deciding to treat HCV, the choice of anti-HIV therapy should be agreed in association with an experienced HIV physician (IV).
- The coadministration of didanosine with ribavirin is contraindicated (II).
- The coadministration of zidovudine and stavudine with pegylated interferon and ribavirin should be avoided (II).
- The coadministration of abacavir with ribavirin should be avoided if possible if there are other background HIV treatment options available (II).
- The coadministration of efavirenz with interferon should be accompanied by careful observation for increased CNS toxicity with consideration of a switch to an alternative antiretroviral agent temporarily if severe (II).
- The coadministration of atazanavir and interferon/ribavirin may be associated with increased hyperbilirubinaemia, but this is unlikely to be of clinical importance (II).

Table 3. Interactions between antiretroviral agents and anti-HCV therapy [186–193].

Anti-HIV agent	Anti-HCV agent	Reason for concern	Data suggesting problem	Recommendation
Abacavir	Ribavirin	Reduced intracellular ribavirin levels leading to possible impaired anti-HCV therapy	Pharmacokinetics; cohort studies suggesting impaired anti-HCV therapy response	Possibly avoid concomitant use
Atazanavir	Interferon/ribavirin	Increased hyperbilirubinaemia	Case reports	Observe
Didanosine	Ribavirin	Significant toxicity; fatal lactic acidosis	Case reports; data from RCTs	Absolute contraindication
Efavirenz	Interferon	Increased CNS disturbance	Case reports; data from RCTs	Close observation and individualised case management
Stavudine	Ribavirin	Significant mitochondrial toxicity	Case reports; data from RCTs	Avoid if at all possible
Zidovudine	Interferon/ribavirin	Increased myelosuppression	Case reports; data from RCTs	Avoid if at all possible

5.3.3 General principles of anti-HCV therapy

The main aims of therapy are to clear HCV and thereby limit liver disease progression and viral transmission. Antiviral therapy may also be helpful for those with extrahepatic manifestations of HCV such as cryoglobulinaemia [193]. A sustained virological response (SVR) is defined as a negative HCV RNA PCR test 6 months following cessation of therapy. Relapse thereafter is very unusual but the patient may be at risk of re-infection so annual testing is recommended following SVR and in any patient with raised liver function tests which had previously normalized.

A negative HCV RNA test 4 weeks into therapy is defined as a rapid virological response (RVR) and is associated with an increased likelihood of SVR [194–196]. The early virological response (EVR) is defined as a negative HCV RNA or reduction of $>2 \log_{10}$ in the HCV viraemia after 12 weeks of therapy [196]. Cessation of ineffective therapy should be considered in patients who do not achieve an EVR or where there is detectable viraemia at 24 weeks [191–196].

In the APRICOT study patients treated with peginterferon and ribavirin had a mean CD4 count decrease of 140 cells/ μL [197] and there have been previous case reports of interferon-treated patients developing opportunistic infections following an interferon-associated CD4 count decline. Ideally, therefore, patients should have a CD4 count of at least 200 cells/ μL and undetectable HIV RNA. CD4 percentage should also be taken into account when making the treatment decision. Patients with low CD4 count (below 300 cells/ μL at baseline) will require more detailed monitoring.

In patients being evaluated for both ARV and HCV treatment it is advisable to stabilise the patient on ARV in the first instance (see above). It has been shown that the immune restoration associated with ARV therapy can limit the progression of HCV-associated disease so that even if they do not respond to HCV therapy there may be some long-term indirect benefit from ARV [172,198–200].

The liver disease should also be staged both clinically and with either non-invasive tests/biomarkers such as hepatic elastography (see General section) or liver biopsy. Consider liver biopsy particularly for those with genotype 1 or 4 infection where the results of HCV therapy remain disappointing [199,201,202]. The risk–benefit of liver biopsy should be considered in the individual patient.

It is particularly important to establish whether the patient has cirrhosis as:

- a) HCV therapy can be potentially dangerous in those with severe liver disease, particularly cirrhosis Child-Pugh stage B/C, as deaths have occurred [202,206,207].
- b) There is less chance of an SVR [197,202–204].
- c) The patient is at risk of varices and hepatocellular carcinoma (HCC), and should be screened for both.
- d) The complications of cirrhosis can be life-threatening and transplantation may need to be considered. The median survival of decompensated cirrhosis in this setting is reported to be 13 months [48] but the long term survival of transplant patients in the setting of HIV/HCV coinfection is currently poor [64].

Overall, the SVR rates in coinfecting patients are approximately 60% of those seen in HCV-mono-infected patients [194–197,201–204]. It is reasonable, therefore, to treat patients with genotype 2 or 3 infection without performing a baseline liver biopsy if there is no evidence of advanced liver disease clinically, or by using non-invasive tests/biomarkers.

In those with genotype 1 or 4 infection, or where there is clinical concern regarding co-existent liver disease such as haemochromatosis, alcohol-related or other liver disease, a biopsy can be helpful in staging the liver disease(s) and determining the need for HCV therapy [194–197,201–205]. In those individuals refusing liver biopsy, non-invasive tests/biomarkers such as hepatic elastography can be useful alternate techniques to identify those with earlier stages of fibrosis not requiring therapy (see General section).

Patients should abstain or minimise their alcohol intake as more rapid progression of liver disease is seen with higher levels of alcohol consumption [85,206]. Patients who are non-immune for HAV and HBV should be vaccinated as superinfection of HCV-infected patients with HAV or HBV can be life-threatening (see General section).

There is a high prevalence of psychiatric comorbidity in patients with HIV/HCV infection. Interferon-based regimens have risks of psychiatric complications so it is recommended that patients with a background of psychiatric disorder are assessed by a psychiatrist or psychiatric nurse prior to commencement of HCV therapy [207,208]. A fundoscopic examination of the eye is also recommended prior to commencement of therapy, and during therapy if eye symptoms occur. A variety of pre-existing eye conditions, such as hypertensive retinopathy, can deteriorate and new conditions, such as central retinal vein occlusion, can occur *de novo* during anti-HCV therapy [209,210].

5.3.4 Treatment options

The risk versus benefit of HCV therapy must be carefully evaluated for the individual patient. A team approach is vital to manage HIV/HCV-coinfecting patients with access to experienced physicians and trained specialist nurses with knowledge of coinfection to support and monitor the patients whilst on therapy [194–197,201–205].

5.3.4.1 Peginterferon

Three large controlled studies (APRICOT, ACTG and RIBAVIC) all showed that peginterferons were more efficacious than standard thrice-weekly interferon [197,201,202]. Both peginterferon alfa2a and peginterferon alfa2b are licensed for treatment of patients with HIV/HCV coinfection. Peginterferon is given by weekly subcutaneous injection: peginterferon alfa2a, 180 µg/week, peginterferon alfa2b 1.5 µ/kg/week – i.e. weight-based [197,201,202].

5.3.4.2 Ribavirin

The initial trials of therapy for coinfecting patients used relatively low-dose ribavirin for patients. For example 800mg/day was prescribed for patients in the APRICOT study (SVR genotype 1 – 29%, SVR genotype 3 – 62 %) [197]. This was mainly

because there were concerns regarding risks of anaemia – particularly for patients on zidovudine-containing regimens. However, it was subsequently recognised that higher doses of ribavirin (1000–1200mg/day) are associated with improved SVR in HCV-monoinfected patients and the PRESCO trial confirmed this finding in coinfecting patients with an overall SVR of 50% (SVR genotype 1 – 35%, SVR genotype 3 – 72%) [211].

Since the APRICOT trial there have been many advances in antiretroviral therapy with many more alternatives to zidovudine (see above). Access to erythropoietin and other growth factors to support the patient with ribavirin-induced marrow suppression has also improved [211,212].

5.3.4.3 *Monitoring*

Monitor the patient weekly for the first 2–4 weeks, with review every 2–4 weeks thereafter if stable [194–197,201–205,211,218]. If the CD4 count falls below 200 cells/ μ L, PCP prophylaxis should be considered. Cotrimoxazole may have haematological side effects and should be used at lowest appropriate dosage.

5.3.4.4 *Treatment duration*

Early trials such as the APRICOT study recognised that this is a “hard-to-treat” group and opted for longer duration of therapy (48 weeks) for all patients whatever the genotype [194–197,201–204]. Detailed analysis of the RVR and EVR from various studies has helped predict the SVR for the individual patient and there is increasing use of ‘tailoring the regimen’ for the individual according to the genotype, baseline viral load and initial virological response [194–197].

5.3.4.5 *‘Easier-to-treat’ genotypes*

In patients with genotypes 2 and 3 infection who have an RVR, the recommended length of treatment is 24 weeks. In patients who do not have an RVR but reach an undetectable HCV viral load by 24 weeks, a 48-week course is recommended [194–197].

Treatment courses longer than 48 weeks are associated with poor compliance but may be considered in an individual patient with a slow but steady decline in the viral load who is tolerating therapy well [211–213].

5.3.4.6 *‘Harder-to-treat’ genotypes*

In patients with genotype 1 and 4, a 48-week course of treatment is recommended [194–197,201–205,211,212]. An extension to 72 weeks of therapy should be utilized in patients with a 2 \log_{10} drop at 12 weeks who become PCR negative at 24 weeks [211–213].

5.3.4.7 *Recommendations*

- Anti-HCV treatment should be started before the CD4 count falls below 350 cells/ μ L and before ART is started, if possible (I).

- Treatment aims for a sustained virological response (SVR: undetectable viral load 24 weeks post treatment) (I).
- Rapid virological response (RVR: VL undetectable) at 4 weeks' treatment predicts response. Lack of early virological response (EVR: non-detectable VL or $>2 \log_{10}$ fall at 12 weeks) or detectable VL at 24 weeks treatment predicts non-response, when cessation of therapy should be considered (I).
- Any ART therapy should be stabilised before anti-HCV therapy is commenced (I).
- Careful assessment of liver fibrosis is recommended, especially for patients with HCV genotypes 1 and 4 or those with suspected cirrhosis (I).
- In patients with genotypes 2 or 3 infection, liver biopsy is not necessary if there is no clinical evidence of advanced liver disease. For genotypes 1 and 4, a pre-treatment liver biopsy is recommended, or a hepatic elastography if the biopsy is refused (I).
- Consider treatment for all patients with genotypes 2/3. Consider treatment for all patients with genotypes 1/4, especially if there is significant liver fibrosis (Ishak grade F3 or more) (I).
- Treatment should be with pegylated interferon weekly plus ribavirin at 1000–1200 mg daily, supported by erythropoietin/growth factors if necessary (I).
- Treat patients with genotypes 2 or 3 infection for 24 weeks if there is an RVR, otherwise for 48 weeks (I).
- Treat patients with genotypes 1 and 4 for 48 weeks, or 72 weeks if there was a $2 \log_{10}$ drop at 12 weeks and they become PCR negative at 24 weeks (I).

5.3.5 Non-responders and relapsers

There is limited data to guide retreatment of non-responders and relapsers in the setting of HIV [214]. In the HIV-negative population retreatment may be considered in individuals who have failed to respond with an SVR to non-gold standard therapy, i.e. non-pegylated interferon with or without ribavirin or in individuals with progression of fibrosis [215,216].

Responses in all groups are less than in individuals receiving pegylated interferon and ribavirin *de novo* [214–216]. Individuals considering retreatment must have all factors known to affect response optimized (see above).

This should include:

- Weight based ribavirin;
- Optimization of HAART with undetectable HIV viral load and substitution of zidovudine, stavudine, didanosine and abacavir with alternative active agents;
- Measurement and control of insulin resistance by weight loss and therapeutic agents such as metformin [217,218];
- Referral to an adherence specialist to ensure maintenance of full adherence to both HIV and hepatitis therapy;
- Use of growth factors where necessary to maintain full dose of pegylated interferon and ribavirin [211,212];

The REPEAT study in HIV-negative individuals suggested a prolongation of therapy to 72 weeks led to a significantly higher SVR than 48 weeks of treatment, and prolongation to 72 weeks should be considered in all HIV-positive patients being retreated who are able to tolerate this length of treatment [219]. Although the REPEAT study showed no effect of double-dose PEGIFN-alpha 2a for the first 12 weeks on the subsequent ability to achieve SVR, a small study in HIV-coinfected patients suggested an improvement in EVR in HIV-positive patients undergoing retreatment with double dose pegylated interferon for the first 4 weeks of therapy [220]. Due to the low rates of response in HIV-positive individuals undergoing retreatment this approach may be considered, although there is no firm evidence to support this.

The NIH-sponsored HALT-C clinical trial failed to show a benefit of maintenance interferon on differences in the rates of mortality, decompensation, hepatocellular carcinoma, or fibrosis progression between the peginterferon alfa-2a maintenance group and the control group [221]. A similar study in HIV-positive individuals – the SLAM C study – was also unable to show any beneficial effect on fibrosis progression rates [222]. Pegylated interferon is thus not recommended as maintenance therapy in HIV-positive individuals who have failed previous anti hepatitis C therapy.

5.3.6 New therapies for Hepatitis C

Several new therapeutic avenues are being explored for the treatment of hepatitis C. These include new forms of interferon, ribavirin analogues, and direct antiviral agents including protease inhibitors and polymerase inhibitors [223–228]. None of these new agents has been trialled yet in HIV-positive patients. When these agents become available for the treatment of HIV-negative patients those caring for the coinfecting population should balance the possible positive effects of greater SVR with the unknown efficacy in an HIV-positive population, drug interactions with HAART and other drugs widely used in HIV practice and possible toxicities (IV).

Coinfected individuals should be encouraged to enter clinical studies of these new agents. Similarly, pharmaceutical companies should be encouraged to remove the barriers for HIV-positive individuals to enter studies and to study possible drug interactions early in the development of such agents and initiate studies of coinfecting populations early in the course of therapy (IV).

5.4 Acute hepatitis C

5.4.1 Epidemiology

Over the past few years there have been increasingly recognised outbreaks of acute hepatitis C amongst men who have sex with men (MSM); whilst initially localised in cities with high MSM populations, cases are now being reported more widely and incidence rates appear to be still increasing [2,3,155,158–161,229]. Whilst the exact mode of transmission remains unclear, associations have been seen with HIV-positive status, recent sexually transmitted infections (syphilis, lymphogranuloma venereum, gonorrhoea), multiple sexual partners, unprotected anal intercourse and recreational drug use [2,3,155,158–161,229].

5.4.2 Clinical picture and natural history

The majority of diagnoses of acute hepatitis C have been made in asymptomatic patients with unexplained transaminase levels or on repeat routine HCV antibody testing. Some patients may exhibit a non-specific illness with jaundice and nausea. The rate of spontaneous clearance of HCV after acute infection in individuals with acute hepatitis is approximately 15–25%. Spontaneous clearance appears to be more commonly seen in those with symptomatic infection, greater transaminase elevations, higher CD4 cell counts, and in those taking antiretroviral therapy [180–182,230].

Three different patterns of HCV RNA evolution have been described following acute infection: persistent high levels of viraemia, rapid RNA reduction with subsequent clearance, and fluctuating high and low levels. Close monitoring of RNA levels may therefore help to identify those individuals who are or are not likely to clear HCV without intervention [231]. After acute infection, it has been suggested that progressive liver damage may occur more rapidly than has been historically reported in coinfecting individuals [232].

5.4.3 Diagnosis of acute HCV

For appropriate tests see section 5.2.1.

The timing of acute infection may be more clearly delineated by retrospective testing of stored specimens (e.g. those previously obtained for HIV viral load or syphilis monitoring) using HCV antibody and/or RNA testing. Determination of the timing of infection is likely to assist surveillance, contact tracing and treatment decisions.

5.4.4 Management

There are no randomised controlled trials to guide decisions over whether to treat, what with, and for what duration in this setting. Initial observational data from HIV-uninfected patients with acute hepatitis C infection showed a remarkably high rate (98%) of sustained virological response in 44 individuals [233].

Several case series report experiences of treatment of acute HCV in HIV-infected individuals [180,181,234–239]. Overall, these suggest that whilst response rates in those with HIV coinfection appear to be lower than that seen in those with HCV mono-infection, clearance is higher than in those with established hepatitis C coinfection, particularly for genotype 1. Whilst there is a suggestion in some cohorts that response rates may be greater with longer duration of therapy and with lower initial HCV viral load, there is no clear data to support the routine addition of ribavirin to pegylated interferon or to prolonged duration of therapy.

Given that spontaneous clearance occurs in a minority of individuals, a period of observation may be warranted. Most cohort data suggest that if a policy of treatment deferral until 24 weeks is used to determine whether spontaneous clearance is achieved, subsequent treatment response is not diminished [236]. However, in one study, deferred therapy for HCV beyond 12 weeks was associated with impaired response [238] and so individualisation in discussion with clinicians experienced in

management of HIV/HCV coinfection is recommended to optimise management and potential of this ‘window of opportunity’ of intervention.

5.4.5 Recommendations

- All HIV-positive patients with unexplained transaminitis should be evaluated for acute hepatitis C infection (with HCV antibody and RNA testing) (II).
- HIV-infected MSM should be tested for HCV antibody on an annual basis (II).
- HIV-infected MSM should be informed about current understanding of acute HCV and possible transmission risks (IV).
- Individuals identified as having acute HCV infection should have quantitative RNA measurements performed on a regular (usually 4-weekly) basis for the first 12–24 weeks to inform treatment decisions (III).
- Those individuals who show no trend towards reduction in HCV RNA or have failed to clear HCV by 3–6 months after initial RNA positivity should be offered treatment (III).
- The optimal duration and mode of treatment has yet to be determined. At present, a 6–12 month course of pegylated interferon with weight-adjusted ribavirin is recommended (II).
- Future clinical trials should be established to determine the benefit, optimal regimen and optimal duration of therapy for acute HCV infection in HIV infected patients (IV).

Appendix

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