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BRITISH HIV ASSOCIATION GUIDELINES

British HIV Association guidelines for the management of coinfection with HIV-1 and hepatitis B or C virus 2010

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Level of evidence

I = randomized controlled trial (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 hepatitis B virus (HBV) and hepatitis C virus (HCV) markers.
2. All HBV nonimmune patients should be vaccinated.
3. All HIV-positive patients should have their HBV and HCV status tests repeated before commencement of antiretroviral therapy.
4. All HBV- and HCV-infected patients should be vaccinated against hepatitis A if nonimmune.
5. 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.
6. Case notes of new HBV-positive patients should contain evidence of an attempt to contact household and sexual contacts and offer vaccination if nonimmune.
7. Case notes of new HCV-positive patients should contain evidence of an attempt to notify parenteral and sexual contacts and offer them a test.
8. All patients who are HBV surface antigen (HBsAg) positive or HCV positive should have a clear antiviral treatment plan written in their notes at least once a year.
9. All HCV RNA-positive patients should have an HCV viral load and genotype determination performed.
10. All HBV-positive patients should have their 'e' status checked, an HBV DNA viral load measurement and an anti-hepatitis delta virus (HDV) antibody test.
11. All patients with chronic HBV or HCV should be offered an assessment of liver fibrosis by liver biopsy, hepatic elastography or other validated noninvasive fibrosis test.
12. All HBV-positive patients with an HBV DNA >2000 IU/mL and evidence of liver damage should be offered treatment.
13. All HCV RNA-positive patients should be considered for treatment unless there is a specific contraindication.
14. All patients with cirrhosis should be jointly treated by a hepatologist and have regular assessments for hepatocellular carcinoma (HCC) according to risk.
15. All patients with decompensated cirrhosis should be referred for liver transplantation assessment unless specifically contraindicated.

1.0 Introduction

The 2010 guidelines have been updated to incorporate all new relevant information that has become available since the previous versions were published in 2005. The 2005 versions came as separate hepatitis B and C guidelines but for 2010 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 4 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 the following:

- increased discussion on hepatitis screening and prevention
- clarification of the role of liver biopsy and noninvasive 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 infection
- revised CD4-based guidance on the management of chronic HBV infection
- management of acute HBV infection
- revised guidance on the management of chronic HCV infection, including antiretroviral therapy (ART) interactions
- management of acute HCV infection
- management of treatment nonresponders and relapsers in both chronic HBV and chronic HCV infection.

2.0 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.

3.0 General section: Prevention of viral hepatitis and management principles for patients with 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 infection amongst HIV-infected men who have sex with men (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 infection is therefore important, as early treatment offers the best chance of viral clearance [4]. Acute HBV infection 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-positive patients should be screened for coinfection with HBV and HCV as part of their initial work-up (III). This screening would normally be with the HBsAg, anti-HBV core antigen (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 if not already infected (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, and more frequent tests if at higher risk [e.g. if injecting drug user (IDU) or MSM at sexual risk] (III).
- All patients with no natural or vaccine-induced protection against HBV should have an annual anti-HBc or HBsAg test and more frequent tests if at higher risk (e.g. if IDU or MSM at sexual risk) (III).
- Any patient with risk factors for acute HBV or HCV infection [e.g. a history of contact with HBV/HCV, current or recent IDU, recent sexually transmitted infection (STI) or MSM with high-risk sexual practices] and with an unexplained rise in serum aminotransferases should be offered an appropriate screening test for acute viral hepatitis [HAV immunoglobulin M (IgM), HBsAg and HCV antibody] (III). If the hepatitis serology is negative, they should be offered testing for HCV RNA and HBV DNA (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).

3.2 Prevention and immunization

Prevention strategies that work for viral hepatitis include immunization against HAV and HBV, and education on safer sex for everyone and on harm reduction for IDUs. Safer blood and blood products, and medical practices are also important.

3.2.1 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 seems likely, given the evidence for condom use and the prevention of many other STIs, that 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 infection 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 lymphogranuloma venereum (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, with emphasis on the risks of catching HCV and STIs through unprotected anal sex, even if partners are HIV sero-concordant (see also section 5.1.1).

3.2.2 Harm reduction in IDUs

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 infection [11,12]. One study showed an incidence of new HIV, HBV and HCV infection of 0, 11 and 26 cases/100 years at risk, respectively, 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].

3.2.3 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 to use 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).

3.2.4 Immunization

Hepatitis B is preventable by vaccination. However, HIV-positive patients respond less well to the vaccine, and the response rate varies with the CD4 count, with greatest response (*c.* 80%) at >500 cells/μL and least response (*c.* 25%) at counts <200 cells/μL [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 an 88% response after six doses [20]. Given the need to immunize patients at higher risk rapidly, this is a strategy that might be considered. Higher dose vaccination may enhance the anti-HBs response [21].

Patients who are anti-HBc positive, but negative for anti-HBs, anti-HBV envelope (anti-HBe) and HBsAg, may either have had previous exposure to HBV and be protected, or have had a false-positive anti-HBc test result and be vulnerable [22]. These patients will need HBV vaccination [23].

Patients coinfected with HBV and/or HCV are also vulnerable to acute HAV infection, which may lead to decompensation of underlying liver disease [24,25]. 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 [23].

3.2.5 Recommendations for immunization

- All newly diagnosed HIV-infected patients should have an anti-HBc test and additionally an anti-HBs test if

they have previously been immunized. If negative for both they should receive a course of vaccination (I).
- The 0, 1 and 6 months schedule and the 0, 1 and 2 months with a subsequent dose at 12 months schedule are acceptable vaccination schedules (II). The 0, 1 and 3 weeks 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 ideally >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 (II).
- Persons who fail to seroconvert to HBV vaccine [23] should have a repeat vaccination course (which may be at double dose) once the CD4 count rises to >500 cells/μL or after significant immune recovery. While nonimmune they should have HBV marker tests performed (anti-HBc/HBsAg) annually or more frequently if at higher risk (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 later. If anti-HBs undetectable consider a full course of vaccination as above (III).
- All HIV and HBV and/or HCV coinfected patients should be tested for immunity against HAV (HAV IgG or total antibody) and nonimmune patients should be vaccinated using standard recommended vaccination schedules (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 IDU (current and remote), past immunization for hepatitis A/B, episodes of jaundice, travel abroad and potential risk activity there (blood transfusion, IDU and 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 and 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 angiotensin converting enzyme (ACE), and alpha 1 antitrypsin levels. A scan of the liver should be performed using imaging with ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI).

3.3.3 Role of liver biopsy, hepatic elastography and other noninvasive markers of liver fibrosis

Liver biopsy remains the silver standard for the staging of liver disease [28]. However, because of sampling error, liver biopsy can overestimate or underestimate the degree of liver fibrosis. 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 who decline 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 genotypes 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, noninvasive 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 noninvasive 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 National Institute for Health and Clinical Excellence (NICE) approved and there may be a charge for performing such a test. Transient elastography should be repeated every 6–12 months because of 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 noninvasive technique for liver fibrosis assessment, such as hepatic elastography, should be used instead (II).

3.4 Antiretroviral therapy 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 caused by hepatitis B or C [37]. This increased risk of hepatotoxicity largely disappears if the hepatitis is successfully treated [37]. Patients should therefore be carefully monitored for hepatotoxicity when highly active antiretroviral therapy (HAART) is commenced or changed. There is some evidence that the risk of early hepatotoxicity with nevirapine and high-dose ritonavir (RTV) (1000 mg/day) is higher than with other ARTs [38,39] and nevirapine 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 protease inhibitors (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, although significant hepatotoxicity was not reported in the clinical trials, there is some evidence from subsequent case reports 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, stavudine and didanosine should be used with caution in HIV/hepatitis virus coinfected individuals (II).
- The possible risks of hepatotoxicity when darunavir is used in coinfected patients should be considered on a case-by-case basis (III).
- RTV-boosted atazanavir, fosamprenavir and lopinavir should be used with caution in patients with Child–Pugh B/C grade liver disease (III).
- In patients on didanosine with abnormal liver function tests (LFTs) or evidence of portal hypertension, idiopathic portal hypertension/liver fibrosis should be excluded and didanosine stopped if these conditions are found (II).

3.5 End-stage liver disease and its complications

Combination ART 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 coinfected 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 of and a faster progression to ESLD.

Moreover, recent evidence suggests that, once cirrhosis is established, the median survival in HIV/HCV coinfected 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-recognized 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 with an HIV-negative population [52].

Furthermore, it is well recognized 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 utilizing serum alpha-feto protein (AFP) measurements together with 6-monthly ultrasound scans (USSs) have been demonstrated to improve survival in non-HIV-infected patients [57]. Although AFP may not add to the value of USSs if done twice or more a year, this screening frequency is often impractical within resources and therefore AFP still has a place. 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 MRI).

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 contraindication 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] showing comparable short- and medium-term graft and patient survival to that for non-HIV recipients. There are, however, reports of aggressive HCV recurrence and shorter post-transplant survival in HIV/HCV coinfected patients [62,65–67]. The use and success of post-transplant anti-HCV therapy in this context are currently under evaluation. What is also not clear is the optimal timing of transplantation in this group of patients. Recent data from a multicentre study suggest increased mortality on transplant waiting lists of HIV-positive patients compared with HIV-negative patients [68]. An important factor in this regard may be late referral for transplantation, as evidenced by higher Model for End-Stage Liver Disease (MELD) 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 carried out in accordance with local and national guidelines on the management of liver disease (I).
- HCC screening with 6-monthly AFP and liver USS should be offered to all cirrhotic patients with HBV and HCV coinfections (II).
- Noncirrhotic HBV coinfected patients with high HBV viral loads (>2000 IU/mL), low CD4 counts (<100 cells/μL), 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 specializing in hepatology or hepatologist) and 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.

4.0 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 world-wide [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 are 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. In a survey of 100 UK clinics in 2004, 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 HBV infection are also seen in IDUs 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, and immune-reconstitution hepatitis [79–81].

4.1.2.2 The influence of HIV on HBV infection. Although the evidence remains conflicting, acute infection with HBV 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 patients with HBV infection alone [52, 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 alanine aminotransferase (ALT) and liver inflammatory scores in HIV coinfected patients are no different to those in HBV monoinfected 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 with HBV mono-infected patients.

There is also a reduction in the rate of natural clearance of HBeAg by about 60% in coinfected patients compared with HIV-negative patients [87]. However, there are reports of patients clearing chronic HBV infection with the recovery of CD4 cell count responses following ART [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% of patients, HBV DNA became positive in 60% of all patients, and about one-third of these had active liver disease [92].

Since the introduction of combination ART and the dramatic improvement in the prognosis of people with HIV, liver disease attributable to chronic viral hepatitis has become an important cause of morbidity and mortality in coinfected patients as a result of 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 the prognosis are 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 have been described (Table 1).

1. Immune tolerant phase (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 type 1 or 2 after many years of infection. Types 2 and 4 may progress to cirrhosis and liver cancer, with type 4 generally progressing most rapidly [94].

The utility of this classification and the frequency of each type are not yet known for HIV-positive patients.

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 summarized in Table 2.

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 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]. However, it must be recognized that some patients with chronic HBV infection, both HBeAg-negative and some HBeAg-positive patients, 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 quantification is useful in distinguishing replicative from nonreplicative 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 nonresponse is defined as a $<1 \log_{10}$ IU/mL drop in HBV DNA level from baseline at 3 months, and response is defined as an undetectable HBV DNA by real-time polymerase chain reaction (PCR) assay within 48 weeks of therapy. Partial virological response is defined as a $>1 \log_{10}$ 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 (which have a low barrier to resistance) and at 48 weeks for entecavir, adefovir and tenofovir (which have a high barrier to resistance) [102]. How this should be applied in coinfected patients is uncertain. Virological breakthrough on treatment,

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)	$>2 \times 10^4$	$>2 \times 10^4$	$<2 \times 10^2$	$>2 \times 10^3$
Inflammation on histology	Normal/mild	Active	Normal	Active

ALT, alanine aminotransferase; CHB, chronic hepatitis B; HBeAg, hepatitis B virus (HBV) envelope antigen; HBsAg, HBV surface antigen.

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)	+	+	+*	+*	+	−	−	↑ ↑ ↑
Acute (resolving)	+	−	+	+	−	±	−	↑ ↑
Chronic (immune tolerant)	+	+	−	+	+ +	−	−	Normal
Chronic (immune active)	+	+	−†	+	+	−	−	↑
Chronic (HBeAg-negative)	+	−	−	+	+	−	−	↑
Chronic (inactive HBsAg carrier)	+	−	−	+	−	+	−	Normal
Resolved (immune)	−	−	−	+	−	±	±	Normal
Successful vaccination	−	−	−	−	−	−	+	Normal

*In very early infection the IgM/IgG anti-core can be negative.
†In chronic hepatitis B, with raised ALT, anti-core IgM may be weakly reactive.
ALT, alanine aminotransferase; CHB, chronic hepatitis B; HBeAg, hepatitis B virus (HBV) envelope antigen; HBsAg, HBV surface antigen; IgG, immunoglobulin G; IgM, immunoglobulin M.

defined as a confirmed increase of $>1\log_{10}$ IU/mL above nadir HBV DNA level on therapy, means either nonadherence 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 may be considered as a baseline pretreatment, especially if there is a history of previous exposure to anti-HBV drugs, as a means to inform treatment decisions in those with nonresponse 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 reverse transcriptase inhibitors [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 among 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 HCC [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 HCC [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 become 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 utilizing serum AFP measurements together with 6-monthly USSs 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 raised ALT 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 marker tests, or ideally liver biopsy should be performed in all patients [120,122]. This informs decisions regarding 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 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].

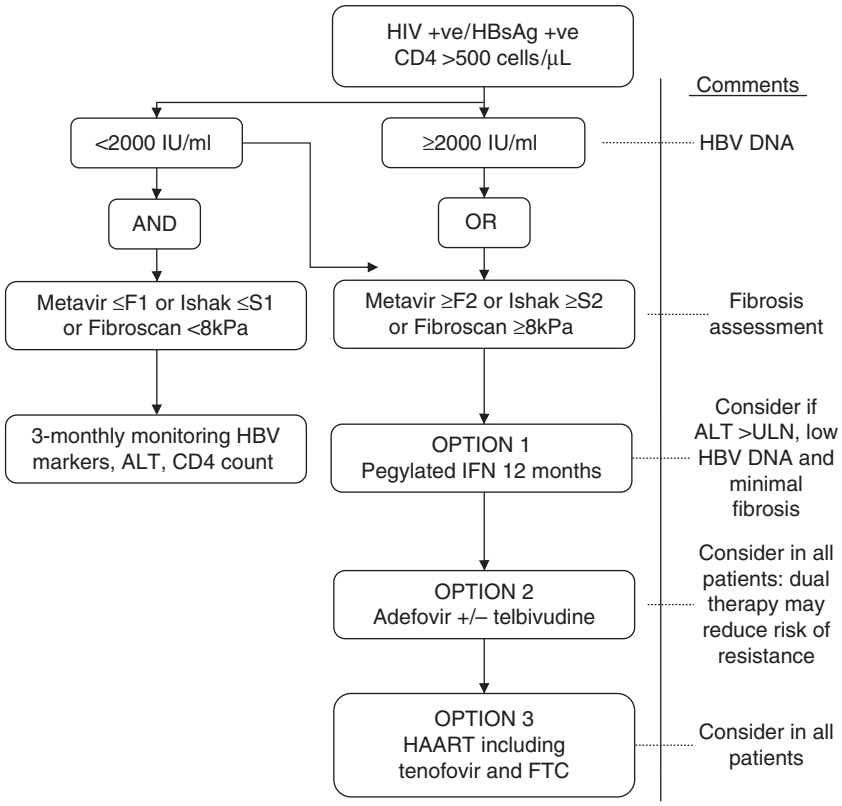

Fig. 1 Flow chart: hepatitis B virus (HBV) management if CD4 count > 500 cells/μL. ALT, alanine aminotransferase; FTC, emtricitabine; HAART, highly active antiretroviral therapy; HBsAg, HBV surface antigen; IFN, interferon; ULN, upper limit of normal.

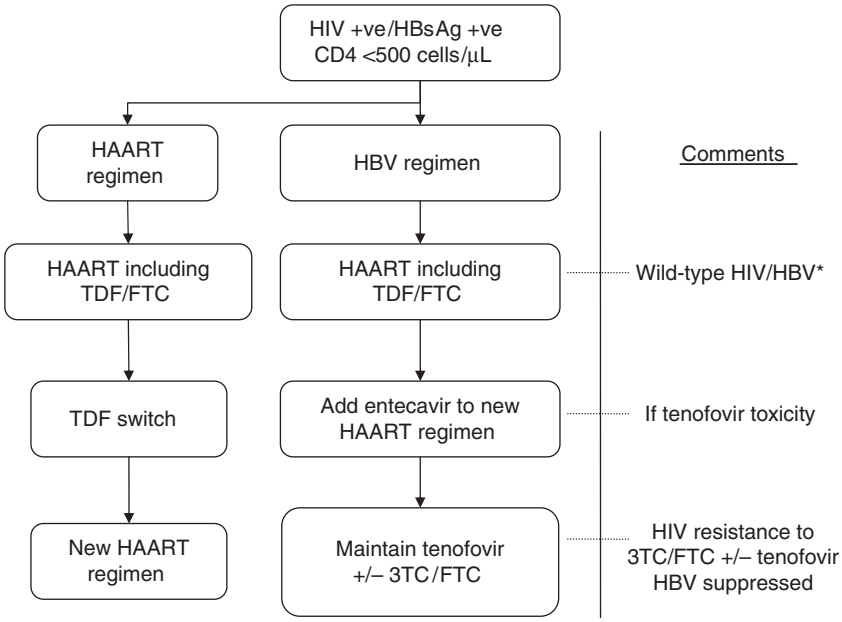

Fig. 2 Flow chart: hepatitis B virus (HBV) management if CD4 count < 500 cells/μL. 3TC, lamivudine; FTC, emtricitabine; HAART, highly active antiretroviral therapy; HBsAg, HBV surface antigen; TDF, tenofovir. *Consider close monitoring as an alternative strategy in a patient with a CD4 count of 350–500 cells/μL, HBV DNA of < 2000 IU/L and no evidence of liver inflammation or fibrosis.

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 monoinfected 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 coinfected 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 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 when to initiate HIV therapy. A threshold of 350 cells/μL 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/μL, coinfected patients with CD4 counts between 350 and 500 cells/μL should also be treated with drugs active at suppressing both viruses [119].

4.3.1.1 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 noninvasive technique, should be performed on all patients to define treatment strategy (I).
- In patients with a CD4 count of >500 cells/μL, 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$9 kPa) should be treated if HBV DNA is detectable, at any level (IV). 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 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 [lamivudine (3TC), emtricitabine (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 are limited and monitoring of HIV viral load and repeat HIV genotyping pre-HAART initiation are advised. The efficacy of these drugs has been assessed in randomized trials extending out to 5 years in monoinfected patients [118].

The strategy used to treat HIV/HBV coinfection depends upon the need for ART determined by the CD4 cell count. Where ART is recommended (all patients with a CD4 count <350 cells/μL), agents with HBV activity should be incorporated into the ART regimen. In patients with CD4 cell counts of 350–500 cells/μL, 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 in patients with CD4 counts of >500 cells/μL, 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 antiretroviral drugs should be considered (e.g. nevirapine).

4.3.2.1 HIV therapy not indicated. If the CD4 count is above 500 cells/μL, 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/μL and HBV therapy is indicated, the options are to use drugs only active against HBV, alone or in combination, or early introduction of antiretroviral drugs including tenofovir with FTC.

Limited evidence exists on the use of pegylated interferon in coinfected persons [125] but it appears to be 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 ($< 2 \times 10^6$ IU/L), and minimal liver fibrosis, especially if genotype A [119]. Lack of response, as judged by failure to reduce HBV DNA by 1 $\log_{10}$ 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 coinfected 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 sufficiently in coinfection. Its efficacy is limited by the development of resistance (25% at 24 months in monoinfected persons), with cross-resistance to 3TC/FTC but not adefovir [118]. Adefovir and telbivudine select for nonoverlapping 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 rt M184 V [130]. This drug should not be used in the absence of fully suppressive antiretroviral therapy (ART).

4.3.2.2 HIV therapy indicated. A preferred antiretroviral drug regimen should be used, with a two-nucleoside reverse transcriptase inhibitor (NRTI) 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 coinfected persons (M204 V 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]. 3TC/FTC-resistant strains will normally respond to tenofovir [118–123,134–137]

Tenofovir is effective at suppressing HBV DNA and may induce HBeAg seroconversion although, as for other antivirals in coinfection, this may be 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 antiretroviral 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 antiretroviral 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/μL

- 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 $\leq$ 8 kPa) or inflammation on biopsy should not be treated and should commence 3–6-monthly sequential monitoring with HBV DNA and ALT (III).
- Early introduction of antiretrovirals, inclusive of tenofovir and FTC, should be considered as an option for naïve patients with wild-type HIV (III).
- 12 months of treatment with pegylated interferon is an option in a patient who is HBeAg positive and has a raised ALT, low HBV DNA ($< 2 \times 10^6$ IU/L), minimal fibrosis and (if tested) genotype A (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 ART 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 HBV resistance to telbivudine (III). The potential for anti-HIV activity in telbivudine is currently unknown and therefore this should be used only if other options are not suitable.

- Patients started on adefovir, with or without telbivudine, who have suppressed HBV DNA should remain on these drugs until HAART is started (III).

4.3.2.4 Recommendations for patients with a CD4 < 500 cells/μL

- Patients with HBV coinfection who have a CD4 count of < 500 cells/μL should commence HAART (II). The only exception to this may be the patient with a CD4 count of 350–500 cells/μL, an HBV DNA level of < 2000 IU/mL, a normal ALT and no evidence of fibrosis or hepatic inflammation: in this situation, close monitoring is essential.
- Tenofovir and 3TC/FTC should form the backbone of an antiretroviral regimen in naïve patients with wild-type virus and no contraindications to either drug (II).
- 3TC/FTC may be omitted from the antiretroviral regimen and tenofovir given as the sole anti-HBV agent if there is clinical or genotypic evidence of 3TC/FTC-resistant HBV (II).
- If tenofovir is not currently 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).
- Tenofovir is active against 3TC/FTC-resistant virus (I).
- Entecavir is an option when tenofovir has to be discontinued, because of toxicity, if given with a fully active antiretroviral regimen. Where 3TC resistance is also possible, entecavir 1.0 mg 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 antiretrovirals 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 normalization 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 coinfected 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 endpoint of HBsAg seroconversion is rarely achieved in coinfected patients, and even if it is achieved reactivation on withdrawal of therapy remains a concern [121,122,124,133–135].

4.3.2.6 Clevudine 2′-fluoro-5-methylarabinosyluracil (L-FMAU). Clevudine is a thymidine analogue with anti-HBV activity [141]. On 20 April 2009 the manufacturers Pharmasset announced that all Phase III trials of clevudine for hepatitis B would stop because of reports of treatment-related myopathy [142].

4.4 Acute hepatitis B

In monoinfected persons, > 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 randomized controlled trials with 3TC have demonstrated a more rapid fall in HBV DNA but no difference in outcome in acute infection [143]. In coinfection, fewer (60–80%) patients with acute HBV clear their infection [82,83]. Data suggest 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 nonfulminant disease, the options include not giving antivirals, using drugs only active against HBV, or early introduction of antiretrovirals 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 found 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 thought to be safe [145] and, although HBV resistance is likely, probably will not interfere with future ART. The addition of adefovir may theoretically improve efficacy and reduce the risk of telbivudine resistance, although there is no research evidence for this.

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 and/or adefovir although their efficacy remains unknown in this situation (IV).

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 IDUs and their sexual partners. Recent evidence suggests 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 pegylated interferon alpha-2b was associated with sustained virological response (SVR) in about 20% of cases, and ribavirin did 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 are 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).

5.0 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 HCV 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 IDUs 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 or were born 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 noninjecting recreational drugs, particularly snorting cocaine.

The prevalence of HCV infection in HIV-positive individuals is higher than in the general population but varies among 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 demonstrated that HCV infection was independently associated with an increased risk of progression to AIDS or death, despite a similar use of antiretroviral therapies in the coinfected group compared with the group infected 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/μL within 1 year of starting HAART than those with monoinfection. 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-infected and HCV/HIV-coinfected individuals, respectively [168]. This is now manifest as a proportional increase in deaths from 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 from 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 survival times of individuals with HIV infection. It should also be noted that men with haemophilia and IDUs, 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.

Coinfected 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 HBV infection [170–178].

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 anti body test [enzyme-linked immunosorbent assay (ELISA) ± recombinant immunoblot assay (RIBA)], confirmed by a positive HCV RNA [reverse transcriptase–polymerase chain reaction (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 nonspecific false positivity [183–187].

RNA levels may be transiently undetectable during acute infection so it is particularly important to repeat HCV RNA tests 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/μL 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 antiretroviral 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 summarized in Table 3. While there currently appear to be no theoretical problems with coadministration of interferon or ribavirin with the newer classes of antiretroviral drugs [integrase inhibitors, CCR5 blockers, and second-generation nonnucleoside reverse

Table 3 Interactions between antiretroviral agents and anti-hepatitis C virus (HCV) therapy [186–192, 239]

Anti-HIV agent	Anti-HCV agent	Reason for concern	Data suggesting problem	Recommendation
Abacavir	Ribavirin (at 800 mg/day)	Reduced intracellular ribavirin levels leading to possible impaired anti-HCV therapy if low-dose ribavirin used	Pharmacokinetics; cohort studies suggesting impaired anti-HCV therapy response although some other cohort studies suggest no impact on response	Possibly avoid concomitant use if ribavirin cannot be given at daily dose of $\geq$ 1000 mg or $\geq$ 13.2 mg/kg
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 individualized 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

CNS, central nervous system; RCT, randomized controlled trial.

transcriptase inhibitors (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).
- Abacavir should only be used as backbone therapy in accordance with the BHIVA HIV treatment guidelines and concomitant use with ribavirin should be avoided if possible (II).
- When abacavir cannot be avoided, maximum weight-based (1000/1200 mg, $>$ 13.2 mg/kg/day) ribavirin should be used and ribavirin dose reductions avoided (II).
- The coadministration of efavirenz with interferon should be accompanied by careful observation for increased central nervous system (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).

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]. An 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 that 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 [194,195]. The early virological response (EVR) is defined as a negative HCV RNA or reduction of $>2\log_{10}$ in HCV viraemia after 12 weeks of therapy [195]. Therapy should be stopped in patients who do not achieve an EVR or where there is detectable viraemia at 24 weeks [194,195].

In the AIDS Pegasys Ribavirin International Co-infection Trial (APRICOT) study, patients treated with peginterferon and ribavirin had a mean CD4 count decrease of 140 cells/μL [196] 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 ($<$300 cells/μL at baseline) will require more detailed monitoring.

In patients being evaluated for both antiretroviral and HCV treatment it is advisable to stabilize the patient on ART in the first instance (see above). It has been shown that the immune restoration associated with ART 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 ART [172,197–199].

The liver disease should also be staged both clinically and with either noninvasive 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 [198,200,201]. The risk–benefit of liver biopsy should be considered in the individual patient. The patient's age should also be taken into account as there is some evidence that response diminishes with increasing age [202].

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 [201,203,204].
(b) There is less chance of an SVR [196,201,202,205].
(c) The patient is at risk of varices and 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 patients with 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 coinfected patients are approximately 60% of those seen in HCV-monoinfected patients [194–196,200–202,205]. 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 noninvasive tests/biomarkers.

In those with genotype 1 or 4 infection, or where there is clinical concern regarding co-existent liver disease such as haemochromatosis, or alcohol-related or other liver disease, a biopsy can be helpful in staging the liver disease(s) and determining the need for HCV therapy [194–196,200–202,205,206]. In those individuals refusing liver biopsy, noninvasive 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 from or minimize alcohol intake, as more rapid progression of liver disease is seen with higher levels of alcohol consumption [85,203]. Patients who are nonimmune 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 [204,207].

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 [208,209].

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-coinfected patients with access to experienced physicians and trained specialist nurses with knowledge of coinfection to support and monitor the patients while on therapy [194–196,200–202,205,206].

5.3.4.1 Peginterferon. Three large controlled studies [APRICOT, AIDS Clinical Trials Group (ACTG) and RIBAVIC] all showed that peginterferons were more efficacious than standard thrice-weekly interferon [196,200,201]. Both peginterferon alpha-2a and peginterferon alpha-2b are licensed for treatment of patients with HIV/HCV coinfection. Peginterferon is given by weekly subcutaneous injection: peginterferon alpha-2a, 180 μg/week, and peginterferon alpha-2b, 1.5 μg/kg/week – i.e. weight-based [196,200,201].

5.3.4.2 Ribavirin. The initial trials of therapy for coinfected patients used relatively low-dose ribavirin. For example, 800 mg/day was prescribed for patients in the APRICOT study (SVR genotype 1, 29%; SVR genotype 3, 62%) [196]. This was mainly because there were concerns regarding risks of anaemia – particularly for patients on zidovudine-containing regimens. However, it was subsequently recognized that higher doses of ribavirin (1000–1200 mg/day) are associated with improved SVR in HCV-monoinfected patients and the Peginterferon Ribavirina España Coinfección (PRESCO) trial confirmed this finding in coinfected patients with an overall SVR of 50% (SVR genotype 1, 35%; SVR genotype 3, 72%) [210].

Since the APRICOT trial there have been many advances in ART, with many more alternatives to zidovudine. Access to erythropoietin and other growth factors to support the patient with ribavirin-induced marrow suppression has also improved [210,211].

5.3.4.3 Monitoring. Monitor the patient weekly for the first 2–4 weeks, with review every 2–4 weeks thereafter if stable [194–196,200–202,205,206,210,212]. If the CD4 count falls below 200 cells/μL, *Pneumocystis carinii* pneumonia (PCP) prophylaxis should be considered. Cotrimoxazole may have haematological side effects and should be used at the lowest appropriate dosage.

5.3.4.4 Treatment duration. Early trials such as the APRICOT study recognized that this is a 'hard-to-treat' group and opted for longer duration of therapy (48 weeks) for all

patients whatever the genotype [194–196,200–202,205]. 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 [194–196].

5.3.4.5 'Easier-to-treat' genotypes. In patients with genotype 2 and 3 infection who have an RVR, a treatment duration of 24 weeks should be strongly considered [194–196]. In patients who do not have an RVR but reach an undetectable HCV viral load by 24 weeks, a 48-week course is recommended [194–196].

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 [210,211,213].

5.3.4.6 'Harder-to-treat' genotypes. In patients with genotypes 1 and 4, a 48-week course of treatment is recommended [194–196,200–202,205,206,210,211]. An extension to 72 weeks of therapy should be utilized in patients not achieving an RVR but who have a 2 $\log_{10}$ drop at 12 weeks and become PCR negative at 24 weeks [210,211,213]. The Sustained Long-term Antiviral Maintenance with Pegylated Interferon in HCV/HIV-co-infected Patients (SLAM-C) study showed 65% completion and 51% SVR after 72 weeks of treatment.

5.3.4.7 Recommendations

- Anti-HCV treatment should be started before the CD4 count falls below 350 cells/μL and before ART is started, if possible (I).
- The aim of treatment is an SVR (undetectable viral load 24 weeks post treatment) (I).
- An RVR (viral load undetectable) at 4 weeks of treatment predicts response. Lack of EVR (nondetectable viral load or $>2\log_{10}$ fall at 12 weeks) or detectable viral load at 24 weeks of treatment predicts nonresponse and therapy should be stopped (I).
- Any ART should be stabilized 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 genotype 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 pretreatment 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 in all genotypes should be with pegylated interferon weekly plus ribavirin at 1000–1200 mg daily, supported by erythropoietin/growth factors if necessary (I).
- Treat patients with genotype 2 or 3 infection for 24 weeks if there is an RVR (II), otherwise for 48 weeks (I).
- Treat patients with genotypes 1 and 4 for 48 weeks if there is an RVR, or 72 weeks if there was a 2 $\log_{10}$ drop but detectable HCV RNA at week 12 and they become PCR negative at 24 weeks (I).

5.3.5 Nonresponders and relapsers

There are limited data to guide re-treatment of nonresponders and relapsers in the setting of HIV [214]. In the HIV-negative population, re-treatment may be considered in individuals who have failed to respond with an SVR to non-gold standard therapy, i.e. nonpegylated 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]. When re-treatment is considered, all modifiable factors known to affect response should be changed to meet optimal conditions, where possible.

The factors optimized should include the following.

- 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 through weight loss and therapeutic agents such as metformin [212,217];
- 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 [210,211].

The REtreatment with PEgasys in pATients Not Responding to Peg-Intron Therapy (REPEAT) study in HIV-negative individuals suggested that 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 [218]. Although the REPEAT study showed no effect of double-dose peginterferon 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 re-treatment with double-dose pegylated interferon for the first 4 weeks of therapy [219]. Currently, therefore, there is no firm evidence to support the use of induction/double-dose pegylated interferon.

The National Institutes of Health (NIH)-sponsored Hepatitis C Antiviral Long-Term Treatment aganist Cirrhosis (HALT-C) clinical trial failed to show a benefit of maintenance interferon on differences in the rates of mortality, decompensation, HCC, or fibrosis progression between the peginterferon alpha-2a maintenance group and the control group [220]. A similar study in HIV-positive individuals – the SLAM-C study – was also unable to show any beneficial effect on fibrosis progression rates [221]. 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 [222–227]. None of these new agents has been subject to clinical trial yet in HIV-positive patients. When these agents become available for the treatment of HIV-negative patients, those caring for the coinfected 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 coinfected 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 recognized outbreaks of acute hepatitis C amongst MSM; while initially localized in cities with high MSM populations, cases are now being reported more widely and incidence rates appear to be still increasing [2,3,155,158–161,228]. While the exact mode of transmission remains unclear, associations have been seen with HIV-positive status, recent sexually transmitted infections (syphilis, lymphogranuloma venereum and gonorrhoea), multiple sexual partners, unprotected anal intercourse and recreational drug use [2,3,155,158–161,228].

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 nonspecific 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 and higher CD4 cell counts, and in those taking ART [180–182,229].

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 of HCV-RNA. Close monitoring of RNA levels may therefore help to identify those individuals who are or are not likely to clear HCV without intervention [230]. After acute infection, it has been suggested that progressive liver damage may occur more rapidly than has been historically reported in coinfected individuals [231].

5.4.3 Diagnosis of acute HCV infection

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 randomized controlled trials to guide decisions on whether to treat, with what, and for what duration in this setting. Initial observational data from HIV-uninfected patients with acute HCV infection showed a remarkably high rate (98%) of sustained virological response in 44 individuals [232].

Several case series report experiences of treatment of acute HCV in HIV-infected individuals [180,181,233–238]. Overall, these suggest that, while response rates in those with HIV coinfection appear to be lower than the rates seen in those with HCV monoinfection, clearance is higher than in those with established HCV coinfection, particularly for genotype 1. While 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 are no clear data to support the routine addition of ribavirin to pegylated interferon or 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 [235]. However, in some studies, deferred therapy for HCV beyond 12 weeks was associated with impaired response, especially to genotype 1 [237,238]. Individualization in discussion with clinicians experienced in management of HIV/HCV coinfection is recommended to optimize the management and potential of this 'window of opportunity' of intervention. It is important to consider entering all patients with acute HCV infection into clinical trials.

5.4.5 Recommendations

- All HIV-positive patients with unexplained transaminitis should be evaluated for acute HCV 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 infection 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 have 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).

Conflicts of interest

Dr Gary Brook has received lecture fees from Bristol-Myers Squibb, Gilead and Jansen-Cilag and participated in clinical trials funded by Gilead.

Dr Janice Main participated in clinical trials, invited talks and advisory committee work for various companies (Roche, Schering-Plough, BMS, GlaxoSmithKline, BI).

Dr Mark Nelson received research grants from Gilead, Schering-Plough, Roche and BMS. He was on the advisory board for Gilead, BMS, Schering-Plough, Roche and Idenix and received speaker fees from Gilead, BMS, Schering-Plough and Roche.

Dr Sanjay Bhagani received speaking honoraria, travel grants and consultation fees from BMS, Gilead Sciences, Roche and Schering Plough. He also received research funding from Gilead Sciences.

Dr Ed Wilkins received educational and personal grants from MSD, Abbott, BMS, GSK, Pfizer, Gilead, and Tibotec for speaking at company-sponsored events, attending conferences and supporting research.

Dr Clifford Leen has received travel grants from, has been on the speakers' bureau of, has received an honorarium for speaking from, has sat on the medical advisory boards of, and/or has acted as an advisor for, the following pharmaceutical companies: Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Gilead, Johnson and Johnson, Roche and Pfizer. He has received research grants from the following companies: ARK, Abbott, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Roche, Pfizer and Tibotec.

Dr Martin Fisher has received honoraria, travelling scholarships and/or research funding from, and/or has acted as an advisor to, the following companies: Abbott, Boehringer Ingelhiem, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck Sharp and Dohme, Pfizer and Roche.

Dr Yvonne Gilleece received sponsorship from Gilead, Tibotec, BMS, Abbott and GSK (conferences, etc).

Dr Richard Gilson has received support from Gilead Sciences, Roche and Schering-Plough to attend conferences, and has received departmental support for research from Gilead Sciences and Roche.

Dr. Andrew Freedman received financial support for attending conferences as well as honoraria for advisory boards and lectures from Tibotec, BMS, Gilead & Abbott.

Dr. Ranjababu Kulasegaram received travel grants and honoraria from Abbott, Bristol-Myers Squibb, GlaxoSmithKline, MSD, Pfizer, Roche and Tibotec.

Dr Kosh Agarwal – None stated.

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Appendix

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