

British HIV Association Guidelines for the Management of Hepatitis Viruses in Adults Infected with HIV 2013

Green highlights denote changes that have been made to the document post-publication for society reference only.

For citation purposes readers should refer to the original text published at

<http://www.bhiva.org/documents/Guidelines/Hepatitis/2013/HepatitisGuidelines2013.pdf>

This version was produced in June 2014, with most recent amendments highlighted in green.



NHS Evidence has accredited the process used by the British HIV Association (BHIVA) to produce guidelines. Accreditation is valid for five years from July 2012 and is applicable to guidance produced using the processes described in the British HIV Association (BHIVA) Guideline Development Manual. More information on accreditation can be viewed at www.nice.org.uk/accreditation

British HIV Association guidelines for the management of hepatitis viruses in adults infected with HIV 2013

Writing Group

Dr Ed Wilkins (Chair)

Consultant Physician in Infectious Diseases and Clinical Lead of the HIV Research Unit, North Manchester General Hospital

Dr Mark Nelson (Vice Chair)

Consultant Physician, Chelsea and Westminster Hospital NHS Foundation Trust, London, and Adjunct Professor and Reader in Human Immunodeficiency Virology, Imperial College London

Dr Kosh Agarwal

Consultant Hepatologist/Transplant Physician, King's College Hospital NHS Foundation Trust, London

Ms Dola Awoyemi

HIV Specialist Pharmacist, Kingston Hospital NHS Foundation Trust

Dr Eleanor Barnes

MRC Senior Clinical Fellow and Honorary Consultant in Hepatology, John Radcliffe Hospital, Oxford

Dr Sanjay Bhagani

Consultant Physician in Infectious Diseases/HIV Medicine, Royal Free Hampstead NHS Trust, London

Dr Gary Brook

Consultant Physician in GUM/HIV, North West London Hospitals NHS Trust

Dr Ashley Brown

Consultant Hepatologist, Imperial College Healthcare NHS Trust, London

Ms Sheena Castelino

Principal HIV Pharmacist, Guy's & St Thomas' NHS Foundation Trust, London

Dr Graham Cooke

Senior Lecturer, Imperial College London, and Honorary Consultant, Imperial College Healthcare NHS Trust, London

Prof Martin Fisher

Consultant Physician in HIV and Genitourinary Medicine, Brighton and Sussex University Hospitals NHS Trust

Prof Anna Maria Geretti

Professor of Virology and Infectious Diseases, Institute of Infection and Global Health, University of Liverpool

Mr Robert James

*Sessional Lecturer in Law, Birkbeck College, University of London
UKCAB*

Dr Ranjababu Kulasegaram

Consultant Physician in HIV and Genitourinary Medicine, Guy's & St Thomas' NHS Foundation Trust, London

Prof Clifford Leen

Consultant Physician in Infectious Diseases, Western General Hospital, Edinburgh and Professor in Infectious Diseases, Edinburgh University

Prof David Mutimer

Professor of Clinical Hepatology, Birmingham University and Honorary Consultant Physician, Queen Elizabeth Hospital, Birmingham

Dr Chloe Orkin

Consultant Physician and Lead for HIV Research, Barts Health NHS Trust, London

Dr Emma Page

Specialist Registrar, Chelsea and Westminster Hospital NHS Foundation Trust, London

Dr Adrian Palfreeman

Consultant in Genitourinary Medicine, University Hospitals of Leicester NHS Trust

Dr Padmasayee Papineni

Specialist Registrar Infectious Diseases/GUM, North West London Hospitals NHS Trust

Dr Alison Rodger

Senior Lecturer and Honorary Consultant in Infectious Diseases, University College London

Dr CY William Tong

Consultant Virologist, Barts Health NHS Trust, London

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1 Introduction

1.1 Scope and purpose

The purpose of these guidelines is to provide guidance on best clinical practice in the treatment and management of adults with HIV and viral hepatitis coinfection. The scope includes: i) guidance on diagnostic and fibrosis screening; ii) preventative measures including immunisation and behavioural intervention; iii) ARV therapy and toxicity; iv) management of acute and chronic HBV/HIV and HCV/HIV; v) monitoring and management of coinfection-related end-stage liver disease (ESLD) including transplantation; and vi) discussion on HDV/HIV and HEV/HIV infection. The guidelines are aimed at clinical professionals involved in and responsible for the care of adults with HIV and viral hepatitis coinfection, and at community advocates responsible for promoting the best interests and care of adults with coinfection. They should be read in conjunction with other published BHIVA and hepatitis guidelines.

1.2 Methodology

1.2.1 Guideline development process

BHIVA revised and updated the Association's guideline development manual in 2011 [1]. BHIVA has adopted the modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for the assessment, evaluation and grading of evidence and the development of recommendations [2,3]. The guideline was developed by a Writing Group comprising professional group members and an elected community representative. The scope, purpose and guideline topics were agreed by the Committee and key questions concerning each guideline topic were drafted (Table 1.1) and a systematic literature review undertaken by an information scientist. Full details of the guideline development process are outlined in the appendices to this document. Review questions were developed in a PICO (patient, intervention, comparison and outcome) framework. This framework guided the literature-searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the Guideline Writing Group. Eleven review questions were identified. Full literature searches and critical appraisals were completed for all specified questions. Because of a lack of comparative data for any of the priority questions in hepatitis/HIV coinfection, no separate meta-analyses were conducted. Members of the Guideline Writing Group declared their conflicts of interests prior

to the commencement of the writing process, and if a vote was necessary any member whose declared interests made this inappropriate did not participate.

BHIVA hepatitis coinfection guidelines for hepatitis B and C were last published in 2010 [4]. For the 2013 guidelines the literature search dates were 1 January 2009 to 30 October 2012, and included Medline, Embase and the Cochrane library. Abstracts from selected conferences (see Appendix 2) were searched between 1 January 2009 and 30 October 2012. For each topic and health care question, evidence was identified and evaluated by Guideline Writing Group members with expertise in that field. Using the modified GRADE system (Appendix 1), panel members were responsible for assessing and grading the quality of evidence for predefined outcomes across studies and developing and grading the strength of recommendations. An important aspect of evaluating evidence is an understanding of the design and analysis of clinical trials including the use of surrogate marker data.

For a number of questions, GRADE evidence profile and summary of findings tables were constructed using predefined and rated treatment outcomes (Appendix 2) to achieve consensus for key recommendations and aid transparency of process. Prior to final approval by the Writing Group the guidelines were published online for public consultation and external peer review commissioned.

1.2.2 Patient involvement

BHIVA views the involvement of patient and community representatives in the guideline development process as essential. The Writing Group included one patient representative who was involved in all aspects of the guideline development process and was responsible for liaising with all interested patient groups.

1.2.3 GRADE

The GRADE Working Group [3] has developed an approach to grading evidence that moves from initial reliance on study design to consider the overall quality of evidence across outcomes. BHIVA has adopted the modified GRADE system for the Association's guideline development.

The advantages of the modified GRADE system are: (i) the grading system provides an informative, transparent summary for clinicians, patients and policy makers by combining an explicit evaluation of the strength of the recommendation with a judgement of the quality of the

Table 1.1

Section	Type of review	Review questions	Outcomes
4	Interventional	Should screening for HCV be performed in adults with HIV infection 6 monthly or 12 monthly?	<ul style="list-style-type: none"> - Missed HCV cases - Cost - Transmission rates
4	Diagnostic	Should the screening test for HCV in adults with HIV infection be HCV antibody, HCV-PCR or HCV antigen?	<ul style="list-style-type: none"> - Missed HCV cases - Cost - Transmission rates
4	Diagnostic	Is liver biopsy or hepatic elastometry the investigation of choice in the assessment of fibrosis?	<ul style="list-style-type: none"> - Distinction of mild/normal vs. moderate/severe disease - Distinction of cirrhosis from non-cirrhosis - Adverse events - Cost - Patient satisfaction
5	Interventional	When deciding ART for adults with HCV/HIV infection, is there a preferred combination which differs from those with HIV mono-infection?	<ul style="list-style-type: none"> - Severe adverse events - Grade 3/4 treatment-associated hepatitis - HIV viral suppression <50 copies/mL
6	Prognostic	When is the optimum time to commence ART in adults with chronic HBV/HIV infection?	<ul style="list-style-type: none"> - Mortality - HBV disease progression (cirrhosis and hepatocellular carcinoma [HCC]) - Response to ART (HIV viral load <50 copies/mL, CD4 count increase) - Severe treatment-associated adverse events
6	Interventional	Which is the anti-HBV treatment option of choice when the CD4 is >500 cells/ μ L in adults with chronic HBV/HIV infection?	<ul style="list-style-type: none"> - Mortality - HIV disease progression - HBV disease progression (cirrhosis, and HCC) - HBV DNA decline on therapy - Severe treatment-associated adverse events - Patient acceptability
6	Interventional	Should FTC or 3TC be used in combination with tenofovir in adults with chronic HBV/HIV infection?	<ul style="list-style-type: none"> - HBV DNA decline on therapy - Cost - Treatment-associated adverse events
8	Diagnostic	Should <i>IL28B</i> be used routinely in determining treatment strategies in adults with chronic HCV/HIV infection?	<ul style="list-style-type: none"> - Sustained virological response (SVR) at 12 and 24 weeks - Cost - Need for triple therapy
8	Interventional	When is the optimum time to commence ART in adults with chronic HCV/HIV infection?	<ul style="list-style-type: none"> - Mortality - Non-hepatic HCV co-morbidity - HCV disease progression (cirrhosis, HCC) - ARV resistance development - Severe treatment-associated adverse events
8	Interventional	In adults with chronic HIV infection who contract acute HCV, are there benefits in giving combination therapy with pegylated interferon (PEG-IFN) and ribavirin over giving PEG-IFN alone, and are there benefits of 48 weeks as opposed to 24 weeks of treatment?	<ul style="list-style-type: none"> - HCV SVR at 24 weeks
10	Prognostic	Should ultrasound scan (USS) surveillance be performed 6 or 12 monthly to detect early hepatocellular carcinoma in adults with chronic viral hepatitis/HIV infection?	<ul style="list-style-type: none"> - HCC mortality - HCC missed diagnoses - Cost of screening

evidence for each recommendation; (ii) the two-level grading system of recommendations has the merit of simplicity and provides clear direction to patients, clinicians and policy makers.

A Grade 1 recommendation is a strong recommendation to do (or not do) something, where benefits clearly outweigh risks (or vice versa) for most, if not all, patients. Most clinicians and patients would want to follow a strong recommendation unless there is a clear rationale for an alternative approach. A strong recommendation usually starts with the standard wording 'We recommend'.

A Grade 2 recommendation is a weaker or conditional recommendation, where the risks and benefits are more closely balanced or are more uncertain. Alternative approaches or strategies may be reasonable depending on the individual patient's circumstances, preferences and values. A weak or conditional recommendation usually starts with the standard wording 'We suggest'.

The strength of a recommendation is determined not only by the quality of evidence for defined outcomes but also the balance between desirable and undesirable effects of a treatment or intervention, differences in values and

preferences, and where appropriate resource use. Each recommendation concerns a defined target population and is actionable.

The quality of evidence is graded from A to D and for the purpose of these guidelines is defined as follows:

Grade A evidence means high-quality evidence that comes from consistent results from well-performed randomised controlled trials (RCTs), or overwhelming evidence from another source (such as well-executed observational studies with consistent strong effects and exclusion of all potential sources of bias). Grade A implies confidence that the true effect lies close to the estimate of the effect.

Grade B evidence means moderate-quality evidence from randomised trials that suffers from serious flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or some combination of these limitations, or from other study designs with specific strengths such as observational studies with consistent effects and exclusion of the majority of the potential sources of bias.

Grade C evidence is low-quality evidence from controlled trials with several serious limitations, or observational studies with limited evidence on effects and exclusion of most potential sources of bias.

Grade D evidence is based only on case studies, expert judgement or observational studies with inconsistent effects and a potential for substantial bias, such that there can be little confidence in the effect estimate.

1.2.4 Good practice points

In addition to graded recommendations, the BHIVA Writing Group has also included good practice points (GPP), which are recommendations based on the clinical judgement and experience of the working group. GPPs emphasise an area of important clinical practice for which there is not, nor is there likely to be, any significant research evidence. They address an aspect of treatment and care that is regarded as such sound clinical practice that health care professionals are unlikely to question it and where the alternative recommendation is deemed unacceptable. It must be emphasised that GPPs are not an alternative to evidence-based recommendations.

1.2.5 Dissemination and implementation

The following measures have, or will be undertaken, to disseminate and aid implementation of the guidelines: i) e-publication on the BHIVA website and the Journal *HIV*

Medicine; ii) publication in the journal *HIV Medicine*; iii) e-learning module accredited for CME; iv) an educational slide set to support local and regional educational meetings; and v) National BHIVA Audit Programme.

1.2.6 Guideline updates and date of next review

The guidelines will be reviewed and updated as required on a 6-monthly basis with a plan for an extensive rewrite in 2016. The Writing Group will continue to meet regularly to consider new information from high-quality studies and publish amendments and addendums to the current recommendations prior to the full revision date where this is clinically important data developed to ensure continued best clinical practice.

1.2.7 Resource use

The BHIVA Writing Group recognises that cost-effectiveness data are important in the formulation of guidelines and it was agreed as a critical outcome for certain priority questions (Table 1.1). There are limited cost-effectiveness data in the UK comparing different antiretroviral drugs in HIV mono-infection and none examining different antiretroviral drugs or anti-HBV or anti-HCV therapies in adults with HBV/HIV or HCV/HIV infection or different screening strategies for hepatitis viruses in HIV infection. Hence, the intervention was deemed cost-effective if it was both less costly in terms of likely resource use and more clinically effective compared with other relevant alternative strategies within the data available to the expert(s) writing the specific guideline. However, the Writing Group believes that reducing management costs should not be at the cost of increased risk of poorer outcomes and quality of care.

1.3 References

- 1 BHIVA Guideline Development Manual, September 2011. Available at: www.bhiva.org/GuidelineDevelopmentManual.aspx (accessed 3 May 2013).
- 2 Guyatt GH, Oxman AD, Kunz R *et al.* Going from evidence to recommendations. *BMJ* 2008; **336**: 1049–1051.
- 3 The Grading of Recommendations Assessment, Development and Evaluation (short GRADE) Working Group. Available at: www.gradeworkinggroup.org (accessed 3 May 2013).
- 4 Brook G, Main J, Nelson M *et al.* for the BHIVA Viral Hepatitis Working Group. British HIV Association guidelines for the management of coinfection with HIV-1 and hepatitis B or C virus 2010. *HIV Med* 2010; **11**: 1–30.

2 Summary of recommendations/good practice points and auditable outcomes

3 Patient involvement in care

3.2 Good practice points

1. We recommend all adults with viral hepatitis and HIV infection are given the opportunity to be actively involved in making decisions about their treatment.
2. We recommend all adults with viral hepatitis and HIV infection should have access to psychosocial support at all times.
3. We recommend provision of treatment-support resources should include in-house, independent and community information providers and peer-support resources.
4. We recommend that all adults with viral hepatitis and HIV infection are offered a copy of the clinic letters and are encouraged to discuss their diagnosis and care with their primary care physician.

3.3 Auditable outcome

- *Proportion of adults with viral hepatitis and HIV infection with documentation in the case records who have been given the opportunity to be involved in making decisions about their treatment*

4 Screening, prevention and immunisation

4.2 Screening investigations at diagnosis

4.2.1 Recommendations

5. We recommend patients with HIV infection should be screened at diagnosis for immunity against hepatitis A (1A).
6. We recommend patients with HIV infection should be screened at diagnosis for hepatitis B using HBsAg and anti-HBc (1B) and for HBV immunity using anti-HBs.
7. We recommend individuals who are HBsAg negative or have no evidence of protective vaccine-induced immunity should have an annual HBsAg test or more frequent testing if there are known and ongoing risk factors for HBV acquisition (1B).
8. We suggest patients with isolated anti-HBc (negative HBsAg and anti-HBs) and unexplained elevated transaminases should have HBV DNA performed to exclude the presence of occult HBV infection (2C).
9. We suggest testing patients for HBV DNA when transaminases are persistently raised and all other tests (including HBsAg, HCV RNA and anti-HEV) are negative to exclude occult HBV infection (2C).
10. We recommend HDV antibody (with HDV RNA if positive) should be performed on all HBsAg-positive individuals (1B).
11. We recommend patients have an HCV antibody test when first tested HIV antibody positive and at least annually if they do not fall into one of the risk groups that require increased frequency of testing (1C) (see Section 8).
12. We recommend patients with HIV infection who have elevated transaminases of unknown cause have an HCV-PCR test (1A).
13. We recommend all patients who are anti-HCV positive are tested for HCV-PCR and, if positive, genotype (1B).
14. We suggest that *IL28B* genotyping need not be performed routinely when considering anti-HCV therapy in HCV/HIV infection (2C).
15. We recommend individuals who achieved SVR following treatment or who have spontaneously cleared HCV infection should be offered annual HCV-PCR and more frequent testing should they have an unexplained rise in transaminase levels (1C) (see Section 8).
16. We recommend HEV is excluded in patients with HIV infection and elevated liver transaminases and/or liver cirrhosis when other common causes of elevated transaminases have been excluded (1D).

4.2.2 Good practice points

Counselling on behaviour modification

17. We recommend all patients should be counselled about using condoms for penetrative sex.
18. We recommend information should be given on factors associated with HCV transmission to patients at HIV diagnosis and on an ongoing basis dependent on risk.
19. We recommend risk reduction advice and education be given to patients diagnosed with HBV and HCV, and should incorporate information about potential risk factors for transmission. For HCV, this should include mucosally traumatic sexual practices (e.g., fisting, use of sex toys), group sex activities, recreational including intravenous drug use, and condomless anal intercourse, as well as advice to those sharing injecting drug equipment.

4.2.3 Auditable outcomes

- *Proportion of adults with newly diagnosed HIV screened for immunity to hepatitis A and hepatitis B (anti-HBc, anti-HBs)*
- *Proportion of adults with newly diagnosed HIV screened for infection with HBV (HBsAg) and HCV (anti-HCV)*
- *Proportion of HIV-positive adults with anti-HBs <10 IU/L screened annually for HBsAg*
- *Proportion of HIV-positive, anti-HCV-negative patients screened at least annually for HCV*
- *Proportion of anti-HCV positive patients tested for HCV RNA and, where positive, HCV genotype*
- *Proportion of patients with chronic HCV/HIV with documented counselling regarding HCV transmission risk factors and safe sex*
- *Proportion of patients with treatment-induced or spontaneous clearance of HCV RNA screened at least annually for HCV by RNA testing*

4.3 Assessment of liver disease

4.3.1 Recommendations

20. We recommend staging of liver disease should be performed in those with chronic HCV/HIV and HBV/HIV infections (1B).
21. We suggest in patients with chronic hepatitis/HIV infection a non-invasive test as the staging investigation of choice (2B).
22. We suggest hepatic transient elastography (TE) (FibroScan™ or ARFI [Acoustic Radiation Force Impulse]) as the non-invasive investigation of choice (2B) but if unavailable, or when reliable TE readings are not obtained, a blood panel test (APRI, FIB-4, ELF, Fibrometer™, Forns Index, FibroTest™) as an alternative (2C).
23. We recommend in chronically infected viral hepatitis/HIV patients, TE readings suggestive of cirrhosis (Metavir >F4) using recommended disease-specific cut-offs (using FibroScan™ these are >11.0 kPa for HBV, >14.5 kPa for HCV), should lead to appropriate monitoring for complications of portal hypertension and HCC screening (1B).
24. We recommend in HCV/HIV viraemic patients, repeated fibrosis assessments using TE, or if unavailable an alternative non-invasive blood panel test, should be performed at least annually (1D).

4.3.2 Good practice point

25. We recommend when the aetiology of underlying liver disease is in doubt, or where factors other than viral hepatitis are likely to have influenced liver disease progression and may be important to address, or there is discordance between non-invasive markers or uncertainty as to their interpretation, liver biopsy is the investigation of choice for assessment.

4.3.3 Auditable outcomes

- *Proportion of patients with chronic HCV/HIV or chronic HBV/HIV with documented staging of liver disease performed at least once before commencing therapy*
- *Proportion of HIV-positive patients with chronic viral hepatitis and Metavir stage 4 fibrosis who are monitored for complications of portal hypertension and have HCC screening performed*
- *Proportion of HIV-positive patients with chronic viral hepatitis and who are viraemic having at least annual repeated fibrosis assessments*

4.4 Immunisation

4.4.1 Recommendations

26. We recommend all non-immune HIV-infected individuals are immunised against HAV and HBV (1A).
27. We recommend the 40 µg (double dose **with most vaccines**) strength of HBV vaccine should be used in HIV-infected patients (1A) and given at months 0, 1, 2 and 6 (1B).
28. We suggest an accelerated vaccination schedule (three single [20 µg] doses given over 3 weeks at 0, 7–10 and 21 days) be considered only in selected patients with CD4 counts >500 cells/µL where there is an imperative need to ensure rapid completion of vaccination and/or where compliance with a full course is doubtful (2B).
29. We recommend anti-HBs levels should be measured 4–8 weeks after the last vaccine dose (1B). Vaccine recipients with anti-HBs <10 IU/L should be offered three further 40 µg doses of vaccine, given at monthly intervals with retesting of anti-HBs recommended 4–8 weeks after the final vaccine dose (2B).
30. We suggest vaccine recipients with an anti-HBs response >10 but <100 IU/L should be offered one additional 40 µg dose of vaccine and the response checked 4–8 weeks later (2B).
31. We recommend a booster (40 µg) dose of vaccine should be offered to those whose anti-HBs levels have declined to <10 IU/L (1C).

4.4.2 Good practice points

32. We recommend patients who are unable to develop an antibody response to vaccine or in whom anti-HBs levels have fallen below 10 IU/L continue to be screened for HBsAg as there remains a risk of infection.
33. We recommend following successful immunisation, the anti-HBs level should be measured regularly. The frequency of screening for anti-HBs should be guided by the anti-HBs level measured after vaccination: every year for levels between 10 IU/L and 100 IU/L and every 2 years for higher levels.

4.4.3 Auditable outcomes

- *Proportion of HAV and HBV non-immune patients who are immunised*
- *Proportion with anti-HBs levels <10 IU/L post-primary vaccination offered three further 40 µg doses at one-month intervals*
- *Proportion with anti-HBs levels between 10–100 IU/L post-primary course of vaccine offered one further 40 µg dose of vaccine*
- *Proportion with successful HBV immunisation receiving annual or bi-annual anti-HBs screening*
- *Proportion following successful HBV vaccination receiving a booster dose of vaccine when anti-HBs levels fall below 10 IU/L*

5 Antiretroviral therapy

5.1.1 Recommendations

34. We recommend ARV choice should take into consideration pre-existing liver disease but ART should not be delayed because of a risk of drug-induced liver injury (1B).
35. We suggest ART should be used with close monitoring in patients with ESLD (Child-Pugh B/C) and consideration given to performing plasma level monitoring of ART agents (2C), particularly for the case where ritonavir-boosted PIs and NNRTIs are used.
36. We suggest when abacavir is prescribed with ribavirin, the ribavirin should be weight-based dose-adjusted (2C).

5.1.2 Good practice points

37. We recommend initiation of ART be considered in all viral hepatitis coinfecting patients irrespective of CD4 cell count.
38. We recommend patients should have baseline transaminases checked before initiating a new ARV and that this is followed by routine monitoring after 1 month, and then every 3–6 months.
39. We recommend where DAAs are used for the treatment of HCV, careful consideration be given to potential drug–drug interactions (DDIs).
40. We recommend ART should be discontinued if grade 4 hepatotoxicity (transaminases >10 times upper limit of normal) develops, even if the patient is asymptomatic.

5.1.3 Auditable outcome

- *Proportion of patients with baseline transaminase checked before and one month after starting a new ARV*

6 Hepatitis B (HBV)

6.2 HBV resistance, genotype testing and treatment response

6.2.1 Recommendations

41. We recommend against HBV resistance testing at baseline in those previously unexposed to antivirals (1C).
42. We recommend, where feasible, HBV resistance testing at baseline in those with detectable HBV DNA and previously exposed to antiviral drugs with anti HBV activity if not on treatment, where there is primary non-response or partial response to HBV-active antivirals, or where there is virological breakthrough (1C).
43. We recommend against a change in HBV-specific therapy in those whose viraemia continues to show improving response to treatment after 48 weeks (1C).
44. We recommend against testing for HBV genotype as an investigation to determine initial treatment (1C).

6.2.2 Good practice point

45. We recommend adherence is discussed with all patients with HBV viraemia receiving antivirals.

6.3 Thresholds for ART treatment

6.3.1 Recommendations

46. We recommend all those with an HBV DNA ≥ 2000 IU/mL should be treated, regardless of fibrosis score (1C).
47. We recommend all those with more than minimal fibrosis on liver biopsy (Metavir $\geq F2$ or Ishak $\geq S2$) or indicative of $\geq F2$ by TE (FibroScan ≥ 9.0 kPa) should be treated, regardless of HBV DNA level (1C) (see Section 4).
48. We suggest those with a CD4 ≥ 500 cells/ μ L, an HBV DNA of < 2000 IU/mL, minimal or no evidence of fibrosis (Metavir $\leq F1$ or Ishak $\leq S1$ or FibroScan < 6.0 kPa) and a repeatedly normal ALT should be given the option to commence treatment or to be monitored not less than 6-monthly with HBV DNA and ALT and at least yearly for evidence of fibrosis (2C).
49. We recommend all patients with a CD4 < 500 cells/ μ L are treated with fully suppressive ART inclusive of anti-HBV-active antivirals (1B).

6.3.2 Good practice points

50. We recommend at least two baseline HBV DNA measurements are obtained 3 to 6 months apart to guide initiation of therapy.
51. We recommend 6-monthly HBV DNA measurements for routine monitoring of therapy.
52. We recommend that an ALT level below the upper limit of normal should not be used to exclude fibrosis or as a reason to defer HBV therapy. Normal levels of ALT should be considered as 30 IU/L for men and 19 IU/L for women.

6.3.3 Auditable outcome

- *Proportion of patients with a CD4 ≥ 500 cells/ μ L and an HBV DNA ≥ 2000 IU/mL and/or evidence of more than minimal fibrosis (Metavir $\geq F2$, Ishak $\geq S2$, or TE ≥ 9.0 kPa) commencing ART inclusive of anti-HBV antivirals*

6.4 Antiviral treatment: CD4 count ≥ 500 cells/ μ L (Algorithm 1)

6.4.1 Recommendations

53. We recommend TDF/FTC as part of a fully suppressive ART combination should be given to all patients where HBV treatment is deemed necessary (1C).
54. We suggest adefovir or 48 weeks of PEG-IFN are alternative options in patients unwilling or unable to receive TDF/FTC as part of a fully suppressive ART combination but requiring HBV therapy (2C).
55. We suggest PEG-IFN is only used in HBsAg-positive patients with a repeatedly raised ALT, low HBV DNA ($< 2 \times 10^6$ IU/mL), and minimal fibrosis, irrespective of HBeAg antigen status (2D). Lack of HBV DNA response (reduction to < 2000 IU/mL at 12 weeks) should prompt discontinuation. Repeat testing should be performed 3-monthly to observe the presence of seroconversion (2C).

6.5 Antiviral treatment: CD4 count < 500 cells/ μ L (Algorithm 2)

6.5.1 Recommendations

56. We recommend TDF/FTC or TDF/3TC as part of a fully suppressive combination ART regimen be used in those with confirmed or presumed sensitive HBV (1C).
57. We recommend where tenofovir is not currently being given as a component of ART it should be added or substituted for another agent within the regimen if there is no contraindication (1C).

58. We recommend neither 3TC nor FTC be used as the sole active drug against HBV in ART due to the rapid emergence of HBV resistant to these agents (1B).
59. We recommend 3TC/FTC may be omitted from the antiretroviral regimen and tenofovir be given as the sole anti-HBV active agent if there is clinical or genotypic evidence of 3TC/FTC-resistant HBV or HIV (1D).
60. We recommend that in the presence of wild-type HBV, either FTC or 3TC can be given to patients requiring ART in combination with tenofovir (1B).
- 6.5.2 Good practice points**
61. We recommend if patients on suppressive anti-HBV therapy require a switch in their antiretrovirals due to HIV resistance to tenofovir and/or 3TC/FTC, their active anti-HBV therapy (tenofovir with or without 3TC/FTC) should be continued and suitable anti-HIV agents added.
62. We recommend if tenofovir is contraindicated, entecavir should be used if retaining activity. Entecavir should only be used in addition to a fully suppressive combination ART regimen.
- 6.5.3 Auditable outcomes**
- *Proportion of patients with a CD4 count <500 cells/μL receiving TDF/FTC or TDF/3TC as part of a fully suppressive combination ART regimen*
 - *Proportion of patients avoiding 3TC or FTC as the sole active drug against HBV in ART*
- 6.6 Antiviral treatment: Acute HBV**
- 6.6.1 Recommendations**
63. We recommend individuals with severe/fulminant acute HBV in the context of HIV should be treated with nucleosides active against hepatitis B (1D).
64. We recommend patients with severe/fulminant acute HBV receive ART inclusive of tenofovir and 3TC or FTC, or entecavir given with ART (1D).
- 6.6.2 Auditable outcome**
- *Proportion of patients with severe/fulminant acute HBV who receive ART inclusive of an antiviral active against HBV*
- 7 Hepatitis delta (HDV)**
- 7.1.1 Recommendations**
65. We recommend all HBsAg-positive patients are tested for HDV antibody (1B).
66. We suggest repeat testing for HDV-seronegative HBsAg-positive patients is required only if the patient has persistent risk factors (2D).
67. We recommend all HDV-seropositive individuals should be tested for HDV RNA (1C).
68. We recommend all HIV/HBV/HDV-infected patients with detectable HBV DNA be treated with tenofovir as part of, or in addition to, ART (1D).
- 7.1.2 Good practice point**
69. We recommend all those with HDV RNA be considered for early treatment by a physician with experience in this condition.
- 7.1.3 Auditable outcome**
- *Proportion of chronic HBV-infected HIV patients who had an HDV antibody test*
- 8 Hepatitis C (HCV)**
- 8.3 Diagnosis of HCV after high-risk exposure**
- 8.3.1 Recommendations**
70. We recommend patients who have raised transaminases or had recent high-risk exposure to an individual known to be HCV positive are tested for anti-HCV and HCV-PCR (1D). When past spontaneous clearance or successful treatment has occurred HCV-PCR should be performed.
71. We recommend the HCV-PCR should be repeated after 1 month if initially negative and if any potential exposure was less than 1 month before the first test, or the transaminases remain abnormal with no known cause (1D).
- 8.3.2 Good practice points**
72. We recommend patients who have experienced a recent high-risk exposure (e.g., unprotected sex between men [especially in the context of concurrent STI, high-risk sexual practices, and recreational drug use] or shared injection drug equipment) but have normal transaminases are tested for anti-HCV, and this is repeated 3 months later.

73. We recommend patients who have repeated high-risk exposures but persistently normal transaminases are screened with anti-HCV and HCV-PCR, or HCV-PCR alone if previously successfully treated for or spontaneously have cleared infection and are HCV antibody positive, at 3–6-monthly intervals.
- 8.3.3 Auditable outcomes**
- *Proportion of patients with acute HCV who had an HCV-PCR assay as the screening test*
 - *Proportion of patients with repeated high-risk exposure who had HCV tests (antibody and PCR) at least twice a year*
 - *Proportion of all adults with HIV infection who had an HCV test within 3 months of HIV diagnosis*
- 8.4 Thresholds and timing of treatment**
- 8.4.1 Recommendations**
74. We recommend commencing ART when the CD4 count is less than 500 cells/ μ L in all patients who are not to commence anti-HCV treatment immediately (1B).
75. We suggest commencing ART when the CD4 count is greater than 500 cells/ μ L in all patients who are not to commence anti-HCV treatment immediately (2D).
- 8.4.2 Good practice points**
76. We recommend commencing ART to allow immune recovery before anti-HCV therapy is initiated when the CD4 count is less than 350 cells/ μ L.
77. We recommend commencing ART to optimise immune status before anti-HCV therapy is initiated when the CD4 count is 350–500 cells/ μ L unless there is an urgent indication for anti-HCV treatment when ART should be commenced as soon as the patient has been stabilised on HCV therapy.
- 8.4.3 Auditable outcome**
- *Proportion of patients with a CD4 count <500 cells/ μ L commencing ART*
- 8.5 Choice of ART**
- 8.5.1 Recommendations**
78. We suggest that if abacavir is to be used with ribavirin, the ribavirin should be weight-based dose-adjusted (2C).
79. We recommend when DAAs are to be used there is careful consideration of possible DDIs (1C) and current or archived HIV resistance. All drug interactions should be checked with an expert source (e.g., www.hiv-druginteractions.org).
80. We recommend if boceprevir is to be used, raltegravir (RAL) with tenofovir (TDF) plus emtricitabine (FTC) should be the treatment of choice for those with wild-type HIV (1C): pharmacokinetic data would support etravirine, rilpivirine and maraviroc as alternatives.
81. We recommend if telaprevir is to be used either RAL or standard-dose ritonavir-boosted atazanavir should be used (1C): pharmacokinetic data would support etravirine, rilpivirine and maraviroc as alternatives. Efavirenz may be used but the telaprevir dose needs to be increased to 1125 mg tds.
82. We recommend that didanosine (ddI), stavudine (d4T) and zidovudine (ZDV) are avoided (1B).
- 8.5.2 Good practice point**
83. We recommend if patients are commencing ART and DAAs are not being considered, standard first-line ART should be commenced (see BHIVA adult treatment recommendations [54]).
- 8.5.3 Auditable outcomes**
- *Among patients receiving DAAs for HCV genotype 1 with ART for wild type HIV, the percentage on a recommended regimen, i.e.: raltegravir (RAL) with tenofovir (TDF) plus emtricitabine (FTC) with boceprevir; or RAL or boosted atazanavir with standard dose telaprevir; or efavirenz with increased dose 1125 mg tds telaprevir*
 - *Proportion of patients on anti-HCV and ART medication with a medication history at each clinic visit documented in the case notes*
 - *Proportion of patients on DAAs with a record in the notes of a discussion of the potential for pharmacokinetic interactions with antiretroviral medication and other medication*

8.6 Assessment and investigation

8.6.1 Good practice points

84. We recommend all patients have a baseline fibrosis stage assessment.
85. We recommend all patients should be managed by a clinician experienced in the management of both HIV and hepatitis C or should be jointly managed by clinicians from HIV and hepatitis backgrounds.
86. We recommend all patients with HCV/HIV infection should be assessed for suitability for treatment of hepatitis C.
87. We recommend consideration for referral to liaison psychiatry services for patients with pre-existing mental health problems prior to initiation of therapy and for patients with treatment-emergent psychiatric problems.
88. We recommend individuals with dependency on alcohol and/or injection drug use are referred to the respective community services before initiation of therapy to minimise non-adherence with treatment.
89. We recommend patients with advanced cirrhosis, low platelet counts and low albumin should be treated in centres experienced in managing patients with advanced disease and potential complications.

8.6.2 Auditable outcome

- *Proportion of patients diagnosed with HCV/HIV receiving a baseline fibrosis stage assessment*

8.7 Antiviral treatment: genotype 1

8.7.1 Recommendations

90. We recommend where there is a current clinical need for treatment (i.e., Metavir F4/cirrhosis), or if the patient wishes to be treated, the standard of care should be with triple therapy consisting of pegylated interferon, ribavirin, and either telaprevir or boceprevir (1C).
91. We recommend 48 weeks of total treatment with a telaprevir- or boceprevir-based regimen for patients who do not have cirrhosis (1C).

8.7.2 Good practice points

92. We recommend all patients should have the option of treatment, and have the pros and cons of opting for initiation of treatment and of deferring treatment discussed with them.
93. We recommend a total of 48 weeks of treatment in patients with cirrhosis and for those who do not achieve an RVR.
94. We suggest non-cirrhotic patients who were previously null responders, partial responders or who experienced breakthrough should, wherever possible, wait for the availability of interferon-sparing regimens or interferon-based regimens including at least two new agents.
95. We recommend that all patients with advanced or decompensated cirrhosis being treated with triple therapy are managed in a tertiary centre.
96. We suggest for patients with genotype 1 infection and non-cirrhotic disease, there is the option to defer treatment until newer funded therapies or a suitable clinical trial become available. Where deferred, close monitoring should take place with hepatic elastography or alternative non-invasive testing at least annually. Where there is confirmed progression of fibrosis, treatment initiation should be reconsidered.

8.7.3 Auditable outcomes

- *Proportion of patients treated for genotype 1 outside of clinical trials receiving triple therapy with telaprevir or boceprevir with pegylated interferon and ribavirin*
- *Proportion of patients treated for genotype 1 with cirrhosis who are offered treatment with telaprevir or boceprevir with pegylated interferon and ribavirin unless contraindicated*
- *Proportion of patients not receiving therapy who undergo repeat non-invasive staging of liver disease within 1 year*

8.8 Antiviral treatment: genotypes 2 and 3

8.8.1 Recommendations

97. We recommend where there is a current clinical need for treatment (i.e., Metavir F4/cirrhosis), or if the patient wishes to be treated, the standard of care should be with pegylated interferon and ribavirin (1C).
98. We recommend where patients receive pegylated interferon and ribavirin, the duration of treatment should be 48 weeks unless RVR is achieved, when treatment should be shortened to 24 weeks if the individual is non-cirrhotic (1C).

8.8.2 Good practice points

99. We recommend all patients should have the option of treatment, and have the pros and cons of opting for initiation of treatment and of deferring treatment discussed with them.
100. We suggest for patients with non-cirrhotic disease there is the option to defer treatment until newer therapies or a suitable trial become available.
101. We recommend those deferring treatment are monitored by non-invasive tests at least annually and if they have confirmed progression of fibrosis are reconsidered for initiation of therapy.

8.8.3 Auditable outcomes

- see Section 8.9.2

8.9 Antiviral treatment: other genotypes

8.9.1 Good practice points

102. We suggest for patients with genotype 4 infection without cirrhosis, there is the option to defer treatment until newer therapies or a suitable clinical trial become available.
103. We recommend if treatment is given now, this should be with pegylated interferon and ribavirin. The duration of therapy should be 48 weeks if RVR is achieved. If the RNA is still detectable at 12 weeks, consideration should be given to discontinuing treatment.
104. For those with previous treatment failure, we recommend waiting for the availability of interferon-sparing regimens with active DAAs.
105. We recommend individuals coinfecting with non-genotype 1–4 should be seen at a tertiary referral centre to determine treatment suitability, nature and duration and a treatment plan made in consultation with the referring hospital.

8.9.2 Auditable outcomes

- *Proportion of patients treated outside of clinical trials for non-genotype 1 who receive therapy with pegylated interferon and ribavirin*
- *Proportion of patients treated for non-genotype 1 with a Metavir score of F4 who are offered treatment with pegylated interferon and ribavirin unless contraindicated*
- *Proportion of patients with non-genotype 1–4 referred to a tertiary centre*
- *Proportion of patients not receiving therapy undergoing repeat non-invasive staging of their liver disease within 1 year*

8.10 Acute hepatitis C

8.10.1 Recommendations

106. We recommend patients without a decrease of 2 log₁₀ in HCV RNA at week 4 post diagnosis of acute infection (1D) or with a positive HCV RNA week 12 post diagnosis of acute infection (1C) are offered therapy.
107. We recommend therapy be commenced prior to an estimated duration of infection of 24 weeks (1D). Patients who have not commenced treatment by this time should be managed as for chronic hepatitis C.
108. We recommend all patients be offered combination therapy with pegylated interferon and weight-based ribavirin (1C). We recommend against treatment with PEG-IFN monotherapy (1C).
109. We recommend treatment is discontinued if patients do not achieve an EVR (1C).
110. We recommend patients with re-emergent virus after spontaneous or therapeutic clearance are assessed for relapse or reinfection (1C).
111. We recommend patients with AHC who relapse are managed as for chronic hepatitis C (1D).
112. We recommend patients who have been re-infected are managed as for AHC (1D).

8.10.2 Good practice points

113. We recommend patients are treated for 24 weeks if RVR is achieved and for 48 weeks if RVR is not achieved.
114. We recommend patients are managed as for chronic hepatitis C where treatment fails.
115. We recommend patients who achieve an undetectable HCV RNA without therapy undergo HCV RNA measurements at 4, 12, 24 and 48 weeks to ensure spontaneous clearance.

8.10.3 Auditable outcomes

- *Proportion of patients who fail to achieve a decrease of 2 log₁₀ in HCV RNA at week 4 post diagnosis of acute infection or with a positive HCV RNA week 12 post diagnosis of acute infection offered therapy*
- *Proportion of patients who are treated for AHC given 24 weeks of pegylated interferon and ribavirin*

9 Hepatitis E

9.1 Recommendations

116. We recommend against routine screening for HEV in HIV-infected patients (1C).
117. We recommend HEV infection is excluded in patients with HIV infection with elevated liver transaminases and/or liver cirrhosis when other causes have been excluded (1D).
118. We suggest the detection of HEV in HIV infection should not rely on the presence of anti-HEV when the CD4 count is <200 cells/ μ L since this may be undetectable and exclusion of HEV should rely on the absence of HEV RNA in the serum as measured by PCR (2C).
119. We suggest acute HEV in the context of HIV does not require treatment (2C).
120. We suggest that patients with confirmed chronic HEV coinfection (RNA positive for more than 6 months) receive optimised ART to restore natural HEV antiviral immunity and suggest if HEV-PCR remains positive this is followed by oral ribavirin (2C).

9.2 Auditable outcome

- *Proportion of patients with elevated liver transaminases and/or liver cirrhosis who are screened for HEV infection*

10 End stage liver disease

10.1.1 Recommendations

121. We recommend screening for and subsequent management of complications of cirrhosis and portal hypertension in accordance with national guidelines on the management of liver disease (1A).
122. We recommend HCC screening with 6-monthly ultrasound (1A) and suggest 6-monthly serum alpha-fetoprotein (AFP) (2C) should be offered to all cirrhotic patients with HBV/HIV and HCV/HIV infection.

10.1.2 Good practice points

123. We recommend cirrhotic patients with chronic viral hepatitis and HIV infection should be managed jointly with hepatologists or gastroenterologists with knowledge of end-stage liver disease, preferably within a specialist coinfection clinic.
124. We suggest all non-cirrhotic patients with HBV/HIV infection should be screened for HCC six monthly.
125. We recommend all patients with hepatitis virus/HIV infection with cirrhosis should be referred early, and no later than after first decompensation, to be assessed for liver transplantation.
126. We recommend eligibility for transplantation should be assessed at a transplant centre and in accordance with published guidelines for transplantation of HIV-infected individuals.

10.1.3 Auditable outcomes

- *Proportion of patients undergoing objective liver staging assessment to identify the risk for/likelihood of cirrhosis*
 - *Proportion of patients with likely cirrhosis undergoing 6 monthly US examination to exclude HCC*
 - *Proportion of patients with cirrhosis or evidence of portal hypertension undergoing upper GI endoscopy*
-

3 Patient involvement in care

3.1 Introduction

BHIVA views the involvement of patient and community representatives in the guideline development process as essential. The Writing Group includes a patient representative appointed through the UK HIV Community Advisory Board (UK-CAB) who was involved in all aspects of the guideline development process.

3.2 Good practice points

- We recommend all adults with viral hepatitis and HIV infection are given the opportunity to be actively involved in making decisions about their treatment.
- We recommend all adults with viral hepatitis and HIV infection should have access to psychosocial support at all times.
- We recommend provision of treatment-support resources should include in-house, independent and community information providers and peer-support resources.
- We recommend that all adults with viral hepatitis and HIV infection are offered a copy of the clinic letters and are encouraged to discuss their diagnosis and care with their primary care physician.

3.3 Auditable outcome

- Proportion of adults with viral hepatitis and HIV infection with documentation in the case records who have been given the opportunity to be involved in making decisions about their treatment

3.4 Rationale

Studies that have evaluated patient perspectives on ART therapy in HIV have shown that trust, a good-quality relationship, and good communication skills between doctor and patient are associated with better adherence and treatment outcomes [1–5]. Also, adherence is affected by patient beliefs about the necessity, efficacy and side effects of treatment, the practicability of taking it, and their ability to adhere to therapy [6–9]. Before starting ART or anti-hepatitis treatments in adults with coinfection, clinicians should consider the factors outlined in Box 3.1.

Community advocacy and peer support are helpful in supporting and educating patients in their understanding of ART and anti-hepatitis therapy and guide the patient in treatment decisions. Working in collaboration with healthcare professionals, community organisations in the UK have been instrumental in providing a range of patient information resources and peer-support services for both

Box 3.1

Patients' readiness to take therapy

Their knowledge of the mode of action and efficacy of the treatments and perceptions of their personal need for treatment
 Concerns about taking treatment, including potential adverse effects and drug–drug interactions
 Concerns with possible adverse social consequences, such as disclosure or interference with lifestyle
 Their confidence that they will be able to adhere to the medication (self-efficacy) and the increased frequency of hospital appointments and venesections if required
 Psychological or neurocognitive issues that could impact on adherence
 Their understanding of the pros and cons of opting for initiation of HCV treatment and deferring treatment discussed with them
 Their understanding of the chances of success and failure of therapy and for HCV, when treatment might be discontinued
 Socio-economic factors that could impact on adherence, including, but not limited to, poverty, housing, immigration status or domestic violence

hepatitis and HIV. These include published and web-based information materials, telephone advice lines, treatment advocates and peer-support groups. They are an important and essential adjunct to clinic-based services.

A number of patient factors may affect adherence, adverse effects and treatment outcomes for both ART and anti-hepatitis treatments. Depression, alcohol and recreational drugs are associated with poor ART adherence [10–13] and provision of social support has been shown to influence experience and reporting of adverse events in hepatitis C treatment [14]. Patients should be screened for mental health illness in the clinic (particularly depression) including specific enquiry about alcohol and recreational drug use with the offer of support to moderate or manage it [15,16]. In addition, clinicians should be aware of each patient's socio-economic status and refer to social support where necessary, as this has been shown to have a direct effect on treatment adherence and other healthcare behaviours. Practical issues such as financial and transport support for the increased number of clinic visits necessary when undergoing treatment for HCV is also important to assess prior to initiation of treatment.

Improved ART adherence has been associated with positive experiences of quality of life such as having a meaningful life, feeling comfortable and well cared for, using time wisely, and taking time for important things [17]. Patient self-management skills and courses that facilitate this have been associated with both improved adherence and better clinical outcomes in a number of studies [18–20] and it may be helpful to inform patients of these and other psychological support options which are locally available in line with the BPS/BHIVA *Standards for Psychological Support for Adults Living with HIV* [21].

Clinicians should establish what level of involvement the patient would like and tailor their consultation style appropriately. They should also consider how to make information accessible and understandable to patients (e.g., with pictures, symbols, large print and different languages) [22], including linguistic and cultural issues. Youth is consistently associated with lower adherence to ART, loss to follow-up, and other negative healthcare behaviours [23] and some studies have found an independent association between poorer adherence and attendance and female gender [24], so information and consultation style should be age and gender appropriate for the patient. Neurocognitive impairment is more common in adults with HCV/HIV infection, and clinical assessment should be made prior to treatment. If there is a question about the patient's capacity to make an informed decision, this should be assessed using the principles in the Mental Capacity Act 2005 [25].

Patients presenting at the clinic may be at different stages of readiness to take ART therapy [26] and the clinician's first task is to assess their readiness, by means of open questions rather than closed, before supporting and furthering patients' decisions on therapy. The benefits of treating HCV or HIV first and of treating HCV now or deferring in the absence of significant liver disease require careful explanation and, where there is clinical equipoise, patients should be given the necessary time and assistance to make a decision. However, if a patient presents in circumstances that necessitate starting ART or HCV treatment urgently, then doctors should explain the reasons carefully and provide regular support for the patient's adherence, especially through the first few weeks. Recognising and appropriately managing symptoms that can be attributed to ART or HCV treatment side effects might avoid loss of adherence and deterioration of trust in the patient-provider relationship [27,28]. This will be especially important when initiating anti-HCV treatment because of the increased likelihood of side effects, hospital visits, and venepunctures; contact details for the treatment unit should be provided.

Supporting patients requires good communication not just between clinician and patient but also between all

healthcare staff involved with their care, including those in their HIV and hepatitis services, their GP, and any clinicians involved in management of further conditions. Patients should be offered copies of letters about them sent to their primary care doctor (GP) and other physicians. The advantages of disclosure of their conditions to the patient's GP should be discussed and considered best practice, as several situations require consensual clinical decision-making. A patient's decision not to disclose to their GP, one or more of their conditions, however, should always be respected, subject to the clinician's duty to protect vulnerable individuals.

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4 Screening, prevention and immunisation

4.1 Introduction

The following recommendations concern the prevention of, and screening for, viral hepatitis in the context of HIV, including immunisation and sexual/injection drug use (IDU) behaviour modification to reduce transmission and progression. For the assessment and evaluation of evidence, priority questions were agreed and outcomes were ranked (critical, important and not important) by members of the Writing Group. Two key questions were identified by the Writing Group in relation to acute HCV diagnosis: i) should screening be performed for HCV in adults with HIV infection 6 monthly or 12 monthly; and ii) should the screening test be HCV antibody, HCV-PCR or HCV antigen (critical outcomes: missed HCV cases, cost and transmission rates). A further key question was whether liver biopsy or hepatic elastometry is the investigation of choice in the assessment of fibrosis (critical outcome: distinction of mild/normal disease *vs.* established fibrosis, distinction of cirrhosis from no cirrhosis, adverse effects, cost and patient satisfaction). Details of the search strategy and literature review are contained in Appendix 2.

4.2 Screening investigations at diagnosis

4.2.1 Recommendations

- We recommend patients with HIV infection should be screened at diagnosis for immunity against hepatitis A (1A).
- We recommend patients with HIV infection should be screened at diagnosis for hepatitis B using HBsAg and anti-HBc (1B) and for HBV immunity using anti-HBs.
- We recommend individuals who are HBsAg negative or have no evidence of protective vaccine-induced immunity should have an annual HBsAg test or more frequent testing if there are known and ongoing risk factors for HBV acquisition (1B).
- We suggest patients with isolated anti-HBc (negative HBsAg and anti-HBs) and unexplained elevated transaminases should have HBV DNA performed to exclude the presence of occult HBV infection (2C).
- We suggest testing patients for HBV DNA when transaminases are persistently raised and all other tests (including HBsAg, HCV RNA and anti-HEV) are negative to exclude occult HBV infection (2C).

- We recommend HDV antibody (with HDV RNA if positive) should be performed on all HBsAg-positive individuals (1B).
- We recommend patients have an HCV antibody test when first tested HIV antibody positive and at least annually if they do not fall into one of the risk groups that require increased frequency of testing (1C) (see Section 8).
- We recommend patients with HIV infection who have elevated transaminases of unknown cause have an HCV-PCR test (1A).
- We recommend all patients who are anti-HCV positive are tested for HCV-PCR and, if positive, genotype (1B).
- We suggest that *IL28B* genotyping need not be performed routinely when considering anti-HCV therapy in HCV/HIV infection (2C).
- We recommend individuals who achieved SVR following treatment or who have spontaneously cleared HCV infection should be offered annual HCV-PCR and more frequent testing should they have an unexplained rise in transaminase levels (1C) (see Section 8).
- We recommend HEV is excluded in patients with HIV infection and elevated liver transaminases and/or liver cirrhosis when other common causes of elevated transaminases have been excluded (1D).

4.2.2 Good practice points

Counselling on behaviour modification

- We recommend all patients should be counselled about using condoms for penetrative sex.
- We recommend information should be given on factors associated with HCV transmission to patients at HIV diagnosis and on an ongoing basis dependent on risk.
- We recommend risk reduction advice and education be given to patients diagnosed with HBV and HCV, and should incorporate information about potential risk factors for transmission. For HCV, this should include mucosally traumatic sexual practices (e.g., fisting, use of sex toys), group sex activities, recreational including intravenous drug use, and condomless anal intercourse, as well as advice to those sharing injecting drug equipment.

4.2.3 Auditable outcomes

- Proportion of adults with newly diagnosed HIV screened for immunity to hepatitis A and hepatitis B (anti-HBc, anti-HBs)

- Proportion of adults with newly diagnosed HIV screened for infection with HBV (HBsAg) and HCV (anti-HCV)
- Proportion of HIV-positive adults with anti-HBs < 10 IU/L screened annually for HBsAg
- Proportion of HIV-positive, anti-HCV-negative patients screened at least annually for HCV
- Proportion of anti-HCV positive patients tested for HCV RNA and, where positive, HCV genotype
- Proportion of patients with chronic HCV/HIV with documented counselling regarding HCV transmission risk factors and safe sex
- Proportion of patients with treatment-induced or spontaneous clearance of HCV RNA screened at least annually for HCV by RNA testing

4.2.4 Rationale

Screening for viral hepatitis infection has been shown to be deficient in HIV-infected populations with a failure to test at both diagnosis and annually reported in a number of studies, including a recent BHIVA audit [1,2], despite recommendations to do so within guidelines [3–5].

Hepatitis A is often sexually transmitted in MSM and is linked to oral–genital contact. It is a vaccine-preventable disease and HIV-infected individuals should be screened for immunity and vaccinated if non-immune. Persistent hepatitis B virus (HBV) infection is associated with chronic progressive liver disease including hepatocellular cancer (HCC). HBV exists as 10 major genotypes (A–J) with a geographic distribution such that an HBV-infected individual's genotype will generally reflect the dominant genotype of their country of birth [6]. There is evidence that genotypes display different phenotypic expression of chronic disease [7], and genotype testing may have value in predicting outcome if treatment with pegylated interferon (PEG-IFN) [8,9] is being considered [10], although this is no longer recommended in HBV-mono-infection [11] (see Section 6). Chronic persistence of HBV is defined as the presence of HBsAg in serum for more than 6 months. The prevalence of detectable HBsAg in HIV patients in a recent study from the UK collaborative HIV cohort (UK CHIC) was 6.9%. Factors associated with a positive HBsAg test in this study were being of Black/other ethnicity, having a history of IDU, or self-reporting as MSM when compared to heterosexuals. This study revealed an incidence rate of HBV infection of 1.7 cases per 100 person-years of follow-up with acute infection leading to persistent hepatitis B infection in 16.5% of cases. The risk of incident HBV infection was higher for IDU than for MSM and higher for MSM than for heterosexuals [12].

Isolated anti-HBc in the absence of other markers of HBV infection (HBsAg) or immunity (anti-HBs and anti-HBe) is a common finding in the setting of HIV infection. The finding of isolated anti-HBc may reflect either a past HBV infection followed by loss of anti-HBs due to immune dysfunction or a false positive result. HBV vaccination has been used to discriminate between the two scenarios (see Section 4.4.3). A less likely scenario is a recent acute infection after loss of HBsAg and before appearance of anti-HBs (anti-HBc IgM will be positive). Development of anti-HBs occurs in approximately 20–40% of patients with isolated anti-HBc over time, and is predicted by use of ART and increasing CD4 cell counts, but not by receipt of drugs with activity against HBV or self-reported HBV vaccination [13,14]. These data support the view that a proportion of HIV-infected patients with isolated anti-HBc have prior HBV infection with anti-HBs that is at an undetectable level due to immune dysfunction. The observed long-term persistence of anti-HBc is not consistent with a false positive result. Those with HCV viraemia are more likely to retain isolated anti-HBc serologic status, possibly reflecting HCV-induced dysfunctional antibody production [15–18].

Testing for anti-HBc IgM is recommended to exclude a recent infection and can remain positive for up to 2 years after acute infection. Two-to-four percent of those with isolated anti-HBc develop HBsAg positivity during long-term follow-up, which may be an indication of HBV reactivation or newly acquired HBV infection. Vaccination is therefore justified in this setting (see Section 4.4.3).

The prevalence of occult HBV (the detection of usually low level HBV DNA in individuals testing HBsAg negative) varies depending on the definition used, population studied and methodology including sensitivity of the assay [19–24]. Two forms exist: In the first, the levels of HBV DNA are very low and there is no association with clinical outcome; this is simply in the spectrum of 'resolved' HBV infection. The second is observed in individuals who test negative for HBsAg but have high levels of HBV DNA and evidence of liver disease activity (see Section 6).

Coinfection with HCV among those with HIV has emerged as an important cause of morbidity and mortality [25]. Worldwide, HCV transmission remains highest in injection drug users (IDU) with parenteral exposure to blood and blood products through sharing needles, syringes and other equipment [26]. The prevalence of HCV in HIV-positive infected individuals in the UK is reported at 8.9%, with risk of infection being highest in those with a history of IDU or who have received contaminated blood products or are MSM in urban centres where predominately sexual risk factors account for transmission [27].

Sexual transmission has emerged as a major mode of HCV transmission in HIV-infected MSM with associated risk factors including multiple sexual partners, infection with syphilis, gonorrhoea and LGV, insertive anal intercourse and use of douches and enemas [27–29]. In many cases, HCV transmission seems to be related to sex between men who are both HIV positive. Multiple studies from Western Europe, the USA and Australia have documented this epidemic among HIV-infected MSM since 2002 [30–36]. The UK Health Protection Agency (HPA) conducts enhanced surveillance for newly acquired hepatitis C infections in MSM in 22 centres in England, and reported 218 incident HCV infections between 2008 and 2010 with 84% located in the London area [37].

A significant proportion of HIV-infected MSM who are successfully treated for hepatitis C become re-infected with the virus. One series in Amsterdam identified a re-infection rate as high as 25% within 2 years [38] and in a cohort of MSM living in London with a documented primary infection, a reinfection rate of 8.0 per 100 person-years (95% CI 5.7–11.3) was found [39, 40]. Early recognition of acute HCV infection is important as treatment with PEG-IFN and ribavirin (RBV) is more successful in acute when compared with chronic HCV infection. The factors associated with HCV transmission in MSM would seem to be modifiable and potentially amenable to behaviour change interventions and education. To date there have been no RCTs or intervention studies to reduce transmission of HCV in MSM and this should be an area of research. There is also a need to target interventions to prevent HCV reinfection in MSM in particular when access to the new direct acting antivirals (DAAs) will possibly make treatment more effective and more tolerable.

There is evidence of delayed anti-HCV seroconversion in HIV-infected individuals. In one study median time from detection of HCV RNA to anti-HCV detection was 91 days (range 0–1206 days) with 10% failing to seroconvert after 9 months. A low ALT and low nadir CD4 cell count were associated with a delayed/null anti-HCV response [41].

If individuals are found to be HCV antibody positive, viral load and genotyping measurement should be performed. In keeping with racial differences in the anti-HCV responses to PEG-IFN and RBV, single nucleotide polymorphisms (SNPs) in the vicinity of the *IL28B* locus on chromosome 19 have been found to be associated with the antiviral response [42,43] and spontaneous clearance of HCV in monoinfected populations [44,45]. The C allele at rs12979860 [46] was associated with a favourable response in patients with chronic genotype 1 HCV/HIV infection but less so in those with genotype 2/3 infection or acute HCV [47]. Although the exact mechanism by which this facili-

tates response to exogenous IFN-alpha is yet to be elucidated, there appears to be a favourable influence on early viral kinetics [48]. Whilst the CC genotype is associated with a favourable response to PEG-IFN and ribavirin in patients with genotypes 1 and 4 HCV/HIV infection, other factors including HCV viral load and hepatic fibrosis stage also make significant contributions to SVR [48] and the probability of response to PEG-IFN and RBV may be predicted by using algorithms such as the Prometheus Index [49]. With the advent of DAAs and less reliance on augmentation of the innate immune response by interferon, the influence of *IL28B* SNPs on treatment response and choice and length of therapy will wane [50].

Screening for HDV and HEV are discussed in Sections 7 and 9.

4.3 Assessment of liver disease

4.3.1 Recommendations

- We recommend staging of liver disease should be performed in those with chronic HCV/HIV and HBV/HIV infections (1B).
- We suggest in patients with chronic hepatitis/HIV infection a non-invasive test as the staging investigation of choice (2B).
- We suggest hepatic transient elastography (TE) (FibroScan™ or ARFI [Acoustic Radiation Force Impulse]) as the non-invasive investigation of choice (2B) but if unavailable, or when reliable TE readings are not obtained, a blood panel test (APRI, FIB-4, ELF, Fibrometer™, Forns Index, FibroTest™) as an alternative (2C).
- We recommend in chronically infected viral hepatitis/HIV patients, TE readings suggestive of cirrhosis (Metavir > F4) using recommended disease-specific cut-offs (using FibroScan™ these are > 11.0 kPa for HBV, > 14.5 kPa for HCV), should lead to appropriate monitoring for complications of portal hypertension and HCC screening (1B).
- We recommend in HCV/HIV viraemic patients, repeated fibrosis assessments using TE, or if unavailable an alternative non-invasive blood panel test, should be performed at least annually (1D).

4.3.2 Good practice point

- We recommend when the aetiology of underlying liver disease is in doubt, or where factors other than viral hepatitis are likely to have influenced liver disease progression and may be important to address, or there is discordance between non-invasive markers or uncertainty as to their interpretation, liver biopsy is the investigation of choice for assessment.

4.3.3 Auditable outcomes

- Proportion of patients with chronic HCV/HIV or chronic HBV/HIV with documented staging of liver disease performed at least once before commencing therapy
- Proportion of HIV-positive patients with chronic viral hepatitis and Metavir stage 4 fibrosis who are monitored for complications of portal hypertension and have HCC screening performed
- Proportion of HIV-positive patients with chronic viral hepatitis and who are viraemic having at least annual repeated fibrosis assessments

4.3.4 Rationale

Liver disease staging and grading is essential, not only for antiviral treatment decisions, but also to identify those with advanced fibrosis who will require monitoring for complications of end-stage liver disease (ESLD). Liver disease stage refers to the level of fibrosis, whilst grade refers to the level of necro-inflammation. Liver disease stage in the context of viral hepatitis/HIV infection is an important predictor of progression to ESLD, hepatocellular carcinoma (HCC) and death, whether assessed by liver biopsy [51] or by non-invasive means [52–54]. Traditionally liver biopsy has been the ‘gold standard’ for staging and grading of liver disease. However, there are issues with both patient and physician acceptance, based on perceptions of post and peri-procedural discomfort, the risk of significant complications, contraindications to a percutaneous needle biopsy in some individuals, issues with sampling errors and inter- and intra-observer variations in interpretation of the biopsy [55].

Peripheral blood panels include algorithms that incorporate a number of biochemical or haematological blood tests that are direct measures of enzymes and processes involved in the collagen matrix turnover and/or fibrogenic cell changes, or indirect measures of liver function and inflammation. Many of these panels include tests that are not routinely available in the majority of hospital laboratories and are commercialised. Of the non-commercial tests, the AST to platelet ratio index (APRI) is the most widely used and easiest to calculate using readily available tests, and provides an accurate assessment of fibrosis and cirrhosis in HCV mono-infection. In a recent analysis, APRI was more accurate in patients with HCV mono-infection than in HIV/HCV infection in the identification of significant fibrosis (AUROC: 0.79 *vs.* 0.75), severe fibrosis (AUROC: 0.80 *vs.* 0.76) and cirrhosis (AUROC: 0.83 *vs.* 0.79) [56]. In a separate study, an APRI > 2 demonstrated a negative predictive value of > 97% in excluding cirrhosis [57]; the results for FIB-4 are similar [58]. Both tests can be considered accu-

rate in identifying those with cirrhosis (AUROC > 0.80), but are less successful than in HCV mono-infection in the identification of significant and severe fibrosis (AUROC < 0.80) [56]. The Forns Index has been validated in HCV/HIV infection [58] and has a high degree of concordance with transient elastography in the identification of advanced fibrosis/cirrhosis. Of the commercially available tests, Fibrometer and FibroTest have both been validated in the HIV coinfection settings and perform well in terms of identification of significant fibrosis (AUROC 0.85 and 0.82 respectively) [59]. The European Liver Fibrosis (ELF) test has been shown to predict overall mortality in HIV/HCV infection, after adjusting for HIV-associated factors, and performs better than APRI and FIB-4 in this regard [60].

Hepatic transient elastography (TE) has become the non-invasive investigation of choice in patients with hepatitis virus/HIV infection. Two ultrasound-based methods (FibroScan and ARFI [Acoustic Radiation Force Impulse]) are effective in the non-invasive assessment of liver fibrosis and are accurate in identifying those with significant fibrosis. Liver fibrosis scores assessed by TE outperform blood panels (APRI, Forns index and FIB-4) at all stages of fibrosis in HIV/HCV infection [61]. TE has good positive and negative predictive values in identifying cirrhosis with recommended disease-specific cut-offs using FibroScan™ of > 11.0 kPa for HBV and > 14.5 kPa for HCV based on meta-analyses. However, it performs less well in separating earlier stages of fibrosis [62]. Optimal cut-offs for different stages of fibrosis in chronic HCV/HIV infection are yet to be defined. In terms of clinically relevant fibrosis (\geq F2 Metavir), an optimal cut-off between 7.2 and 7.7 kPa has been suggested [62–64]. However, at these cut-offs both positive and negative predictive values are less than 100%. Correctly identifying cirrhosis is less problematic, but the issue of disease-specific cut-off values must be borne in mind [66]. AUROCs for the prediction of cirrhosis by TE are consistently high and therefore patients identified as having cirrhosis by TE should proceed to appropriate monitoring for associated complications. Thus, where it is felt important to accurately differentiate between the non-cirrhotic stages of liver disease, for instance where this may affect initiation of therapy, a second corroborative test, either a blood panel or liver biopsy, should be performed [63]. Where there is non-concordance between TE and a blood panel test, a liver biopsy is indicated [65].

4.4 Immunisation

4.4.1 Recommendations

- We recommend all non-immune HIV-infected individuals are immunised against HAV and HBV (1A).

- We recommend the 40 µg (double dose **with most vaccines**) strength of HBV vaccine should be used in HIV-infected patients (1A) and given at months 0, 1, 2 and 6 (1B).
- We suggest an accelerated vaccination schedule (three single [20 µg] doses given over 3 weeks at 0, 7–10 and 21 days) be considered only in selected patients with CD4 counts > 500 cells/µL where there is an imperative need to ensure rapid completion of vaccination and/or where compliance with a full course is doubtful (2B).
- We recommend anti-HBs levels should be measured 4–8 weeks after the last vaccine dose (1B). Vaccine recipients with anti-HBs < 10 IU/L should be offered three further 40 µg doses of vaccine, given at monthly intervals with retesting of anti-HBs recommended 4–8 weeks after the final vaccine dose (2B).
- We suggest vaccine recipients with an anti-HBs response > 10 but < 100 IU/L should be offered one additional 40 µg dose of vaccine and the response checked 4–8 weeks later (2B).
- We recommend a booster (40 µg) dose of vaccine should be offered to those whose anti-HBs levels have declined to < 10 IU/L (1C).

4.4.2 Good practice points

- We recommend patients who are unable to develop an antibody response to vaccine or in whom anti-HBs levels have fallen below 10 IU/L continue to be screened for HBsAg as there remains a risk of infection.
- We recommend following successful immunisation, the anti-HBs level should be measured regularly. The frequency of screening for anti-HBs should be guided by the anti-HBs level measured after vaccination: every year for levels between 10 IU/L and 100 IU/L and every 2 years for higher levels.

4.4.3 Auditable outcomes

- Proportion of HAV and HBV non-immune patients who are immunised
- Proportion with anti-HBs levels < 10 IU/L post-primary vaccination offered three further 40 µg doses at one-month intervals
- Proportion with anti-HBs levels between 10–100 IU/L post-primary course of vaccine offered one further 40 µg dose of vaccine
- Proportion with successful HBV immunisation receiving annual or bi-annual anti-HBs screening
- Proportion following successful HBV vaccination receiving a booster dose of vaccine when anti-HBs levels fall below 10 IU/L

4.4.4 Rationale

In a systematic review and meta-analysis of five studies, an increased-dose HBV vaccination schedule improved anti-HBs response rates compared to standard-dose HBV vaccination (OR 1.96; 95% CI: 1.47, 2.61) with separate randomised trial data demonstrating improved serological response with four-dose regimens [67–71]. An accelerated course (three doses given at 0, 1 and 3 weeks) of low-dose vaccine was non-inferior to a standard course (three doses given at months 0, 1 and 6) only in those with CD4 counts above 500 cells/µL with no data existing for a similar schedule using **high-dose** vaccine [72]. Therefore **high-dose** (40 µg) vaccine is recommended with a schedule of 0, 1, 2 and 6 months. Only in selected patients with CD4 counts > 500 cells/µL, where there is a need to ensure rapid completion of vaccination, and/or where compliance with completion of the vaccination schedule is doubtful, should a more rapid course be considered. In patients with detectable HIV RNA and/or low CD4 cell counts, a proportion of those immunised will seroconvert. In those who do not respond, depending on the level of risk, it may be appropriate to delay re-vaccination until the HIV RNA is suppressed and the CD4 cell count has increased with ART.

The effectiveness of vaccination depends on the immune response achieved. One study found that among 409 vaccinees with an anti-HBs level less than 10 IU/L, 46 (11.2%) developed HBV infection compared with 11 of 217 (5.1%) vaccinees with an anti-HBs level greater than 10 IU/L (HR 0.51; 95% CI: 0.3, 1.0). In those with an anti-HBs level less than 10 IU/L, 16 of the 46 (35%) infections progressed to become chronic, compared with none of the 11 whose initial anti-HBs level was greater than 10 IU/L ($p = 0.02$) [73]. This emphasises the importance of measuring anti-HBs levels ideally 4–8 weeks post completion of the vaccination course and re-immunising with three 40 µg doses of vaccine in those whose anti-HBs level remains less than 10 IU/L, which should be administered at monthly intervals.

Anti-HBs levels at week 28 post vaccination are predictive of the durability of an appropriate anti-HBs response. In a cohort study of 155 patients, the mean time to loss of anti-HBs was 2.0, 3.7 and 4.4 years respectively, for patients with an anti-HBs titre of 10–100 IU/L, > 100–1000 IU/L and > 1000 IU/L. Therefore schedules to improve the vaccination response in HIV-infected individuals are needed [74]. Anti-HBs monitoring should occur annually in those with initial responses between 10 and 100 IU/L and every 2 years for those with a higher response. Those with isolated anti-HBc should be given a single dose of HBV vaccine to discriminate between those with a true past HBV infection followed by loss of anti-HBs due to immune dysfunction [75,76] and those with a false positive result.

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5 Antiretroviral therapy

5.1 Introduction

The following recommendations concern ART toxicity in the context of viral hepatitis/HIV infection, particularly HCV. For the assessment and evaluation of evidence, priority questions were agreed and outcomes ranked (critical, important and not important) by members of the Writing Group. One key question was identified by the Writing Group: when deciding ART for adults with HCV/HIV infection, is there a preferred combination which differs from those with HIV mono-infection (critical outcome: severe adverse events, grade 3/4 treatment-associated hepatitis, and HIV viral suppression <50 copies/mL). Treatments were compared where data were available and differences in outcomes assessed. Details of the search strategy and literature review are contained in Appendix 2.

5.1.1 Recommendations

- We recommend ARV choice should take into consideration pre-existing liver disease but ART should not be delayed because of a risk of drug-induced liver injury (1B).
- We suggest ART should be used with close monitoring in patients with ESLD (Child-Pugh B/C) and consideration given to performing plasma level monitoring of ART agents (2C), particularly for the case where ritonavir-boosted PIs and NNRTIs are used.
- We suggest when abacavir is prescribed with ribavirin, the ribavirin should be weight-based dose-adjusted (2C).

5.1.2 Good practice points

- We recommend initiation of ART be considered in all viral hepatitis coinfecting patients irrespective of CD4 cell count.
- We recommend patients should have baseline transaminases checked before initiating a new ARV and that this is followed by routine monitoring after 1 month, and then every 3–6 months.
- We recommend where DAAs are used for the treatment of HCV, careful consideration be given to potential drug-drug interactions (DDIs).
- We recommend ART should be discontinued if grade 4 hepatotoxicity (transaminases >10 times upper limit of normal) develops, even if the patient is asymptomatic.

5.1.3 Auditable outcome

- Proportion of patients with baseline transaminase checked before and one month after starting a new ARV

5.1.4 Rationale

Liver toxicity is one of the commonest serious adverse events associated with ART. In retrospective studies of patients receiving early ART regimens, the incidence of ART-related severe hepatotoxicity was approximately 10%, and life-threatening events occurred at a rate of 2.6 per 100 person-years [1,2]. All antiretrovirals have the potential to cause acute and long-term drug-related liver injury, which is a common cause of morbidity and treatment discontinuation in persons with HIV infection. The risk is increased in hepatitis coinfection [3–5] and for HCV, reduced if successfully treated [6]. Attention should be given to addressing predisposing conditions or potentially modifiable risk factors to antiretroviral-induced hepatotoxicity, including alcohol and cocaine use and non-ART-related medication toxicity as part of choosing ART [7]. Patients should be educated prior to ART initiation as to possible adverse effects including hypersensitivity reactions.

Abnormal LFTs need careful interpretation and an alternative cause for liver injury should always be considered, including other prescribed or non-prescribed drugs, viral hepatitis, alcohol and other toxins. A raised bilirubin may reflect an increase in unconjugated bilirubin from atazanavir; an increase in transaminases may result from withdrawal of antivirals in HBV; and any underlying liver disease may result in patterns of LFTs simulating liver ARV-related toxicity. Severity of ARV-related hepatotoxicity may range from a subclinical mild derangement which resolves spontaneously to fulminant hepatitis with acute liver failure. Mechanisms include hypersensitivity (e.g., with nevirapine, other NNRTIs, darunavir and fosamprenavir) where concomitant rash may occur, mitochondrial toxicity and steatosis (e.g., with d4T, ddI and ZDV), and direct hepatic toxicity (e.g., with ddI and tipranavir) [2,4]. The greatest risk of ARV-induced hepatotoxicity is observed in those with advanced liver disease. Didanosine (ddI), stavudine (d4T) and ritonavir-boosted tipranavir should be avoided and zidovudine (ZDV) only used in the absence of an alternative option [8–11]; nevirapine should be used with caution. In addition, didanosine is associated with non-cirrhotic portal

hypertension [12]. Some retrospective studies have shown abacavir to be associated with a decreased response to PEG-IFN/RBV therapy in patients treated for HCV genotype 1 infection, possibly due to intracellular reductions in ribavirin level (see Section 8). Several factors (use of non-weight-based RBV dosing and differential baseline HCV viral loads) have made these data difficult to interpret and the findings have recently been disputed [13]. Nevertheless, we advise when abacavir is to be used, ribavirin should be dosed ≥ 1000 mg or ≥ 13.2 mg/kg [14–16].

Individuals may develop immune restoration on initiation of ART and need to be carefully monitored for hepatotoxicity when ART is commenced or changed [17,18]. See Sections 6 and 8 for recommendations on ARV use when treating HBV and HCV coinfection. In addition, when DAAs are chosen, there are restrictions on choice of first-line ARV due to drug-drug interactions [19–23].

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6 Hepatitis B (HBV)

6.1 Introduction

The following recommendations concern the management of patients with HBV/HIV infection. This includes the utility of laboratory investigations and management strategies for patients with HIV who develop acute HBV infection, as well as those with chronic HBV/HIV infection with CD4 cell counts both above and below the threshold where ART is recommended for treatment of HIV alone. For the assessment and evaluation of evidence, priority questions were agreed and outcomes were ranked (critical, important and not important) by members of the Writing Group.

Three key questions were identified by the Writing Group. For deciding on when is the optimum time to commence ART in adults with chronic HBV/HIV infection, the following were ranked as critical outcomes: mortality, HBV disease progression (cirrhosis, HCC), response to ART (HIV viral load <50 copies/mL, CD4 cell count increase), and severe treatment-associated adverse events. For deciding on which is the anti-HBV treatment of choice when the CD4 count is >500 cells/ μ L, the following were regarded as critical outcomes: mortality, HIV disease progression, HBV disease progression (cirrhosis, HCC), HBV DNA decline on therapy, severe treatment-associated adverse events and patient acceptability. For deciding whether FTC or 3TC should be used in combination with tenofovir, the following were regarded as critical outcomes: HBV DNA decline on therapy, cost and adverse events. Treatments were compared where data were available and differences in outcomes assessed. Details of the search strategy and literature review are contained in Appendix 2.

6.1.1 Natural history

There are approximately 240 million individuals with HBsAg-positive hepatitis B (HBV) infection globally compared to an estimated 33.1 million with HIV infection [1]. The prevalence of HBV is related to patient characteristics, with the shared global endemicity and risks for transmission of both HIV and HBV resulting in a high prevalence of coinfection. An estimated 6.9% of adults with HIV infection in the UK have evidence of HBsAg positivity, with those of Black or other ethnicity and those with a history of injection drug use (IDU) having the highest prevalence. In some European cohorts the overall prevalence is slightly higher. Incidence of new HBV infection in patients with HIV infection is estimated at 1.7 cases per 100 years of follow-up in the UK [2].

In the HIV non-infected, chronic HBV infection is classified into different stages, which are not necessarily sequential (see Box 6.1 and Table 6.1). These distinguish between the level of viral replication and the extent of immunopathology. Whilst the validity of such classifications is not well established in HBV/HIV infection, these distinctions are helpful in framing an understanding of coinfection.

Occult HBV (HBV DNA in the absence of HBsAg) is well recognised, with two forms existing. In the first, levels of HBV DNA are very low and there is no association with clinical outcome, reflecting resolved HBV infection. The second form is seen in those who test HBsAg negative with high levels of HBV DNA and raised transaminases. This has been described especially in African HIV cohorts accessing 3TC as part of ART where drug selective pressure has induced mutations in the overlapping surface gene [3].

Box 6.1 Stages of HBV infection

Type	Description
1	Immune tolerant: HBsAg positive, HBeAg positive, high HBV DNA, normal ALT/AST, little or no necro-inflammation on liver biopsy and no or slow progression of fibrosis. Generally seen in those infected vertically or in early childhood as a transient phase before the onset of the immune-active phase.
2	Immune active: HBsAg positive, HBeAg positive, high HBV DNA, raised ALT/AST, progressive necro-inflammation and fibrosis. Generally seen in those infected as older children or adults.
3	Inactive hepatitis B immune control: HBsAg positive, HBeAg negative usually with anti-HBe, persistently undetectable or very low levels of HBV DNA, and persistently normal transaminases after at least 1 year of monitoring every 3–4 months.
4	HBeAg-negative chronic active hepatitis: HBsAg positive, HBeAg negative usually with anti-HBe, fluctuating HBV DNA and ALT/AST levels, progressive necro-inflammation and fibrosis. Patients harbour HBV strains with mutations in the pre-core, core promoter region, which markedly reduce HBeAg production.

Table 6.1 Patient populations in chronic HBV

Marker	Immune tolerant (type 1)	Immune active (type 2)	Immune control (type 3)	HBeAg-negative CHB (precore/core promoter mutant) (type 4)
HBsAg	+	+	+	+
HBeAg	+	+	-	-
Anti-HBe	-	-	+	+
ALT	Normal	↑	Normal	↑
HBV DNA (IU/mL)	$>2 \times 10^4$	$>2 \times 10^4$	$<2 \times 10^4$	$>2 \times 10^4$
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.

There is no obvious impact of HBV on HIV disease and responses to anti-HIV treatment. By contrast, HIV has an impact on HBV infection, affecting all phases of the natural history of adult-acquired hepatitis. Patients living with HIV who are infected with HBV are more likely to progress to chronic HBV infection [4,5], demonstrate a reduction in the rate of natural clearance of HBeAg, and have a higher HBV viral load than those with HBV monoinfection [6,7]. In HIV-non-infected populations, high HBV viral load (VL) is associated with faster disease progression [8] and this is one possible reason why progression to cirrhosis and HCC is more rapid in HBV/HIV infection. In those with either a resolved or controlled hepatitis B infection, HIV-associated immunodeficiency can lead to HBV reactivation [9].

In cohort studies of those with HBV/HIV infection, the relationship between HBV VL and necro-inflammation is complex. In those with a high HBV viral load, although there are lower transaminase levels and milder necro-inflammatory scores, progression to fibrosis and cirrhosis is more rapid. Multiple factors are likely to be involved, including the pro-fibrogenic effect of HIV, drug toxicity, and immune restoration disease on initiation of ART.

In the setting of HIV, the diagnosis of HBV relies on establishing evidence of exposure to the virus and, if present, the extent to which the virus is replicating. Anti-HBc IgG will be present in the majority of those exposed to HBV unless infection is acute, where antibody may be yet to develop or there is advanced immunosuppression. Acute infection is characterised by the presence of HBsAg, HBeAg, high HBV DNA levels and anti-HBc IgM. As anti-HBc IgM can become positive during flares of chronic HBV infection, it cannot be relied upon as the sole indicator of acute infection. Resolving infection is characterised by the loss of HBeAg and development of anti-HBe, the reduction of HBV DNA levels and the eventual loss of HBsAg with the development of anti-HBs. Persistence of HBsAg for longer than 6 months is diagnostic of chronic infection.

Studies indicate that HBsAg levels are predictive of response to both PEG-IFN and nucleoside analogue (NA)

therapy. Quantification of HBsAg is not widely available in routine diagnostic laboratories. Further studies are required to make firm recommendations about the optimal use of HBsAg levels in the setting of HIV infection. HBV DNA assays that have a wide range of quantification should be used, and should be reported in IU/mL.

6.2 HBV resistance, genotype testing and treatment response

6.2.1 Recommendations

- We recommend against HBV resistance testing at baseline in those previously unexposed to antivirals (1C).
- We recommend, where feasible, HBV resistance testing at baseline in those with detectable HBV DNA and previously exposed to antiviral drugs with anti HBV activity if not on treatment, where there is primary non-response or partial response to HBV-active antivirals, or where there is virological breakthrough (1C).
- We recommend against a change in HBV-specific therapy in those whose viraemia continues to show improving response to treatment after 48 weeks (1C).
- We recommend against testing for HBV genotype as an investigation to determine initial treatment (1C).

6.2.2 Good practice point

- We recommend adherence is discussed with all patients with HBV viraemia receiving antivirals.

6.2.3 Rationale

Primary infection with lamivudine-resistant HBV has been detected in HIV populations [10]. The prevalence of mutations at baseline is low [11]. Both major resistance mutations and compensatory mutations have been described [12]. These mutations are not thought to confer resistance to tenofovir and thus baseline genotypic testing is not routinely recommended, whereas it is appropriate in those with treatment experience, especially in those unable to receive tenofovir (Table 6.2). The risk of development of

Table 6.2 Anti-HBV drug resistance mutations

HBV	3TC/FTC	Entecavir	Adefovir	Telbivudine	Tenofovir
WT	S	S	S	S	S
M204V/I	R	I	I	S	S
L180M + M204V	R	S	S	R	S
A181T/V	R	S	R	R	I
N236T	S	S	R	S	I
A181T/V + N236T	R	R	S	S	I/R
L180M + M204V/I + I169T + V173L + M250V	R	R	S	R	S
L180M + M204V/I + T184G + S202I/G	R	R	S	R	S

S, sensitive; I, intermediate resistance; R, resistant.

Box 6.2 Definitions of treatment response to NA therapy:

Primary non-response	<1 log ₁₀ IU/mL drop in HBV DNA at 12 weeks
Virological response	Undetectable HBV DNA using a sensitive assay (threshold 10–20 IU/mL) at 24 weeks
Partial response	Fall of >1 log ₁₀ IU/mL in HBV DNA but not undetectable at 24 weeks
Virological breakthrough	Rise of >1 log ₁₀ IU/mL HBV DNA from nadir level on therapy
Definitions of treatment response to PEG-IFN therapy:	
Primary non-response	Not well defined
Virological response	HBV DNA <2000 IU/mL after 6 months, at the end of therapy, and 6 and 12 months after the end of therapy
Sustained response	HBV DNA <2000 IU/mL at least 12 months after end of therapy

resistance is associated with the HBV DNA level and the type of nucleoside/nucleotide analogue the individual is receiving. In previously untreated patients, the genetic barrier to resistance is low with 3TC, FTC and telbivudine (TBV); low to intermediate with adefovir (ADV); and high with entecavir and tenofovir (TDF). The genetic barrier of entecavir is lowered by previous exposure to 3TC monotherapy. There is potential cross-resistance between ADV and TDF, which is overcome by the greater potency of TDF.

HBV is classified into ten genotypes (A–J) on the basis of divergence of 8% or more in the nucleotide sequence, the most common in the UK being genotype D (31%) [13]. HBV genotyping is not widely utilised in clinical practice. Genotypes do not appear to influence the response to NA therapies, and although in the HIV-negative population differential responses dependent on HBV genotype have been observed with pegylated interferon alpha (PEG-IFN) therapy, it is not recommended as an investigation to determine initial treatment. The effect of genotype on the response to PEG-IFN in the setting of HIV is unclear.

Responses to antiviral therapy are classified as serological, virological, biochemical and histological.

The two serological end-points are: i) loss of HBeAg in those who are HBeAg positive at the start of therapy with development of anti-HBe, and ii) loss of HBsAg with development of anti-HBs.

In HBV/HIV infection, the majority of published data relate to combinations including tenofovir. Patients tend to have high HBV viral loads at baseline and thus take longer to achieve a full virological response [14]. The proportion achieving undetectability is, however, similar in coinfection to mono-infection [15,16]. A change in HBV-specific therapy is not warranted in patients whose viraemia continues to show improving response to treatment after 48 weeks.

In those with non-response or virological breakthrough, it may be difficult to distinguish resistance from poor adherence: in one study 50% of patients with primary non-response were found to have no detectable drug level [17]. A rising HIV viral load will provide a clue to poor adherence [16] and HBV resistance testing may have a role, although an undetectable viral load does not negate suboptimal adherence. Tenofovir resistance has not been clearly described and resistance is unlikely to provide an explanation for most cases of suboptimal responses to tenofovir [17,18].

Clearance of HBeAg in coinfection has been observed in 15–57% of patients, and HBsAg clearance in up to 8–29%, over a 5-year period in some studies [19–21]. These higher rates of antigen clearance than observed in HBV mono-infection are likely to be secondary to immune reconstitution with ART initiation. HBV treatment interruption or cessation is rarely recommended in the setting of HIV. In clinically stable patients, serological monitoring is recommended on an annual basis.

6.3 Thresholds for ART treatment

6.3.1 Recommendations

- We recommend all those with an HBV DNA ≥ 2000 IU/mL should be treated, regardless of fibrosis score (1C).
- We recommend all those with more than minimal fibrosis on liver biopsy (Metavir $\geq F2$ or Ishak $\geq S2$) or indicative of $\geq F2$ by TE (FibroScan ≥ 9.0 kPa) should be treated, regardless of HBV DNA level (1C) (see Section 4).
- We suggest those with a CD4 ≥ 500 cells/ μ L, an HBV DNA of < 2000 IU/mL, minimal or no evidence of fibrosis (Metavir $\leq F1$ or Ishak $\leq S1$ or FibroScan < 6.0 kPa) and a repeatedly normal ALT should be given the option to commence treatment or to be monitored not less than 6-monthly with HBV DNA and ALT and at least yearly for evidence of fibrosis (2C).
- We recommend all patients with a CD4 < 500 cells/ μ L are treated with fully suppressive ART inclusive of anti-HBV-active antivirals (1B).

6.3.2 Good practice points

- We recommend at least two baseline HBV DNA measurements are obtained 3 to 6 months apart to guide initiation of therapy.
- We recommend 6-monthly HBV DNA measurements for routine monitoring of therapy.
- We recommend that an ALT level below the upper limit of normal should not be used to exclude fibrosis or as a reason to defer HBV therapy. Normal levels of ALT should be considered as 30 IU/L for men and 19 IU/L for women.

6.3.3 Auditable outcome

- Proportion of patients with a CD4 ≥ 500 cells/ μ L and an HBV DNA ≥ 2000 IU/mL and/or evidence of more than minimal fibrosis (Metavir $\geq F2$, Ishak $\geq S2$, or TE ≥ 9.0 kPa) commencing ART inclusive of anti-HBV antivirals

6.3.4 Rationale

Central to the optimal management of patients infected with HBV and HIV is the need for adequate assessment of both HBV and HIV status to inform the decision as to whether neither, HBV alone or both viruses require treatment. Recommendations for the patient with HBV mono-infection are generally based on HBV DNA levels, evidence of liver inflammation and degree of fibrosis, and the same is true for those with coinfection. A raised ALT most often reflects HBV-induced inflammation and the need for treatment, although significant liver damage may be present without raised transaminases, especially in the setting of HIV coinfection [7]. Hence, assessment of liver fibrosis by TE or liver biopsy should be performed in all

patients, and will guide decisions including the need for therapy in those with high CD4 cell counts and no HIV indication for ART, the choice of drug treatment, and the need for HCC screening. Liver biopsy may provide additional information on the degree of inflammation and fibrosis and exclude the presence of other pathology.

No RCT evidence exists, and the assessment and recommendations on when to initiate ART are based on theoretical considerations and indirect data: i) observational data demonstrating HBV/HIV infection is associated with a faster rate of fibrosis progression and an increased risk of cirrhosis, ESLD, HCC and liver-related death when compared to HBV mono-infection [7,22–27]. The risk of liver-related mortality and HCC increases as the CD4 cell count declines [28,29] and is reduced by ART inclusive of HBV-active drugs [30,31]; ii) higher levels of HBV DNA are present in coinfection compared with HBV alone and are correlated with the natural history of disease progression [7]; and iii) long-term observational data demonstrate that HBV replication drives fibrosis and that this is unlikely to regress unless HBV is effectively treated. There are preliminary data demonstrating a direct effect of HIV on the fibrogenic process through the binding of gp120 to CCR5 receptors on hepatic stellate cells, the principal fibrogenic cell type in the liver [32,33] which triggers an increased expression of collagen and inflammatory chemokines. Additional data suggest that microbial translocation [34] plays a role in accelerating liver fibrosis through toll-like receptor (TLR) signalling [35] and HIV may have a direct role through suppression of a major transcription factor in fibrogenesis (PPAR γ).

No RCT evidence exists addressing the HBV DNA level at which anti-HBV treatment should be commenced in HBV/HIV-infected individuals. The choice of > 2000 IU/mL is based on indirect data: i) the level of HBV DNA is proportional to the risk of cirrhosis and HCC in observational studies in mono-infection [8,36–39]; ii) the degree of HBV viral suppression achieved during treatment is an important determinant in reducing progression to cirrhosis, liver failure, HCC and need for liver transplantation [8,40]; iii) prolonged low level viraemia may be associated with progressive liver damage in HBV-mono-infection [37] and; iv) levels of HBV DNA 2000–20 000 IU/mL may be associated with a histological indication for treatment.

6.4 Antiviral treatment: CD4 count ≥ 500 cells/ μ L (Algorithm 1)

6.4.1 Recommendations

- We recommend TDF/FTC as part of a fully suppressive ART combination should be given to all patients where HBV treatment is deemed necessary (1C).

- We suggest adefovir or 48 weeks of PEG-IFN are alternative options in patients unwilling or unable to receive TDF/FTC as part of a fully suppressive ART combination but requiring HBV therapy (2C).
- We suggest PEG-IFN is only used in HBsAg-positive patients with a repeatedly raised ALT, low HBV DNA ($<2 \times 10^6$ IU/mL), and minimal fibrosis, irrespective of HBeAg antigen status (2D). Lack of HBV DNA response (reduction to <2000 IU/mL at 12 weeks) should prompt discontinuation. Repeat testing should be performed 3-monthly to observe the presence of seroconversion (2C).

6.4.2 Rationale

Where ART is not indicated for HIV, and the CD4 count is ≥ 500 cells/ μ L, the optimum strategy is uncertain: to use agents with exclusive HBV and no HIV activity (i.e., PEG-IFN and adefovir) so that HIV resistance is not induced, or earlier initiation of ART. Seven drugs are available with HBV activity: pegylated interferon (PEG-IFN), lamivudine (3TC), emtricitabine (FTC), adefovir (ADV), entecavir, telbivudine and tenofovir (TDF). Four have additional HIV activity (3TC, FTC, TDF and entecavir) and two are only active against HBV at licensed doses (PEG-IFN, ADV). There is conflicting evidence on whether telbivudine exerts activity against HIV.

Entecavir and tenofovir are recommended first-line therapies for HBV mono-infection and have demonstrated high efficacy with low rates of resistance and a favourable safety profile. Both are safe in patients with decompensated liver disease. Entecavir demonstrates modest anti-HIV activity and can select for HIV resistance, and thus should not be used in the absence of fully suppressive ART. Telbivudine has greater intrinsic activity than adefovir or 3TC but has not been studied extensively in coinfection. Its efficacy is limited by the development of resistance with cross-resistance to 3TC/FTC but not adefovir [40]. Although decreases in HIV RNA have been observed, no HIV mutations have developed *in vitro* and in small case series but if used as monotherapy, monitoring of HIV viral load and repeat HIV genotyping pre-ART initiation are essential.

There is no RCT or observational evidence that a 12-month course of pegylated interferon or adefovir monotherapy for HBV in coinfecting individuals is as effective as, or more effective than, combination ART [41].

6.4.2.1 Pegylated interferon (PEG-IFN)

Pegylated interferon is effective in the treatment of HBeAg-positive and HBeAg-negative mono-infected patients, does not select resistance for either HBV or HIV, and is an option for the management of HBV/HIV-infected persons when ART is not indicated.

No RCT evidence exists for PEG-IFN in coinfection and the data available are insufficient to identify predictors of response or appropriate candidates for this treatment. In HBV/HIV infection, interferon has been evaluated in small cohorts of patients either alone, with adefovir, or sequentially with tenofovir [42,43]. Therefore recommendations are based on theoretical considerations, minimal cohort and indirect data: i) in treating HBV mono-infection, IFN is most effective in those with a low level of viraemia and elevated transaminases, and therefore may be less useful in those with HIV/HBV infection as both occur less frequently; ii) in several large RCTs for HCV coinfection, PEG-IFN has been associated with lower rates of treatment success and relatively high toxicity; iii) in those with compensated cirrhosis there is a risk of hepatic decompensation and where decompensation exists pre-treatment, interferon-induced acute necro-inflammation may lead to liver failure and; iv) RCT evidence has shown that PEG-IFN is associated with a higher HBeAg seroconversion rate in HBV mono-infection than that reported for adefovir. With standard IFN treatment of HBV in HIV infection, the differentiating factors for response were higher pre-treatment CD4 cell count and higher necro-inflammatory scores on baseline liver biopsy.

In HBeAg-positive disease in HBV mono-infection, those with genotypes A and B have higher response rates than those with genotypes C and D, with higher rates of anti-HBe conversion and HBsAg loss. An HBV DNA fall to $<20\,000$ IU/mL or an HBsAg level fall to <1500 IU/mL at 12 weeks of treatment is a strong predictor of anti-HBe seroconversion in HBeAg-positive disease, whereas failure to achieve a 2 log drop in HBV DNA and no decline in HBsAg level is a strong predictor of subsequent treatment failure in HBeAg-negative patients [44].

6.4.2.2 Adefovir

Adefovir (ADV) has been evaluated in the coinfecting population and is active against wild-type and 3TC-resistant virus, but is less potent than tenofovir [45,46]. At the dose used in HBV treatment (10 mg once daily), it has no effect on HIV replication and thus does not select for HIV resistance mutations [47].

There is no RCT or observational evidence comparing ADV as monotherapy for HBV in coinfecting patients with combination ART for the treatment of hepatitis B. The assessment and recommendations are based on RCT evidence comparing ADV with TDF, theoretical considerations and indirect data: i) in two RCTs evaluating ADV versus TDF for 48 weeks in HBV mono-infection, HBeAg-positive and -negative patients were more likely to achieve an undetectable HBV DNA if receiving TDF. Both drugs displayed similar safety profiles [48]; ii) in a meta-analysis

comparing ADV and TDF, tenofovir was superior to ADV in inhibiting HBV replication in CHB but there was no significant difference in ALT normalisation, HBeAg seroconversion and HBsAg loss rate [49]; and iii) in HBV/HIV infection in patients receiving stable ART, one RCT showed non-inferiority of TDF when compared with ADV, although a greater decline of HBV DNA was observed [15], whereas another study demonstrated that TDF is more effective than ADV in such patients as measured by decline in HBV DNA levels and time to undetectability [46]. Unsuppressed HBV DNA on ADV is associated with higher baseline HBV DNA and a higher rate of the selection of mutations conferring HBV resistance to ADV. In view of these data, we recommend against use of adefovir in those whose CD4 count is >500 cells/ μ L, although in a patient unwilling to take ART and requiring therapy, it remains an option. We recommend individuals treated with adefovir who have suppressed HBV DNA should remain on this agent until the need for ART arises (which should be TDF based).

6.5 Antiviral treatment: CD4 count <500 cells/ μ L (Algorithm 2)

6.5.1 Recommendations

- We recommend TDF/FTC or TDF/3TC as part of a fully suppressive combination ART regimen be used in those with confirmed or presumed sensitive HBV (1C).
- We recommend where tenofovir is not currently being given as a component of ART it should be added or substituted for another agent within the regimen if there is no contraindication (1C).
- We recommend neither 3TC nor FTC be used as the sole active drug against HBV in ART due to the rapid emergence of HBV resistant to these agents (1B).
- We recommend 3TC/FTC may be omitted from the antiretroviral regimen and tenofovir be given as the sole anti-HBV active agent if there is clinical or genotypic evidence of 3TC/FTC-resistant HBV or HIV (1D).
- We recommend that in the presence of wild-type HBV, either FTC or 3TC can be given to patients requiring ART in combination with tenofovir (1B).

6.5.2 Good practice points

- We recommend if patients on suppressive anti-HBV therapy require a switch in their antiretrovirals due to HIV resistance to tenofovir and/or 3TC/FTC, their active anti-HBV therapy (tenofovir with or without 3TC/FTC) should be continued and suitable anti-HIV agents added.

- We recommend if tenofovir is contraindicated, entecavir should be used if retaining activity. Entecavir should only be used in addition to a fully suppressive combination ART regimen.

6.5.3 Auditable outcomes

- Proportion of patients with a CD4 count <500 cells/ μ L receiving TDF/FTC or TDF/3TC as part of a fully suppressive combination ART regimen
- Proportion of patients avoiding 3TC or FTC as the sole active drug against HBV in ART

6.5.4 Rationale

Tenofovir is a nucleotide reverse transcriptase inhibitor with activity against both HIV and HBV [50,51]. There is RCT and observational evidence that tenofovir should be included within ART for HBV coinfection: i) HBV as a cause of end-stage liver disease in coinfecting patients has reduced significantly since the large scale use of tenofovir [30,52,53]; ii) TDF is effective in suppressing HBV replication and reducing DNA viral load in monoinfected and coinfecting persons, whether they are HBeAg positive or negative, and independent of the presence of 3TC resistant virus [54,55], and is also active against some ADV-resistant HBV strains; iii) regression of extensive fibrosis has been demonstrated with use of TDF in coinfection [30]; and iv) a systematic review of RCTs of available HBV antiviral agents in HBV mono-infection demonstrated that TDF had the best results as regards HBV DNA decline, normalisation of ALT and HBeAg seroconversion [56]. Additionally, the majority of patients reach and maintain an undetectable HBV viral load on TDF-based ART, which is correlated with a lower baseline HBV VL and longer duration of treatment. Also: i) high rates of HBeAg seroconversion and HBsAg loss can be achieved; ii) TDF-based ART is effective irrespective of baseline CD4+ cell counts; and iii) switching to TDF-3TC or TDF alone in HBV/HIV-infected patients with HBV resistant to 3TC is effective in achieving suppression of HBV replication.

Combining TDF with either FTC or 3TC provides benefits, with improved HBV DNA level responses. Previous RCT or cohort analyses have not reported the superior efficacy of dual therapy over TDF monotherapy in long-term HBV suppression in coinfection [19,57,58], although this has recently been reported [59] and additionally has been demonstrated in mono-infection for patients in the immune tolerant phase [60]. In a mouse model, TDF/FTC combination therapy provides more effective HBV suppression than therapy with either drug alone [61]. In a small study on antiviral-naïve coinfecting individuals, combining FTC with

tenofovir has been shown to be more effective than FTC alone [62] and in decompensated HBV mono-infection and minimal prior treatment, TDF/FTC was more likely to result in viral suppression than TDF monotherapy [63]. Dual therapy may theoretically protect against the development of resistance and reactivation. Although TDF phenotypic resistance has not been documented in coinfecting patients with up to 5 years of follow-up, a mutation (A194T) has been identified in individuals treated under suboptimal viral control which *in vitro* imparts partial TDF resistance [58].

There are no direct data to support FTC in preference to 3TC when combined with TDF in the treatment of HBV/HIV infection. Both nucleosides have been observed in HBV mono-infection to result in significant histologic, virologic and biochemical improvement. The choice of 3TC versus FTC will most likely be made in the context of whether tenofovir is available as a co-formulated drug as both fixed-dose combinations are available in different areas of the world. The evidence supporting FTC in preference is marginal: FTC has a longer intracellular half-life and is more potent *in vitro* and *in vivo* in monotherapy in the treatment of naïve patients with HIV and HBV [64]. It also selects for resistance for both HBV and HIV less rapidly and less often.

6.6 Antiviral treatment: Acute HBV

6.6.1 Recommendations

- We recommend individuals with severe/fulminant acute HBV in the context of HIV should be treated with nucleosides active against hepatitis B (1D).
- We recommend patients with severe/fulminant acute HBV receive ART inclusive of tenofovir and 3TC or FTC, or entecavir given with ART (1D).

6.6.2 Auditable outcome

- Proportion of patients with severe/fulminant acute HBV who receive ART inclusive of an antiviral active against HBV

6.6.3 Rationale

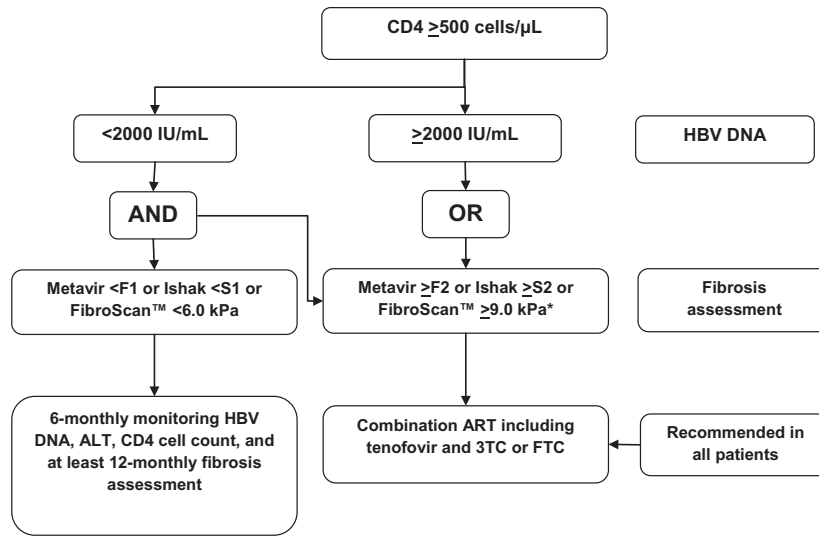
Acute hepatitis B has a variety of outcomes. In 60–80% of individuals the infection will resolve in less than 6 months

with loss of HBsAg and acquisition of anti-HBs [4,5]. The remainder will progress to chronic hepatitis B [4,5]. In a minority (<0.1%), acute infection will be severe (defined as acute HBV with an INR > 1.5) or fulminant (defined as severe acute HBV with associated hepatic encephalopathy) [4,5,65]. There is no evidence that antiviral treatment of acute hepatitis B in those who do not meet the criteria for severe or fulminant acute hepatitis B is of benefit in either mono-infected or HIV-co-infected patients [66].

The evidence that antiviral therapy is beneficial in severe and fulminant hepatitis B comes from studies in mono-infected patients treated with 3TC, although the evidence is conflicting. One placebo-controlled RCT showed that although HBV DNA fell more rapidly in those treated with 3TC for acute severe HBV, there was no difference in clinical outcomes or progression to chronic HBV [66]. Another RCT in mono-infected patients treated with either 3TC or no antivirals for acute severe HBV showed a three-fold reduction in liver failure and death in the 3TC arm, although the survivors in the placebo arm were less likely to become chronically infected [67]. Two retrospective case-control studies of mono-infected patients treated with 3TC for fulminant hepatitis B showed a three-fold reduction in mortality in the treated patients, and none of the survivors progressed to chronic infection [68,69].

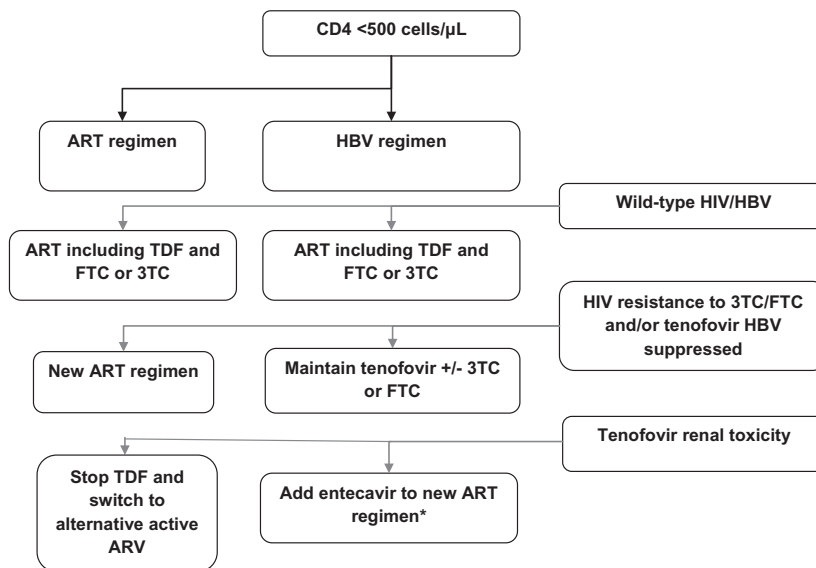
In HIV-infected patients the evidence for treatment of acute severe or fulminant HBV with 3TC/FTC and tenofovir (usually together) comes from case reports [70–73]. There is some evidence to support the efficacy of tenofovir in acute severe/fulminant HBV from case reports in HIV-infected individuals, although in these it was administered in combination with 3TC or FTC [70–73]. In published studies, the anti-viral agent has been given until the patient seroconverts from HBsAg positive to anti-HBs, which in most cases is within 3–6 months [67–76], or if the infection becomes chronic, continued indefinitely as per recommendations. All patients with acute severe/fulminant HBV need to be cared for in a hospital with expertise in the specialised care of this issue and with access to a specialised ITU.

Algorithm 1



*Patients with a TE liver stiffness by FibroScan™ of between 6.0–9.0 kPa should have a corroborative blood panel test or liver biopsy to determine the need for treatment.

Algorithm 2



*Entecavir needs to be dose-adjusted with close monitoring of renal function. If HBV unsuppressed and 3TC/FTC resistance consider renal-adjusted tenofovir dosing.

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7 Hepatitis delta (HDV)

7.1 Introduction

Hepatitis delta virus (HDV) is a defective virus that is dependent on HBV for replication. It can appear as coinfection or superinfection with hepatitis B.

7.1.1 Recommendations

- We recommend all HBsAg-positive patients are tested for HDV antibody (1B).
- We suggest repeat testing for HDV-seronegative HBsAg-positive patients is required only if the patient has persistent risk factors (2D).
- We recommend all HDV-seropositive individuals should be tested for HDV RNA (1C).
- We recommend all HIV/HBV/HDV-infected patients with detectable HBV DNA be treated with tenofovir as part of, or in addition to, ART (1D).

7.1.2 Good practice point

- We recommend all those with HDV RNA be considered for early treatment by a physician with experience in this condition.

7.1.3 Auditable outcome

- Proportion of chronic HBV-infected HIV patients who had an HDV antibody test

7.1.4 Rationale

In the UK, the reported prevalence of HDV among HBsAg-positive patients ranges from 2.1 to 8.5% [1–3] and in those with HBV/HIV infection from 2.6 to 6.0% [2,4,5], which is lower than the prevalence of 14.5% reported from a European HIV cohort [6]. This observed variation is most likely due to differences in patient populations in terms of risk factors, countries of origin and disease severity. The two main risk factors associated with HDV are injection drug use (IDU) and origin from an HDV-endemic area, which includes Eastern and Southern Europe, sub-Saharan Africa and the Amazon Basin of South America [7]. Due to successful strategies to prevent HBV infection in IDUs, the relative contribution of patients from HDV-endemic areas has increased.

The usual screening test for HDV is total HDV antibody, using enzyme immunoassay, although this does not discriminate between active or past infection. HDV IgM has

been used by some as a surrogate marker of disease activity [8,9]. However, a sensitive HDV RNA test is preferred to determine viral activity [8]. HDV RNA assays that can detect and quantify all clades of HDV are available in the UK in specialist hepatitis reference laboratories [10,11]. HDV superinfection frequently results in the suppression of replication of other hepatitis viruses [12,13]. It is therefore important to exclude HDV in every HBsAg-positive individual as the apparent suppression of HBV DNA may be incorrectly interpreted as indication of inactive liver disease. Patients with HDV superinfection are more likely to have severe hepatitis with progression of liver disease and development of cirrhosis and hepatocellular carcinoma [14–17].

Results of treatment outcome have mostly been obtained in HIV non-infected populations. A one year course of interferon therapy has been effective in sustaining a virological response in 28–41% of monoinfected patients [18,19]. Small case series with HIV-infected patients treated with pegylated interferon showed a similar outcome [20]. No significant benefit was observed by using anti-HBV nucleoside or nucleotide analogues such as entecavir [21] or adefovir [19] alone or together with interferon, although tenofovir may have some effect [22–25]. Despite the lack of direct benefit for HDV, HDV/HBV/HIV-coinfected patients with detectable HBV DNA should be treated with tenofovir as part of, or in addition to, ART [23].

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8 Hepatitis C (HCV)

8.1 Introduction

The following recommendations concern the management of patients with HCV/HIV infection. This includes the utility of pre-treatment screening and both ART and anti-HCV treatment strategies in those with acute and chronic HCV coinfection. For the assessment and evaluation of evidence, priority questions were agreed and outcomes were ranked (critical, important and not important) by members of the Writing Group.

For the assessment and investigations of HCV/HIV infection, the key question identified by the Writing Group was whether *IL28B* should be used routinely as a screening test in determining treatment strategies in adults with chronic HCV/HIV infection. The following were regarded as critical outcomes: sustained virological response (SVR) rates at 12 and 24 weeks, cost and need for triple therapy. For deciding on when is the optimum time to commence ART the following were ranked as critical outcomes: mortality, non-hepatic HCV comorbidity, HCV disease progression (cirrhosis, hepatocellular carcinoma), ARV resistance development and severe treatment-associated adverse events. It was decided by the Writing Group that the questions of: i) whether treatment with an NRTI combination including tenofovir demonstrated efficacy benefits compared with one containing abacavir when ribavirin is used; and ii) whether there are efficacy or toxicity benefits as regards choice of third agent in ART when DAAs are not co-prescribed, were important to address, but did not represent priority questions (see Section 6). It was also decided by the Writing Group that insufficient efficacy data were available to address the question as to which of boceprevir or telaprevir should be used when treating genotype (GT) 1 coinfection. Existing PK drug-drug interaction data permit recommendations to be made on the choice of ART with boceprevir or telaprevir. For acute hepatitis C in the context of HIV, the key questions identified were whether there are benefits in giving combination therapy with pegylated interferon (PEG-IFN) and ribavirin over giving PEG-IFN alone, and are there benefits of 48 weeks of treatment as opposed to 24 weeks of treatment. The critical outcome was HCV sustained virological response (SVR). Treatments were compared where data were available and differences assessed. Details of the search strategy and literature review are contained in Appendix 2.

8.2 Natural history

Hepatitis C is an RNA virus with high genetic heterogeneity. Eleven different genotypes have been identified, with phylogenetic analysis further distinguishing subtypes [1]. The distribution of genotypes varies across the world; in the UK genotypes 1 and 3 predominate. Genotypes vary in their clinical response to therapy.

The estimated prevalence of chronic hepatitis C infection is 3% globally [2,3]. The estimated prevalence of hepatitis C in the UK general population is approximately 0.4% [2]. The primary mode of transmission is via the parenteral route, and therefore injection drug users (IDUs) have traditionally comprised the majority of infected individuals. Other groups at risk include those infected via blood products, including haemophiliacs, those born abroad and infected through contaminated medical equipment, healthcare workers via occupational exposure, and infants born to HCV-infected mothers through vertical transmission. Although the risk of transmission through heterosexual intercourse is low [4], partners of HCV-infected individuals may be infected through sexual exposure. The prevalence of HCV infection is higher in HIV-infected individuals than in the general population, with a cumulative prevalence of HCV in the UK Collaborative HIV Cohort Study of 8.9% [5]. The prevalence varies by population group, with IDUs having higher rates of coinfection than MSM.

A global epidemic of acute hepatitis C (AHC) in HIV-infected MSM has been observed over the past decade [6]. Transmission appears to occur permucosally rather than parenterally and is associated with behavioural (traumatic sexual practices and mucosally administered drugs) and biological (pre-existing HIV infection and sexually transmitted infections such as syphilis) risk factors [7]. A meta-analysis has estimated the incidence of AHC in HIV-uninfected MSM as 1.4 per 1000 patient-years, compared to an incidence in UK cohorts of HIV-infected MSM ranging from 7.8–11.8 per 1000 patient-years (see Section 8.10) [8].

Various pathways through which HCV infection may impact on HIV have been suggested, but the main mechanism proposed is chronic immune activation leading to immune dysfunction and cytokine production, with ensuing enhanced viral replication and CD4 T-cell apoptosis [9]. There has been debate on whether HCV infection affects progression of HIV disease, although a

recent meta-analysis suggested this not to be the case [10,11]. Adults with HCV/HIV infection may experience smaller increases in CD4 lymphocyte counts than HCV-negative patients, although this difference attenuates with time [12]. Other studies have found no difference in rates of CD4 cell count gain between HCV-infected and -uninfected populations [13,14]. Virological response to ART is not associated with HCV serostatus [15–17].

HCV/HIV-infected patients have higher HCV viral loads [18,19] and accelerated liver fibrosis rates [20], with one meta-analysis finding that the estimated risk of cirrhosis was two-fold higher [21]. The mechanisms by which HIV causes accelerated fibrosis include direct entry of HIV virus into hepatic stellate cells [22]; immune activation by HIV inducing cytokine changes that increase liver inflammation; and an increase in tumour necrosis factor (TNF)-induced apoptosis [23].

HCV/HIV infection increases the risk of hepatocellular carcinoma, which tends to occur at a younger age and within a shorter time period since infection than in HCV mono-infection [24,25]. A number of studies have shown that coinfection is associated with increased mortality over HIV alone [26,27]. A 20-year prospective study found increased risk of hepatitis/liver-related deaths despite ART among coinfecting IDUs compared to HCV-mono-infected IDUs [28]. Both the EuroSIDA study and data from the Swiss HIV Cohort Study have confirmed that HCV infection is associated with an increased risk of death [29].

8.3 Diagnosis of HCV after high-risk exposure

8.3.1 Recommendations

- We recommend patients who have raised transaminases or had recent high-risk exposure to an individual known to be HCV positive are tested for anti-HCV and HCV-PCR (1D). When past spontaneous clearance or successful treatment has occurred HCV-PCR should be performed.
- We recommend the HCV-PCR should be repeated after 1 month if initially negative and if any potential exposure was less than 1 month before the first test, or the transaminases remain abnormal with no known cause (1D).

8.3.2 Good practice points

- We recommend patients who have experienced a recent high-risk exposure (e.g., unprotected sex between men [especially in the context of concurrent STI, high-risk sexual practices, and recreational drug use] or shared injection drug equipment) but have normal transaminases are tested for anti-HCV, and this is repeated 3 months later.

- We recommend patients who have repeated high-risk exposures but persistently normal transaminases are screened with anti-HCV and HCV-PCR, or HCV-PCR alone if previously successfully treated for or spontaneously have cleared infection and are HCV antibody positive, at 3–6-monthly intervals.

8.3.3 Auditable outcomes

- Proportion of patients with acute HCV who had an HCV-PCR assay as the screening test
- Proportion of patients with repeated high-risk exposure who had HCV tests (antibody and PCR) at least twice a year
- Proportion of all adults with HIV infection who had an HCV test within 3 months of HIV diagnosis

8.3.4 Rationale

Studies have shown that in HCV/HIV the first test to become positive is the HCV-PCR, often within 1 month [30,31]. It is difficult to be precise about time of exposure to infection but the HCV-PCR is positive a median of 3 months (range 1–9 months) after the last negative PCR test. Transaminases are abnormal in 78% of patients at the time of first positive PCR, rising to 88% 3 months later. The combined HCV antigen/antibody test is more sensitive than the antibody test alone in detecting acute infection and is being used in many centres for screening patients with risk factors for infection. It is not as sensitive as the PCR assay and is positive in 52% of patients at the time of the first PCR being positive [31]. HCV antibody tests are the least sensitive for acute infection, being positive in 20–25% at the time of the first PCR positive test. On average, HCV Ab becomes positive 3–7 months after the first positive PCR test but at 9 months 10% of patients remain HCV Ab negative which reduces to 5% at 1 year. Individuals with HCV infection may thus have a negative antibody test. Individuals with unexplained abnormal transaminases, especially if they are in a risk group for HCV exposure, should have an HCV-PCR assay in order to exclude acute HCV infection.

In MSM and IDUs who have cleared HCV infection either spontaneously or through treatment, the rate of HCV reinfection is up to 10-times higher than in previously uninfected patients [32–36]. In the EuroSIDA study of HIV-infected patients, 20% of MSM and IDUs who are cured of HCV will be re-infected subsequently [37,38]. Therefore it is important to monitor previously infected individuals frequently, with HCV-PCR being the only reliable assay [35–38]. In HIV-infected men who have sex with men, there is an appreciable rate of HCV infection (6/1000 patient-years in one study [8]), and given the benefits of

HCV being diagnosed early, all HIV-infected patients should be tested annually and more frequently if transaminases are raised without obvious cause [30,31,34].

Therefore, patient categories who require immediate anti-HCV and HCV-PCR are MSM with newly raised transaminases or with recent exposure to a known anti-HCV-positive partner; IDUs who share injecting equipment with newly raised transaminases [2, 38–42]; and recent recipients of blood or organs abroad or a high-risk needle-stick [2]. Those requiring 3–6 monthly anti-HCV testing are MSM with normal transaminases but with regular high risk exposure (e.g., unprotected sex between men [especially in the context of concurrent STI, high risk sexual practices, and recreational drug use]), and those regularly sharing drug equipment or snorting cocaine but with normal transaminases. However, despite the known link between cocaine snorting and acute HCV, the best screening strategy for patients remains unclear.

8.4 Thresholds and timing of treatment

8.4.1 Recommendations

- We recommend commencing ART when the CD4 count is less than 500 cells/ μ L in all patients who are not to commence anti-HCV treatment immediately (1B).
- We suggest commencing ART when the CD4 count is greater than 500 cells/ μ L in all patients who are not to commence anti-HCV treatment immediately (2D).

8.4.2 Good practice points

- We recommend commencing ART to allow immune recovery before anti-HCV therapy is initiated when the CD4 count is less than 350 cells/ μ L.
- We recommend commencing ART to optimise immune status before anti-HCV therapy is initiated when the CD4 count is 350–500 cells/ μ L unless there is an urgent indication for anti-HCV treatment when ART should be commenced as soon as the patient has been stabilised on HCV therapy.

8.4.3 Auditable outcome

- Proportion of patients with a CD4 count < 500 cells/ μ L commencing ART

8.4.4 Rationale

The assessment and recommendations on when to initiate ART in patients with HCV/HIV infection are based on theoretical considerations and indirect data as no RCT evidence exists. Observational data demonstrate that individuals with HCV coinfection have faster rates of fibrosis

progression and an increased risk of cirrhosis, ESLD, HCC and liver-related death than those with HCV mono-infection, and the risk of liver-related mortality and HCC increases as the CD4 cell count declines [43]. Successful treatment outcome with pegylated interferon (PEG-IFN) and ribavirin (RBV) therapy for hepatitis C in the context of HCV/HIV infection lessens as the CD4 cell count declines [44–48]. ART slows the progression of liver disease by improving immune function and reducing HIV-immune activation [49–51], although patients with coinfection are more likely to experience drug-induced liver injury (DILI), especially in the context of advanced liver disease. ART-mediated benefits to the prognosis of hepatitis C outweigh the risks of DILI, even in the setting of cirrhosis, but the importance of correct ART choice in HCV coinfection should be emphasised [52,53]. The advent of direct acting antivirals (DAAs) for HCV has increased the need of awareness of drug–drug interactions (DDI) in planning treatment strategies.

There are no direct data to support early initiation of ART in individuals with HCV/HIV infection. It is important to time the start of ARVs to fit with whether or not HCV therapy is required imminently. Patients should start ART if the CD4 count is less than 350 cells/ μ L as per BHIVA adult treatment guidelines [54]. Once HIV control has been achieved and CD4 cell count optimised, anti-HCV treatment can be commenced [55–58]. If the CD4 count is 350–500 cells/ μ L, treatment should be individualised depending on whether HCV or HIV treatment takes precedence. Biopsy studies indicate less liver necro-inflammation in those receiving ART, thus supporting a recommendation to start ART above 350 cells/ μ L [59]. In addition, HIV exerts a direct effect on the fibrogenic process through the binding of gp120 to CCR5 receptors on hepatic stellate cells and hepatocytes, the principle fibrogenic cell type in the liver [22,60]. Microbial translocation [61] may accelerate liver fibrosis through toll-like receptor (TLR) signalling [55,62,63]. Early initiation of ART may reverse or prevent this developing.

Hence, if anti-HCV treatment can be deferred, ART should be commenced when the CD4 count is less than 500 cells/ μ L. Once established on ART, hepatitis C treatment can be initiated. However, if HCV treatment takes precedence, then ART should be commenced once the patient is stabilised on successful HCV therapy. Individuals with CD4 counts over 500 cells/ μ L should be offered ART to improve outcome of the HCV infection, and those who defer should be closely monitored. In terms of infectivity, patients with lower CD4 cell counts are known to have higher levels of HCV viraemia in plasma and other body fluids. This also favours earlier initiation of treatment with ART which has been associated with declines in HCV viral load with ART-associated immune reconstitution.

8.5 Choice of ART

8.5.1 Recommendations

- We suggest that if abacavir is to be used with ribavirin, the ribavirin should be weight-based dose-adjusted (2C).
- We recommend when DAAs are to be used there is careful consideration of possible DDIs (1C) and current or archived HIV resistance. All drug interactions should be checked with an expert source (e.g., www.hiv-druginteractions.org).
- We recommend if boceprevir is to be used, raltegravir (RAL) with tenofovir (TDF) plus emtricitabine (FTC) should be the treatment of choice for those with wild-type HIV (1C): pharmacokinetic data would support etravirine, rilpivirine and maraviroc as alternatives.
- We recommend if telaprevir is to be used either RAL or standard-dose ritonavir-boosted atazanavir should be used (1C): pharmacokinetic data would support etravirine, rilpivirine and maraviroc as alternatives. Efavirenz may be used but the telaprevir dose needs to be increased to 1125 mg tds.
- We recommend that didanosine (ddl), stavudine (d4T) and zidovudine (ZDV) are avoided (1B).

8.5.2 Good practice point

- We recommend if patients are commencing ART and DAAs are not being considered, standard first-line ART should be commenced (see BHIVA adult treatment recommendations [54]).

8.5.3 Auditable outcomes

- Among patients receiving DAAs for HCV genotype 1 with ART for wild type HIV, the percentage on a recommended regimen, i.e.: raltegravir (RAL) with tenofovir (TDF) plus emtricitabine (FTC) with boceprevir; or RAL or boosted atazanavir with standard dose telaprevir; or efavirenz with increased dose 1125 mg tds telaprevir
- Proportion of patients on anti-HCV and ART medication with a medication history at each clinic visit documented in the case notes
- Proportion of patients on DAAs with a record in the notes of a discussion of the potential for pharmacokinetic interactions with antiretroviral medication and other medication

8.5.4 Rationale

The potential for drug–drug interactions and overlapping toxicities must be considered when co-treating HIV and hepatitis C infection. The assessment and subsequent rec-

ommendations are based on limited RCT data and PK interaction studies with available DAAs.

ARV regimens should be selected or modified to suit the planned hepatitis C treatment. If DAAs are not being considered, standard first-line ART can be used: efavirenz, ritonavir-boosted atazanavir, ritonavir-boosted darunavir, or raltegravir with TDF/FTC. Didanosine (increased intracellular didanosine levels and risk of toxicity with ribavirin), d4T (increase in risk of mitochondrial toxicity with ribavirin), and ZDV (overlapping toxicity with PEG-IFN and ribavirin) are contraindicated [64]. Some retrospective studies have shown abacavir to be associated with a decreased response to PEG-IFN/RBV therapy, possibly due to intracellular reductions in ribavirin level. However, factors including non-weight-based RBV dosing and differential baseline HCV VLs have made these data difficult to interpret. A recent study suggested no negative interaction when weight-based ribavirin was utilised. Nevertheless, caution should be applied when abacavir is to be used with a ribavirin dose of ≤ 1000 mg or ≤ 13.2 mg/kg [65].

When DAAs are chosen, some restriction on first-line ARV choice exists due to drug–drug interactions. Boceprevir (BOC) and telaprevir (TPV) are currently licensed DAAs for the treatment of hepatitis C genotype 1 infection, and are substrates and inhibitors of cytochrome P (CYP) 3A4/5 and p-glycoprotein (p-gp), and therefore interact with several ARVs. Boceprevir is also metabolised by aldo-ketoreductase. When using TPV and BOC, only certain ARV agents are recommended for routine use due to DDI concerns (see Table 8.1). Choice of available, safe third agents differs with use of BOC and TPV. From the limited data and drug–drug interaction studies, we recommend that if BOC is to be used, raltegravir with TDF/FTC should represent first-line ART in the presence of wild-type HIV. For TPV, we recommend that standard-dose ritonavir-boosted atazanavir or raltegravir (RAL) should be used – efavirenz can also be used but TPV dose needs to be increased to 1125 mg tds. Alternative ARVs when treating with either boceprevir or telaprevir are etravirine, rilpivirine and maraviroc, based on available pharmacokinetic (PK) data [66–68]. Multiple DAAs are currently in Phase III trials in coinfecting patients. Each drug has particular DDIs when combined with ART agents, and expert opinion should be sought on possible PK interactions (see Table 8.1). Clinicians should refer to an online information resource (such as <http://www.hep-druginteractions.org>) or seek expert opinion on possible PK interactions.

8.6 Assessment and investigation

8.6.1 Good practice points

- We recommend all patients have a baseline fibrosis stage assessment.

Table 8.1 Interactions between antiretrovirals (ARVs) and drugs used to treat hepatitis C

PI/r + DAA	ARV and DAA		Telaprevir		Recommendation
	Boceprevir	Interaction	Boceprevir	Telaprevir	
Interaction - Atazanavir - Boceprevir	AUC ↓ 35% ↓ 5%	Interaction - Atazanavir - Telaprevir	C _{min} ↓ 49% ↓ 18%	AUC ↑ 17% ↓ 20%	C _{min} ↑ 85% ↓ 15%
	AUC ↓ 44% ↓ 22%	Interaction - Darunavir - Telaprevir	C _{min} ↓ 59% ↓ 35%	AUC ↓ 40% ↓ 35%	C _{min} ↓ 42% ↓ 32%
	AUC Not studied	Interaction - Fosamprenavir - Telaprevir	C _{min} ↓ 43% ↓ 57%	AUC ↓ 47% ↓ 32%	C _{min} ↓ 56% ↓ 30%
Interaction - Lopinavir - Boceprevir	AUC ↓ 34% ↓ 45%	Interaction - Lopinavir - Telaprevir	C _{min} ↓ 43% ↓ 57%	AUC ↑ 6% ↓ 54%	C _{min} ↑ 14% ↓ 52%
	Boceprevir AUC ↓ 19%	Interaction - Efavirenz * - Telaprevir	C _{min} NIL ↓ 44%	AUC ↑ 18% ↓ 18%	C _{min} ↓ 10% ↓ 25%
	AUC ↓ 23% ↓ 10%	Interaction - Etravirine - Telaprevir	C _{min} ↓ 29% ↓ 12%	AUC NIL ↓ 16%	C _{min} NIL ↓ 25%
Interaction - Rilpivirine - Boceprevir	AUC ↓ 39% ↓ 6%	Interaction - Rilpivirine - Telaprevir	C _{min} ↑ 51% ↑ 4%	AUC ↑ 1.78 fold ↓ 5%	C _{min} ↑ 1.93 fold ↓ 11%
	Boceprevir AUC ↑ 5% ↑ 8%	Interaction - Tenofovir - Telaprevir	C _{min} NIL ↑ 8%	AUC ↑ 30% NIL	C _{min} ↑ 41% ↑ 3%
	AUC Not studied	Interaction - Abacavir - Telaprevir	C _{min} Not studied	AUC Not studied	C _{min} Not studied
Interaction - Zidovudine - Boceprevir	AUC Not studied	Interaction - Zidovudine - Telaprevir	C _{min} C _{min}	AUC Not studied	C _{min} C _{min}
	Boceprevir NIL ↑ 3.0	Interaction - Maraviroc - Telaprevir	↑ 2.8 NIL	Telaprevir ↑ 9.5 NIL	↑ 10.2 NIL
	Boceprevir AUC ↑ 1%	Interaction - Raltegravir - Boceprevir	C _{min} NIL NIL	Telaprevir AUC ↑ 3.1% ↑ 7%	C _{min} ↑ 78% ↑ 14%
ARV + PEG-IFN PI + PEG-IFN	Pegylated IF NIL	Ribavirin Increased haemolysis and inhibition of glucuronosyltransferase, leading to hyperbilirubinaemia			
	Overlapping toxicity; ↑ CNS disturbance	NIL			
NNRTI + PEG-IFN - Efavirenz	NIL	NIL			
	NIL	NIL			
	NIL	NIL			
NRTI + PEG-IFN - Abacavir	NIL	Reduced intracellular ribavirin levels and possibly a reduced response to PEG-IFN/RBV with low dose ribavirin. Studies have shown conflicting clinical results			
	NIL	Increased intracellular didanosine levels and risk of toxicity; fatal lactic acidosis, hepatic failure, pancreatitis			
	NIL	Possible increase in risk of mitochondrial toxicity			
- Didanosine - Stavudine - Zidovudine	Overlapping toxicity; increased myelosuppression				

- We recommend all patients should be managed by a clinician experienced in the management of both HIV and hepatitis C or should be jointly managed by clinicians from HIV and hepatitis backgrounds.
- We recommend all patients with HCV/HIV infection should be assessed for suitability for treatment of hepatitis C.
- We recommend consideration for referral to liaison psychiatry services for patients with pre-existing mental health problems prior to initiation of therapy and for patients with treatment-emergent psychiatric problems.
- We recommend individuals with dependency on alcohol and/or injection drug use are referred to the respective community services before initiation of therapy to minimise non-adherence with treatment.
- We recommend patients with advanced cirrhosis, low platelet counts and low albumin should be treated in centres experienced in managing patients with advanced disease and potential complications.

8.6.2 Auditable outcome

- Proportion of patients diagnosed with HCV/HIV receiving a baseline fibrosis stage assessment

8.6.3 Rationale

In patients with chronic hepatitis C, the aim of anti-HCV treatment is to achieve clearance of the virus as measured by a negative HCV-PCR 24 weeks after completion of therapy (SVR: sustained virological response). The decisions on whether or not to commence therapy for HCV, what to start treatment with, and the duration of therapy, will depend upon several factors. These can be summarised as ‘patient’ factors (preference, risk of transmission and re-infection, adherence, age, and co-morbidities including potential for DDIs), ‘viral’ factors (genotype, HCV viral load and interferon responsiveness), ‘hepatic’ factors (degree of fibrosis and risk of decompensation) and ‘genetic’ factors (IL28B status). In addition, availability of research studies is an important consideration.

The advent of DAAs has dramatically altered the outcome of treatment of hepatitis C in both monoinfected and coinfecting patients. Two HCV protease inhibitors are presently licensed and have NICE approval for the treatment of HCV in coinfecting patients: telaprevir and boceprevir [69,70]. Both are active only against HCV genotype 1 and when combined with pegylated interferon and ribavirin have led to higher rates of success in the monoinfected population. Small clinical trials have reported similar success rates with both boceprevir and

telaprevir in the coinfecting population [71–74]. Data in HCV/HIV-infected cirrhotics or in individuals who have previously failed interferon and ribavirin therapy are very limited, although small series of case reports and the early results of two ANRS studies in individuals previously failing therapy with interferon and ribavirin have been reported [75,76]. Several new agents are being studied both in the monoinfection and coinfection setting [77]. Early reports of two alternative protease inhibitors, faldaprevir and simeprevir in combination with PEG-IFN/RBV have shown high rates of RVR and EVR, comparable to monoinfection studies where these agents have been associated with higher rates of SVR than presently available PIs [78,79]. Studies of interferon-sparing approaches have commenced in the setting of HIV. Results of interferon-sparing approaches have, in the monoinfected population, shown very high rates of response with relatively short periods of treatment [80].

Treatment with boceprevir and telaprevir have the disadvantages of requiring co-prescribing of PEG-IFN and ribavirin, difficult dosing schedules as both must be administered three times a day (although TPV has been shown to be equally effective in monoinfection when administered twice per day); difficult toxicity profiles (anaemia, neutropenia and dysgeusia with boceprevir; and anaemia, skin rash [including the rare occurrence of Stevens–Johnson syndrome] and anal discomfort with telaprevir); multiple drug interactions (including with components of ART); and cost. Comorbidities should also be taken into account when considering the need for initiation of therapy (see Table 8.2). These include those that may be worsened by the agents being considered, for example pre-existing psychiatric conditions and blood dyscrasias, and the expected benefits associated with triple therapy should be balanced with the risks of severe adverse events in cirrhotic patients, particularly in prior null responders [81]. In such individuals expert opinion from related health care professionals should be sought and maintained throughout the treatment programme. Other comorbidities should also be taken into account as they may be influenced by the presence of HCV, for example the risks of developing cardiovascular, renal and bone disease.

IL28B genotype has been associated with response to pegylated interferon and ribavirin in monoinfected and coinfecting populations with a similar effect on outcome in both in a recent meta-analysis [82]. The Sprint 2 study demonstrated response rates to PEG-IFN and RBV with boceprevir were 80%, 71% and 59% with CC, CT and TT genotype respectively [83]. Similar data have been reported with telaprevir [84]. In the context of DAA-based therapy the role of *IL28B* testing is unclear. If the very high rate of

Table 8.2. Adverse event and pharmacokinetic profiles of hepatitis therapy

Generic name (Trade name) Formulation	Dose and Indication	Side effects	Dose adjustment in renal impairment	Dose adjustment in hepatic impairment	Pregnancy category	Cost Excluding VAT
Boceprevir (Victrelis)	Chronic hepatitis C genotype 1 infection with compensated liver disease, in combination with peginterferon alpha and ribavirin 800 mg tds po	Rash, dry skin, anaemia, dysgeusia, nausea, vomiting, diarrhoea, fatigue	None	Not in mild, moderate or severe hepatitis. Not studied in decompensated cirrhosis	B	£2800 for 28 days £30,800 for a 44-week course
200 mg capsule Pegylated interferon alpha-2a/(Pegasys)	Chronic hepatitis C in combination with ribavirin (bitherapy), with or without boceprevir/telaprevir* in genotype 1 infection with compensated liver disease (tritherapy). 180 µg once weekly s/c	Anorexia, depression, anxiety and insomnia, headache, diarrhoea, nausea, abdominal pain, alopecia, dry skin, dermatitis, arthralgia, myalgia, thrombocytopenia, anaemia, lymphadenopathy, injection site reaction	CrCl ≥ 30 mL/min: Initiate at normal dose CrCl < 30 mL/min: initiate 135 µg Avoid in combination with ribavirin when CrCl < 50 mL/min	None in mild and moderate impairment Avoid in decompensated cirrhosis	C	£497.60 for 28 days £5971.20 for 48-week course
135 µg, 180 µg, prefilled pen, prefilled syringe						
Pegylated interferon alpha-2b (ViraferonPeg)	Chronic hepatitis C in combination with ribavirin (bitherapy), with or without boceprevir/telaprevir* in genotype 1 infection with compensated liver disease (tritherapy). 1.5 µg/kg/week	Depression, anxiety, emotional lability, headache, dizziness, vomiting, nausea, abdominal pain, diarrhoea, dry mouth, myalgia, arthralgia, musculoskeletal pain, fatigue, alopecia, pruritis, dry skin, rash	CrCl > 50 mL/min: Initiate at normal dose CrCl 30–50 mL/min: reduce by 25% CrCl 15–29 mL/min: reduce by 50% CrCl < 15 mL/min: avoid Avoid in combination with ribavirin when CrCl < 50 mL/min	None in mild and moderate impairment Avoid in decompensated cirrhosis	C	£638.04 for 28 days £7656.48 for 48-week course (person of average weight 79 kg)
50 µg, 80 µg, 100 µg, 120 µg prefilled pen, powder for reconstitution						
Ribavirin (Copegus or Rebetol)	Chronic hepatitis C infection in adults without liver decompensation, in combination with peginterferon alpha 2a or 2b. In triple therapy with boceprevir or telaprevir in genotype 1 infection, with compensated liver disease* Copegus Genotype 1: <75 kg: 1000 mg; ≥ 75 kg: 1200 mg [off-label] Copegus Genotype 2–4: 800 mg daily Rebetol Genotype 1–4: <65 kg: 800 mg; 65–80 kg: 1000 mg; 81–105 kg: 1200 mg; > 105 kg: 1400 mg Chronic hepatitis C genotype 1 with compensated liver disease, in combination with peginterferon alpha and ribavirin 750 mg tds po***	Anaemia, thrombocytopenia, lymphadenopathy, thrombocytopenia, anorexia, depression, insomnia, headache, dizziness, impaired concentration, myalgia, arthralgia	Ribavirin should not be used	No dose reduction required in patients with compensated cirrhosis Use with caution with careful monitoring in patients with decompensated liver disease	X	£267.81 to £321.38 for 28 days (Rebetol) £308.31 to £369.98 for 28 days (Copegus)
Copegus 200 mg tablet						
Rebetol 200 mg capsule						
Telaprevir (Incivo)	Chronic hepatitis C genotype 1 with compensated liver disease, in combination with peginterferon alpha and ribavirin 750 mg tds po***	Anaemia, nausea, diarrhoea, pruritis, rash, haemorrhoids, proctalgia	None	Use with caution and with careful monitoring in patients with decompensated liver disease	B	£1866.50 for 7 days £22,398 For a 12-week course
375 mg tablet						

Costs are based on UK prices at the time of going to print.

*Unlicensed.

**Doses > 800 mg in genotypes other than 1 are 'off label'; licensed medication for unlicensed applications.

***Dose 1125 mg tds if given with efavirenz.

durable virological success reported with newer PIs and interferon-sparing approaches in monoinfected patients is translated into similar results in the coinfecting, the use of *IL28B* testing will become redundant in the clinical setting. Although some physicians and patients may find *IL28B* testing of use in making a decision to initiate or defer therapy, *IL28B* testing is not routinely recommended. In a potentially rapidly changing landscape of treatment it is essential that all individuals with chronic HCV undergo adequate liver disease staging prior to a decision being made on whether anti-HCV therapy should be deferred or initiated. If deferred, restaging should occur at least annually (Section 4).

An accurate assessment of alcohol and injecting drug use should be sought. Alcohol use should be minimised as this not only accelerates disease progression but also may reduce treatment efficacy through non-compliance; ongoing injecting drug use has previously been considered a relative contraindication for anti-HCV therapy, but there is now a growing body of experience of treatment in this group. Those continuing to inject should be warned about the potential for re-infection and receive education to prevent this.

If a patient has been previously treated for hepatitis C, the nature and duration of treatment, tolerability, outcome and adherence, should all be established as clearly as possible. Previous treatment failure should be classified as: null response ($<2 \log_{10}$ reduction in HCV viraemia at 12 weeks), partial response ($\geq 2 \log_{10}$ reduction at 12 weeks but failure to achieve undetectable levels throughout treatment), breakthrough (achievement of undetectable levels by 12 weeks but subsequent rebound during treatment), or relapse (undetectable HCV RNA at the end of treatment but subsequent rebound after discontinuation). Reasons for failure should be sought, for example adherence issues, insulin resistance, DDIs, and should be addressed prior to commencement of retreatment.

The decision regarding whether to treat now or to wait for newer therapies involves a careful assessment of the risks and benefits of treatment and the potential risks of deferring. Central to this are the patient's views and adequate time must be made available for a full discussion of the pros and cons of whether therapy should be initiated or deferred. Many patients, particularly those who have experienced or have concerns about interferon toxicity, may prefer to delay treatment.

In an era of expanding therapeutic options for HCV, all patients should be offered the option of participating in clinical trials. Since the number of sites involved in coinfection trials is limited, clinical networks should be established, if not already present, to ensure that clinicians are aware of available trials.

8.7 Antiviral treatment: genotype 1

8.7.1 Recommendations

- We recommend where there is a current clinical need for treatment (i.e., Metavir F4/cirrhosis), or if the patient wishes to be treated, the standard of care should be with triple therapy consisting of pegylated interferon, ribavirin, and either telaprevir or boceprevir (1C).
- We recommend 48 weeks of total treatment with a telaprevir- or boceprevir-based regimen for patients who do not have cirrhosis (1C).

8.7.2 Good practice points

- We recommend all patients should have the option of treatment, and have the pros and cons of opting for initiation of treatment and of deferring treatment discussed with them.
- We recommend a total of 48 weeks of treatment in patients with cirrhosis and for those who do not achieve an RVR.
- We suggest non-cirrhotic patients who were previously null responders, partial responders or who experienced breakthrough should, wherever possible, wait for the availability of interferon-sparing regimens or interferon-based regimens including at least two new agents.
- We recommend that all patients with advanced or decompensated cirrhosis being treated with triple therapy are managed in a tertiary centre.
- We suggest for patients with genotype 1 infection and non-cirrhotic disease, there is the option to defer treatment until newer funded therapies or a suitable clinical trial become available. Where deferred, close monitoring should take place with hepatic elastography or alternative non-invasive testing at least annually. Where there is confirmed progression of fibrosis, treatment initiation should be reconsidered.

8.7.3 Auditable outcomes

- Proportion of patients treated for genotype 1 outside of clinical trials receiving triple therapy with telaprevir or boceprevir with pegylated interferon and ribavirin
- Proportion of patients treated for genotype 1 with cirrhosis who are offered treatment with telaprevir or boceprevir with pegylated interferon and ribavirin unless contraindicated
- Proportion of patients not receiving therapy who undergo repeat non-invasive staging of liver disease within 1 year

8.7.4 Rationale

The outcome of treatment for HCV/HIV-infected patients with genotype 1 HCV has been less successful than in mono-infection, with sustained virological response rates of 14–38% reported from clinical studies with pegylated interferon and ribavirin [85–88]. The advent of boceprevir and telaprevir has led to higher rates of success in the mono-infected population, and small clinical trials have reported similar success rates in the coinfected population with both boceprevir and telaprevir. In a study of individuals with HCV/HIV infection where telaprevir was administered in combination with PEG-IFN and RBV and compared with PEG-IFN/RBV alone, SVR rates at 24 weeks were 74% and 45%, respectively [71]. A similar study in coinfection has been performed with boceprevir in which SVR rates at 24 weeks were reported as 29% for PEG-IFN/RBV and 63% for PEG-IFN, RBV and boceprevir [72]. No completed study has been performed in HCV/HIV-infected cirrhotics or in individuals who have previously failed interferon and ribavirin therapy, although small series of case reports have been presented. Also, preliminary data from two ANRS studies in individuals previously failing therapy with PEG-IFN and RBV have been reported and show virological response rates at week 16 of 88% with telaprevir, including 86% of null responders, and 63% with boceprevir, but only 38% in previous null responders [75,76], although longer-term data are needed before the utility of these drugs in this setting becomes clear.

In mono-infected patients, a recent meta-analysis has suggested a higher response rate when pegylated α -interferon 2a is employed when compared to pegylated α -interferon 2b, although studies involving patients with HIV infection were excluded and therefore no recommendation can be given as to which interferon should be chosen. Nevertheless, based on the mono-infection analysis, physicians may prefer to utilize pegylated α -interferon 2a [89]. Ribavirin should always be given based on weight (1000 mg per day if less than 75 kg and 1200 mg per day if above this weight) [90].

Both telaprevir and boceprevir have drawbacks which include toxicities, drug–drug interactions with antiretrovirals and other commonly used agents, two-or-three-times-daily dosing, and both must be administered with PEG-IFN and RBV. Potential drug–drug interactions of DAAs with both anti-HIV agents and other prescribed medications are of particular importance (see Table 8.1). All individuals should be stabilized on an ART regimen without potential harmful interactions prior to commencement of anti-HCV therapy. The probable rapid advent of PEG-IFN-sparing approaches means that many physicians

and patients are deciding to defer therapy rather than initiating therapy with presently available regimens. HIV is associated with a higher frequency and more rapid progression of hepatitis C-associated fibrosis, and where deferral of therapy is the preference, monitoring of progression of liver disease should occur by non-invasive tests (see Section 4) at least annually. In cases of confirmed progression of fibrosis treatment initiation with HCV therapy should be reconsidered. A number of clinical trials are presently recruiting and, with a large number of new agents being developed, all patients and physicians should ideally be part of a clinical trial network, permitting access to new therapies and strategies.

Individuals with liver staging suggesting a Metavir score of 4 should be offered therapy where there is no contraindication. Individuals with a score of this level are at risk of the complications of hepatoma and portal hypertension, and rates of decompensation are higher in the context of coinfection. All other individuals should be considered for treatment but be well informed of the option of deferring therapy until new treatments and strategies are available. Patients with F2/F3 disease should be monitored at least annually by TE and if there is evidence of progression they should be offered treatment. Some physicians may feel that the risk of progression for these patients overrides the potential benefits of deferring therapy until newer agents are available [91]. However, data from a Spanish cohort [92] suggest that in the era of ART, very few F3 patients (assessed either by biopsy or TE) developed decompensation at 2 years. Results of clinical trials in the mono-infected population have shown very high SVR, both with newer agents in combination with PEG-IFN/RBV, and with some interferon-sparing regimens, and so the current recommendations are likely to change and will be updated accordingly.

Individuals who have previously failed PEG-IFN and RBV therapy may also defer treatment if they have non-cirrhotic disease (Metavir \leq F4), but consideration should be given to commencing therapy if it is in the individual's best interests (e.g., if there is concern over a missed opportunity to treat). Where initiation of treatment is deferred, monitoring of progression of liver disease should occur by non-invasive tests (see Section 4) at least annually. In cases of confirmed progression of fibrosis, treatment initiation should be considered.

Telaprevir is dosed three times daily in combination with PEG-IFN and RBV. Although there are data on twice daily dosing with telaprevir in the context of HCV mono-infection, no such data exist in coinfected populations. Telaprevir is administered for the initial 12 weeks of therapy. The total duration of recommended therapy in mono-infection is dependent on whether the patient

achieves an RVR and if the patient has received PEG-IFN in the past and the type of response/failure to this treatment. The available study of telaprevir in coinfection in individuals utilized 48 weeks of treatment, and there are no data to guide on whether shortened durations of therapy may be utilized in coinfecting patients. As the response rates in coinfecting patients appear similar to those observed in monoinfected, 24 weeks of therapy may be considered in those individuals naïve to therapy, without cirrhosis, who achieve an RVR. However, in individuals who have previously failed an interferon-based therapy, treatment duration should be 48 weeks due to the higher rates of failure in this population and the lack of clinical trial data.

Boceprevir must also be prescribed in combination with PEG-IFN and weight-based RBV. Boceprevir is dosed three times a day. Boceprevir is licensed to be administered after a 4-week lead-in of PEG-IFN and RBV to establish the degree of interferon responsiveness, and is then continued for the remainder of the therapeutic course. In the RESPOND 2 study, as an example, 76% of individuals who achieved a 1 log₁₀ decline in HCV viral load after 1 month PEG-IFN/RBV went on to an SVR compared with 33% of those not reaching this level of decline. Similar data are observed in some but not all studies with telaprevir [93]. In the REALIZE study, 82% and 33% of individuals, respectively, gained an SVR after achieving or not achieving a 1 log₁₀ decline in HCV with a 1-month lead-in of PEG-IFN/RBV [94].

In monoinfection, the recommendation on duration of boceprevir is dependent on whether the HCV viral load after a 4-week PEG-IFN/RBV lead-in and subsequent 4 weeks of boceprevir therapy is undetectable. In individuals who are monoinfected and achieve a viral load that is undetectable at this time point, a total of 28 weeks of therapy is recommended where the lead-in is utilised. Clinical trials in the coinfecting population are limited to 48 weeks of treatment duration. As with telaprevir use in coinfecting individuals, a treatment duration course of 24 weeks of triple therapy may be considered in the coinfecting individual achieving an RVR, although some clinicians and patients may choose to prolong this to 48 weeks. There are no treatment-completed data on the use of boceprevir in coinfecting patients who have previously received interferon and until the data are available, all such individuals should receive a total of 48 weeks' duration.

Treatment should be supported with growth factors as required. In HIV-uninfected patients, ribavirin dose reduction for anaemia has been shown to have no effect on SVR success in studies employing boceprevir and telaprevir, and may negate the need for use of erythropoietin.

8.8 Antiviral treatment: genotypes 2 and 3

8.8.1 Recommendations

- We recommend where there is a current clinical need for treatment (i.e., Metavir F4/cirrhosis), or if the patient wishes to be treated, the standard of care should be with pegylated interferon and ribavirin (1C).
- We recommend where patients receive pegylated interferon and ribavirin, the duration of treatment should be 48 weeks unless RVR is achieved, when treatment should be shortened to 24 weeks if the individual is non-cirrhotic (1C).

8.8.2 Good practice points

- We recommend all patients should have the option of treatment, and have the pros and cons of opting for initiation of treatment and of deferring treatment discussed with them.
- We suggest for patients with non-cirrhotic disease there is the option to defer treatment until newer therapies or a suitable trial become available.
- We recommend those deferring treatment are monitored by non-invasive tests at least annually and if they have confirmed progression of fibrosis are reconsidered for initiation of therapy.

8.8.3 Auditable outcomes (see Section 8.9.2)

8.8.4 Rationale

The response rates of genotypes 2 and 3 infection to pegylated interferon and ribavirin regimens are much higher than in genotype 1 infection in both monoinfected and coinfecting individuals. In a recent meta-analysis, treatment response rates of genotype 2 and 3 did not differ between HIV-infected and -uninfected populations [95]. Neither telaprevir nor boceprevir has substantial activity against genotypes 2 and 3, although second-generation protease inhibitors and other DAA classes as well as several interferon-sparing strategies have reported high rates of SVR in monoinfected populations [77,96–98]. Because of differential activity of the newer DAAs on GT2 and GT3 virus, there may be a requirement to separate recommendations in future guidelines [99,100].

Therefore the only available therapy for genotype 2 and 3 hepatitis C in the context of HIV infection remains pegylated interferon and ribavirin. Ribavirin should be prescribed as weight-based due to higher response rates when this method is employed. In individuals who are naïve to hepatitis C therapy, do not have cirrhosis (Metavir F4) and achieve an RVR, treatment duration should be 24

weeks, as longer courses of therapy have not translated into higher rates of SVR. Individuals not achieving an RVR but reaching an EVR should receive 48 weeks of therapy. All individuals receiving treatment after failing a previous interferon-based regimen should receive 48 weeks of therapy.

Erythropoietin and granulocyte colony stimulating factors should be used as required and should be given in preference to interferon and ribavirin dose reduction.

8.9 Antiviral treatment: other genotypes

8.9.1 Good practice points

- We suggest for patients with genotype 4 infection without cirrhosis, there is the option to defer treatment until newer therapies or a suitable clinical trial become available.
- We recommend if treatment is given now, this should be with pegylated interferon and ribavirin. The duration of therapy should be 48 weeks if RVR is achieved. If the RNA is still detectable at 12 weeks, consideration should be given to discontinuing treatment.
- For those with previous treatment failure, we recommend waiting for the availability of interferon-sparing regimens with active DAAs.
- We recommend individuals coinfecting with non-genotype 1–4 should be seen at a tertiary referral centre to determine treatment suitability, nature and duration and a treatment plan made in consultation with the referring hospital.

8.9.2 Auditable outcomes

- Proportion of patients treated outside of clinical trials for non-genotype 1 who receive therapy with pegylated interferon and ribavirin
- Proportion of patients treated for non-genotype 1 with a Metavir score of F4 who are offered treatment with pegylated interferon and ribavirin unless contraindicated
- Proportion of patients with non-genotype 1–4 referred to a tertiary centre
- Proportion of patients not receiving therapy undergoing repeat non-invasive staging of their liver disease within 1 year

8.9.3 Rationale

The response rate of genotype 4 HCV mono-infection to a PEG-IF/RBV regimen is similar to that seen with genotype 1, with a figure ranging between 43–50% being observed in clinical trials. As with genotypes 2 and 3, neither of the two currently available HCV protease inhibitors has been

studied, but the newer anti-HCV agents are being studied across all genotypes with excellent initial responses in mono-infected patients [101]. Due to the low rates of success with pegylated interferon and ribavirin we suggest that treatment is deferred where possible and treatment with newer agents within clinical trials actively sought. Where the individual has liver disease staging suggestive of Metavir stage 4, a complication of disease, or it is the informed wish of the patient to commence therapy, then treatment is recommended. This should be with pegylated interferon and ribavirin. The duration of therapy should be 48 weeks if an undetectable HCV RNA is achieved at 4 weeks, with a consideration to extend this to 72 weeks if achieved by 12 weeks. If the RNA is still detectable at 12 weeks, consideration should be given to discontinuing treatment. All individuals deferring therapy should undergo hepatic elastography or an alternative non-invasive test at least annually. Individuals infected with genotypes other than 1–4 should be referred to a centre with experience of treating HCV infection with these genotypes for a treatment plan to be made in consultation with the host centre.

8.10 Acute hepatitis C

8.10.1 Recommendations

- We recommend patients without a decrease of 2 log₁₀ in HCV RNA at week 4 post diagnosis of acute infection (1D) or with a positive HCV RNA week 12 post diagnosis of acute infection (1C) are offered therapy.
- We recommend therapy be commenced prior to an estimated duration of infection of 24 weeks (1D). Patients who have not commenced treatment by this time should be managed as for chronic hepatitis C.
- We recommend all patients be offered combination therapy with pegylated interferon and weight-based ribavirin (1C). We recommend against treatment with PEG-IFN monotherapy (1C).
- We recommend treatment is discontinued if patients do not achieve an EVR (1C).
- We recommend patients with re-emergent virus after spontaneous or therapeutic clearance are assessed for relapse or reinfection (1C).
- We recommend patients with AHC who relapse are managed as for chronic hepatitis C (1D).
- We recommend patients who have been re-infected are managed as for AHC (1D).

8.10.2 Good practice points

- We recommend patients are treated for 24 weeks if RVR is achieved and for 48 weeks if RVR is not achieved.

- We recommend patients are managed as for chronic hepatitis C where treatment fails.
- We recommend patients who achieve an undetectable HCV RNA without therapy undergo HCV RNA measurements at 4, 12, 24 and 48 weeks to ensure spontaneous clearance.

8.10.3 Auditable outcomes

- Proportion of patients who fail to achieve a decrease of 2 log₁₀ in HCV RNA at week 4 post diagnosis of acute infection or with a positive HCV RNA week 12 post diagnosis of acute infection offered therapy
- Proportion of patients who are treated for AHC given 24 weeks of pegylated interferon and ribavirin

8.10.4 Rationale

Since the initial report from the UK in 2004 of an increase in the incidence of acute hepatitis C (AHC) in HIV-positive MSM [102], recognised epidemics have been reported in Europe, Australia and America [103–105]. More recently, an outbreak in Asia has been reported [106]. The outbreaks primarily affect HIV-positive MSM, the majority of whom deny IDU. Patients are often diagnosed with concomitant sexually transmitted infections and admit to participation in high-risk sexual practices. Phylogenetic data have demonstrated the introduction of the virus into MSM populations from IDU populations as early as 1960 [107]. Several studies have shown that expansions in transmission did not occur until around the mid-1990s, coinciding with the introduction of ART and an increase in high-risk sexual practices [107–109]. The exact mode of transmission remains unclear, but a number of retrospective case-control studies have identified several factors associated with the acquisition of AHC: group sex, fisting and recreational drug use during sex [105,108,110]. National data on the current incidence of HCV in HIV-positive MSM in the UK are lacking. Recent data from EuroSIDA continue to show a year-on-year increase in HIV-positive MSM, with an incidence of greater than 1.5 per 100 person-years in 2010 [111].

Due to the higher treatment success rates for AHC when compared to chronic HCV, all adults with HIV infection diagnosed with AHC should be considered for early initiation of anti-HCV therapy. There are no RCTs to guide the management of AHC in the HIV-positive population, although there are a number of observational cohort studies. It is important to predict progression to chronicity to permit early initiation of therapy in those who require it, and prevent unnecessary therapy in those who would spontaneously clear. As initiation of therapy in the acute

phase has generally been regarded as best practice, few cohorts of untreated HIV-infected individuals with AHC exist. The largest is a European cohort of 92 individuals; of those who did not achieve a 2 log₁₀ drop in HCV RNA 4 weeks after diagnosis, 85% developed chronic HCV while 92% of those still positive at week 12 developed chronic HCV [112]. Findings from a UK single centre cohort study support this strategy [113].

In the HIV-negative population, delaying treatment until 12 weeks after diagnosis does not compromise treatment success [114]. However a delay of more than 1 year after the onset of hepatitis leads to a reduction in sustained virological response (SVR) rates [115]. Most studies in the HIV-infected population initiated treatment between 12 and 24 weeks after diagnosis, and the length of time between the start of acute hepatitis and treatment initiation does not appear to influence treatment response. In the Australian Trial in Acute HCV (ATAHC) there appeared little difference in SVR in individuals commenced on therapy prior to 27 weeks, 27 to 52 weeks and > 52 weeks: 67% (10 of 15), 73% (11 of 15), and 100% (5 of 5), respectively [116]. This finding has been confirmed by other studies with SVRs of 76% (13/17) versus 76% (25/33) in those commenced on therapy less than 24 weeks or greater than and equal to 24 weeks after estimated HCV infection [117].

In AHC mono-infection, SVR rates between 72% and 94% have been reported with IFN α and PEG-IFN monotherapy [118–120]. Due to reduced treatment responses of AHC in HIV-infected individuals, physicians have opted for combination therapy with ribavirin. Few studies have directly compared monotherapy to combination therapy. One small prospective trial reported SVR rates of 80% with PEG-IFN monotherapy compared to 48% in combination therapy, but this did not reach statistical significance [121]. Studies comparing combination therapies with PEG-IFN and ribavirin have demonstrated SVR rates of between 47% and 91%. A recent prospective cohort achieved an SVR of only 37% with peg-IFN α monotherapy, resulting in early discontinuation of the study [122].

Studies have shown improved viral kinetic responses with combination therapy, with a greater reduction in HCV RNA between weeks 8 and 12 of treatment in HCV/HIV-infected individuals receiving combination therapy compared to mono-infected individuals receiving PEG-IFN alone [123]. Therefore, evidence supports the use of combination therapy with PEG-IFN and ribavirin over monotherapy with PEG-IFN. Preliminary data on the use of DAA in AHC are available suggesting a reduction in total duration is possible to 12 weeks [124]. It is likely, with several small molecules in Phase II and III clinical trials, some of which have cross-genotype activity, a high genetic

barrier to resistance, and lack the cytochrome P450 3A4 interactions, that DAAs will play a key role in future recommendations, with the possibility of shorter or interferon-free regimens.

The usual duration of therapy in AHC mono-infection is 24 weeks, with shorter durations of therapy failing to demonstrate similar SVR rates. Cohort studies in AHC have varied widely in duration of therapy administered, with the most common durations being either 24 or 48 weeks [116,117,121,122,125–132]. In the treatment of chronic HCV, viral kinetics are used to determine treatment duration. RVR determines length of therapy while EVR determines therapy continuation. Therefore, physicians treating AHC have investigated the use of viral kinetics in determining treatment duration.

The European multicentre cohort study in HCV/HIV-infected patients showed that in those who achieved an RVR, 93% achieved an SVR [125]. Sub-analysis demonstrated that after a first undetectable HCV RNA, those who received at least 20 weeks of treatment achieved SVR of 96% compared with only 20% in those who received less than 20 weeks of therapy. Together, these findings suggest that 24 weeks of therapy may be sufficient in HIV-infected individuals with AHC who achieve an RVR. This has been supported by a number of other studies. In the Australian Trial in Acute Hepatitis C, where 24 weeks of combination therapy was used, RVR yielded a positive predictive value (PPV) for SVR of 75% and negative predictive value (NPV) of 13% [116,126]. The high PPV supports 24 week treatment duration for those who achieve an RVR, while the low NPV suggests that 24 weeks of therapy may also be sufficient in those who do not achieve an RVR. However, not all studies demonstrate similarly low levels of relapse in non-RVR subjects treated for only 24 weeks. A recent Spanish study investigated 24 weeks of combination therapy with a low overall SVR of 47%. While 92% of those who achieved an RVR also achieved an SVR, only 20% of non-RVR individuals did, suggesting that 24 weeks of therapy may have been insufficient [133].

Few studies have compared short and long treatment durations. Observational cohort data are difficult to interpret as it is unclear how to deal with 'null responders' whose therapy is discontinued early [134]. Results exist from a prospective study where individuals were treated for either 24 or 48 weeks with combination therapy: SVRs were achieved in 71% and 79%, respectively, with PPV of RVR for SVR also similar (81% and 89%). However, those without RVR in the 24-week group only achieved a 40% (2/5) SVR, compared to a 64% (7/11) SVR in the 48-week group [117]. A 48-week therapy duration may thus be necessary to achieve acceptable SVR rates in those who do not achieve an RVR. Due to these results, a treatment

strategy where RVR is used to determine duration of therapy (24 weeks if RVR is achieved and 48 weeks if it is not) has been suggested. Data from a London cohort have demonstrated that this strategy can lead to an SVR of 91%, similar to that observed in the HCV-mono-infected population [135].

In chronic HCV, week-12 HCV RNA levels are routinely used to determine the likely futility of therapy and thus the need to discontinue treatment. Interpreting week-12 data within the available AHC cohort studies is difficult as it is not always transparent whether failure to achieve an EVR has been used as a stopping rule, thus heavily biasing its NPV. However, the frequency at which week-12 HCV RNA data are used to determine futility of AHC therapy suggests that expert opinion advocates the use of EVR as a stopping rule.

Immune responses to HCV are not sufficient to protect against reinfection. High rates of reinfection have been reported following both therapeutic and spontaneous clearance. The initial report came from a UK centre; between 1999 and 2008, 22 individuals were identified with re-emergent HCV viraemia. Nine had stored paired serum samples from both episodes of viraemia and seven were shown to have been infected with genetically divergent strains [36]. Recent data from the same unit have shown that between January 2004 and April 2012 there was a reinfection rate of 8 per 100 person-years. A number of these individuals had a second reinfection with a rate of 23.2-per-100 person-years [136]. In those who did not spontaneously clear, a second infection SVR of 65% was observed. Similar reinfection rates have been seen in other European centres, with one recent retrospective study in the Netherlands revealing a reinfection rate of 15.2 per 100 person-years [34]. There is also a need to target interventions to prevent HCV reinfection in MSM, in particular when access to the new direct-acting antivirals (DAAs) makes treatment more effective and more tolerable.

8.11 References

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9 Hepatitis E

9.1 Recommendations

- We recommend against routine screening for HEV in HIV-infected patients (1C).
- We recommend HEV infection is excluded in patients with HIV infection with elevated liver transaminases and/or liver cirrhosis when other causes have been excluded (1D).
- We suggest the detection of HEV in HIV infection should not rely on the presence of anti-HEV when the CD4 count is <200 cells/ μ L since this may be undetectable and exclusion of HEV should rely on the absence of HEV RNA in the serum as measured by PCR (2C).
- We suggest acute HEV in the context of HIV does not require treatment (2C).
- We suggest that patients with confirmed chronic HEV coinfection (RNA positive for more than 6 months) receive optimised ART to restore natural HEV antiviral immunity and suggest if HEV-PCR remains positive this is followed by oral ribavirin (2C).

9.2 Auditable outcome

- Proportion of patients with elevated liver transaminases and/or liver cirrhosis who are screened for HEV infection

9.3 Rationale

Hepatitis E virus (HEV) infection was thought to be predominantly a disease of developing countries but is becoming increasingly prevalent in the UK, with the number of cases now outnumbering those from HAV. Spread is by faecal-oral transmission through contaminated water sources. The clinical picture is varied: serological testing shows that whilst many develop asymptomatic infection, others present with symptoms typical of viral hepatitis [1]. At the more severe end of the clinical spectrum, HEV is also a recognised cause of fulminant liver failure. The clinical course is particularly severe in pregnant women, with high maternal and foetal mortality [2], and in those with pre-existing liver disease [3]. Prevalence rates vary widely, which in part is explained by the use of serological assays varying in sensitivity. HEV is frequently detected in the UK in patients with liver disease where the clinical index of suspicion is high [4] and is endemic in parts of France where it is associated with the consumption of wild boar [5]. There is an increased HEV seroprevalence rate in those

at risk for blood-borne infections, including individuals on haemodialysis, haemophiliacs and intravenous drug users [6].

Although HEV viraemia lasts for typically less than 15 days, chronic infection is now well described and is defined as the presence of HEV RNA for more than 6 months. Persistent HEV with detectable RNA has been observed at low frequencies in solid organ transplant populations. In HIV-infected patients, seroprevalence rates have been found to be 2.6–9%, and in those with unexplained elevated transaminases approximately 0.05% have been found to have chronic HEV/HIV infection. However, the number of studies evaluating this in large numbers of HIV-infected patients is small, and none have used the most sensitive serological assay for screening. Persistent HEV infection has been described in individuals with undetectable HEV IgG [7,8] and the use of anti-HEV IgG for the diagnosis of HEV infection in patients with CD4 counts below 200 cells/ μ L may be inappropriate.

Host factors associated with HEV persistence in organ transplant recipients include lower CD4+ T cell counts and tacrolimus (as opposed to cyclosporine) therapy. A single study has revealed a higher prevalence rate in those with AIDS, compared to those with HIV infection at other stages [9]. Persistent HEV has been identified as a cause for liver cirrhosis in immunosuppressed patients [9].

In those with persistent HEV and solid organ transplants, HEV viral clearance has been obtained either (i) through the reduction of immunosuppressive therapy or (ii) following treatment. To date there are fewer than 10 individuals with HIV infection and detectable HEV RNA described in the literature, but one small case series would recommend initial use of ribavirin alone [10] and, if this fails to eradicate infection, the addition of or a switch to PEG-IFN [11].

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10 End-stage liver disease

10.1 Introduction

The following recommendations concern the management of patients with HBV/HIV or HCV/HIV who have developed end-stage liver disease (ESLD) and/or hepatocellular carcinoma (HCC). For the assessment and evaluation of evidence, the single priority question agreed was whether ultrasound scan (USS) surveillance testing should be performed 6- or 12-monthly to detect early HCC in adults with chronic viral hepatitis/HIV infection. Outcomes were ranked (critical, important and not important) by members of the Writing Group. The following were agreed as critical outcomes: HCC mortality, HCC missed diagnoses and cost of screening. Surveillance methods were compared where data were available and differences in outcome assessed. No study was identified that specifically examined chronic viral hepatitis in HIV infection. Recommendations and links to evidence for HBV mono-infection, including management of HBV-related ESLD, have recently been published in NICE guidance [1]. Details of the search strategy and literature review are contained in Appendix 2.

10.1.1 Recommendations

- We recommend screening for and subsequent management of complications of cirrhosis and portal hypertension in accordance with national guidelines on the management of liver disease (1A).
- We recommend HCC screening with 6-monthly ultrasound (1A) and suggest 6-monthly serum alpha-fetoprotein (AFP) (2C) should be offered to all cirrhotic patients with HBV/HIV and HCV/HIV infection.

10.1.2 Good practice points

- We recommend cirrhotic patients with chronic viral hepatitis and HIV infection should be managed jointly with hepatologists or gastroenterologists with knowledge of end-stage liver disease, preferably within a specialist coinfection clinic.
- We suggest all non-cirrhotic patients with HBV/HIV infection should be screened for HCC six monthly.
- We recommend all patients with hepatitis virus/HIV infection with cirrhosis should be referred early, and no later than after first decompensation, to be assessed for liver transplantation.

- We recommend eligibility for transplantation should be assessed at a transplant centre and in accordance with published guidelines for transplantation of HIV-infected individuals.

10.1.3 Auditable outcomes

- Proportion of patients undergoing objective liver staging assessment to identify the risk for/likelihood of cirrhosis
- Proportion of patients with likely cirrhosis undergoing 6 monthly US examination to exclude HCC
- Proportion of patients with cirrhosis or evidence of portal hypertension undergoing upper GI endoscopy

10.1.4 Rationale

Cirrhosis and HCC are the two most important consequences of chronic hepatitis B or C infection in the HIV population. ART has improved the prognosis of HIV-infected patients, resulting in a reduction in fibrosis progression and a decrease in liver disease-associated mortality. As mortality from AIDS has fallen, the importance of ESLD as a cause of significant morbidity and mortality in patients coinfecting with HIV and HCV and/or HBV has become apparent, with hepatic complications accounting for more than 80% of deaths [2–7]. HIV is associated with acceleration in liver disease progression to ESLD in those with HBV and/or HCV infection [8]. HCV/HIV infection is also associated with rapid deterioration after the development of cirrhosis, with a median survival after first episode of liver decompensation of 13 months compared with approximately 5 years in the HCV mono-infected patient [9]. The epidemic of acute hepatitis C in the HIV MSM population has been associated with reports of rapid progression to cirrhosis with development of decompensated liver disease within 6 years [10].

Episodes of decompensation are associated with significant morbidity and mortality in HIV-infected patients [11]. Many cirrhosis-related complications and episodes of decompensation are avoidable. Patients need to be managed in conjunction with hepatologists or gastroenterologists who are experienced in the care of those with cirrhosis. Liver disease progression can be monitored by the application of simple and routinely available laboratory blood tests, which can be used in isolation or in combination to calculate prognosis risk scores, including the Child Pugh class and MELD score (Model for End-stage Liver Disease) (www.mdcalc.com/meld-score-model-for-end-stage-liver-disease-12-and-older and

www.mdcalc.com/child-pugh-score-for-cirrhosis-mortality). Recent evaluation of HIV patients with ESLD has demonstrated that the MELD score is the best prognostic factor [12]. There is growing interest in the use of non-invasive methods to diagnose disease stage and risk. Transient elastography may provide an estimate of risk for decompensation in HIV/HCV-infected patients [13] and may obviate the need for liver biopsy (see Section 4.3).

Cirrhosis associated with chronic viral hepatitis coinfection is a well-recognised risk factor for the development of HCC which is seldom seen prior to the development of cirrhosis in HCV. HCV/HIV-infected patients develop HCC at a younger age and after a shorter duration than is observed for those with HCV-monoinfection, and survival may be shorter [14–17]. HBV is directly carcinogenic and is associated with the development of HCC prior to the development of cirrhosis, particularly in those where HBV has been acquired at birth or in early childhood [18]. High serum HBV DNA titre and low CD4 cell count have both been associated with an increased risk of development of HCC [19,20].

There are a number of treatment options for HCC. Amongst these, liver transplantation is an appropriate treatment for some individuals, particularly when complicating established cirrhosis [21]. In a single centre cohort univariate analysis, HCC had no impact on overall or recurrence-free survival post transplant despite a higher drop-out rate prior to transplant [22]. Individuals with a significant risk for the development of HCC should undergo surveillance. Most screening programmes use 6-monthly ultrasound scans, with or without serum alpha-fetoprotein (AFP) measurement. The merits of serum AFP measurement as an adjunct to high quality 6-monthly ultrasound examinations is debated, and many units have deleted its measurement from surveillance practice in the monoinfected population. Appropriate surveillance may permit treatment for HCC to be offered at a potentially curable stage, and thus prolong life [23].

Since the advent of ART, a number of programmes have undertaken liver transplantation in HIV-infected individuals. HIV infection is not considered a contraindication to liver transplantation, and published guidelines support its use in HIV-infected patients [24,25]. Successful outcome of transplantation has been reported by a number of groups [26–30]. Indications for liver transplantation in HIV patients include hepatitis virus-induced cirrhosis with or without HCC, HIV drug-induced liver injury, and other HIV (e.g., non-cirrhotic portal hypertension) and non-HIV (e.g., steatosis, alcohol)-associated disease. The post-transplant outcome is mainly determined by the aetiology of the liver disease and by the severity of recurrent disease. Independent pre-transplant factors that have been associated with a

worse prognosis include genotype 1 HCV infection and MELD score. Post-transplant prognosis is superior for patients with HBV (HR: 8.28 95%, CI 2.26–30.3) than those with HCV/HIV or other liver conditions [31] in HIV-infected persons as prevention of HBV recurrence can be achieved by the use of HBV antiviral drugs with or without hepatitis B immunoglobulin (HBIG) [32]. However, there are no current strategies to prevent recurrent HCV infection. The outcome of transplantation of HCV/HIV-coinfected patients is inferior to that achieved for HCV-monoinfected patients, with both worse graft and patient survival [29,30]. Those patients with aggressive, early recurrence (known as fibrosing cholestatic hepatitis) have a very poor outcome with a low chance of survival beyond 3 years post transplant [33].

Transplantation of patients with a predictable poor outcome should be avoided if possible. Recent publications have identified such characteristics and associated these with outcome after transplantation in HCV/HIV-coinfected patients. Appropriate selection and matching of recipients and donors may improve the outcome of HCV/HIV-transplanted patients and permit more appropriate use of donor livers for the competing HIV-negative population [29,30,34]. The poor outcome of transplanted HCV/HIV patients could be improved by successful HCV antiviral treatment post transplant, and the current and ongoing development and incorporation of direct-acting antiviral drugs into combination therapy for HCV may have a significant impact on this, although drug-drug interactions will need careful management.

The optimal timing of listing and transplantation of the HCV/HIV patient remains a challenge, and waiting list mortality appears higher than in HIV-negative patients [12]. Poor outcome might reflect late referral for transplant assessment and/or more rapid deterioration after the onset of hepatic decompensation. In either case, it is imperative that HIV-positive patients with a diagnosis of ESLD are co-managed by an experienced HIV physician and a hepatologist with close links to a transplant unit, thus permitting expeditious referral and assessment at the first sign of decompensation.

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12 List of Abbreviations

3TC	Lamivudine (2', 3'-dideoxy-3'-thiacytidine)	HBV	Hepatitis B virus
ADV	Adefovir	HCV	Hepatitis C virus
AHC	Acute hepatitis C	HDV	Hepatitis D virus
AIDS	Acquired immune deficiency syndrome	HEV	Hepatitis E virus
ALT	Alanine transaminase	HIV	Human immunodeficiency virus
ANRS	Agence Nationale de Recherché sur le Sida	HR	Hazard ratio
Anti-HBc	Hepatitis B core antibody	IDU	Injection drug user
Anti-HBe	Hepatitis B 'e' antibody	IFN	Interferon
HBeAg	Hepatitis B 'e' antigen	IL28	Interleukin 28
Anti-HBs	Hepatitis B surface antibody	INI	Integrase inhibitor
APRI	Aspartate transaminase to platelet ratio index	ITU	Intensive therapy unit
ARFI	Acoustic radiation force impulse	LGV	Lymphogranuloma venereum
ART	Antiretroviral therapy	MELD	Model for end-stage liver disease
ARV	Antiretroviral	MSM	Men who have sex with men
AST	Aspartate transaminase	NA	Nucleoside analogue
AUC	Area under the curve	NICE	National Institute for Health and Clinical Excellence
AUROC	Area under the receiver operating characteristic	NNRTI	Non-nucleoside reverse transcriptase inhibitor
BHIVA	British HIV Association	NPV	Negative predictive value
BOC	Boceprevir	NRTI	Nucleos(t)ide reverse transcriptase inhibitor
BPS	British Psychological Society	PCR	Polymerase chain reaction
CCR5	C-C chemokine receptor type 5	PEG-IFN	Pegylated interferon
CD4	Cluster of differentiation 4	P-GP	p-glycoprotein
CHB	Chronic hepatitis B	PI	Protease inhibitor
CHIC	Collaborative HIV Cohort Study	PI/r	Ritonavir-boosted protease inhibitor
CI	Confidence interval	PICO	Patient, intervention, comparison and outcome
C _{min}	Minimum concentration	PK	Pharmacokinetic
CrCL	Creatinine clearance	PPV	Positive predictive value
CYP	Cytochrome P	RAL	Raltegravir
D4T	Stavudine (2'-3'-dideoxy-2'-3'-dideoxythymidine)	RBV	Ribavirin
DAA	Directly acting antiviral	RCT	Randomised controlled trial
ddI	Didanosine (2',3'-dideoxyinosine)	RNA	Ribonucleic acid
DDI	Drug-drug interaction	RVR	Rapid virological response
DILI	Drug-induced liver injury	SNP	Single-nucleotide polymorphism
DNA	Deoxyribonucleic acid	STI	Sexually transmitted infection
ELF	Enhanced liver fibrosis	SVR	Sustained virological response
ESLD	End-stage liver disease	TBV	Telbivudine
EVR	Early virological response	TDF	Tenofovir disoproxil fumarate
FTC	Emtricitabine	TE	Transient elastography
GPP	Good practice point	TLR	Toll-like receptor
GRADE	Grading of recommendations assessment, development and evaluation	TNF	Tumour necrosis factor
GT	Genotype	TPV	Telaprevir
HAV	Hepatitis A virus	UK-CAB	UK Community Advisory Board
HBsAg	Hepatitis B surface antigen	USS	Ultrasound scan
		VL	Viral load
		ZDV	Zidovudine

13 List of Appendices

The appendices can be found on the BHIVA website (<http://www.bhiva.org/Hepatitis-2013.aspx>)

Appendix 1: Summary modified GRADE system

Appendix 2: Literature search

A2.1 Questions and PICO criteria

A2.2 Search protocols