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

• **Aim**: provide guidance on best clinical practice
• **Guidance**: treatment and management of adults with HIV and viral hepatitis coinfection
• **Target**: clinical professionals involved in and responsible for care, and community advocates responsible for promoting best interests and care
• **Setting**: read in conjunction with other published BHIVA and hepatitis guidelines
• **Excluded**: do not cover other infections outside hepatitis A–E or non-infection related hepatic disease
Scope and purpose

• Included:
  • Guidance on diagnostic and fibrosis screening
  • Preventative measures including immunisation and behavioural intervention
  • ART therapy and toxicity in the context of co-infection
  • Management of acute and chronic HBV/HIV, HCV/HIV, HDV/HIV and HEV/HIV infection
  • Monitoring and management of co-infection-related end-stage liver disease (ESLD) including transplantation
Methodology

- Modified GRADE system for review of evidence
- Multidisciplinary writing group including HIV specialists, hepatologists, and pharmacists
  - Section leads with subsection writing teams
- Elected community representative involved in all aspects of guideline development process and responsible for liaising with all interested patient groups
- Literature and conference abstract search 1 January 2009–31 October 2012
Methodology

- The scope, purpose and guideline topics were agreed by the Writing Committee.
- Review questions were developed in a PICO (patient, intervention, comparison and outcome) framework.
- This framework guided the literature-searching process and critical appraisal, and facilitated the development of recommendations.
- The draft guidelines were peer-reviewed and published on-line for consultation.
Eleven review questions identified by Writing Group

Chronic HBV/HIV

- When is the optimum time to commence ART in chronic HBV/HIV infection?
- Which is the anti-HBV treatment of choice when the CD4 cell count is >500 cells/μL in chronic HBV/HIV infection?
- Should FTC or 3TC be used in combination with tenofovir in chronic HBV/HIV infection?

Acute HCV/HIV

- In adults who contract acute HCV are there benefits in giving combination therapy with pegylated interferon (PEG-IFN) and ribavirin over PEG-IFN alone, and are there benefits from 48 weeks as opposed to 24 weeks of treatment?
Eleven review questions identified by Writing Group

Chronic HCV/HIV

• Should screening for HCV be performed 6 monthly or 12 monthly?
• Should the screening test be HCV antibody, HCV-PCR or HCV antigen?
• When deciding ART in HCV/HIV infection, is there a preferred combination that differs from that given to those with HIV monoinfection?
• Should \textit{IL28B} be used routinely in determining treatment strategies in chronic HCV/HIV infection?
• When is the optimum time to commence ART in adults with chronic HCV/HIV infection?
Eleven review questions identified by Writing Group

Chronic HBV/HIV and HCV/HIV

- Is liver biopsy or hepatic elastometry the investigation of choice in the assessment of fibrosis?
- Should ultrasound scan (USS) surveillance be performed 6 or 12 monthly to detect early hepatocellular carcinoma (HCC)?
Screening investigations at diagnosis

- HBV and HCV are common co-infections and cause accelerated fibrosis
- All patients should be screened for immunity against HAV and HBV and vaccinated if non-immune
- All patients should have HBsAg checked and in addition if positive:
  - HBV DNA, HBeAg and anti-HBe
  - Anti-HDV with HDV RNA if positive (up to 6% of patients with HBV/HIV in the UK are HDV positive)
Screening investigations at diagnosis

- HCV should be screened for at diagnosis and at least annually
- HCV-RNA should be checked in addition if:
  - Raised LFTs despite negative anti-HCV
  - When past spontaneous clearance or successful treatment (SVR)
  - Recent or repeated high-risk exposure (e.g. MSM and UPSI, concurrent STI, high-risk sexual practices, recreational drug use)
- If anti-HCV positive, an HCV-PCR and genotype should be performed
- Anti-HEV should be checked if raised transaminases and/or cirrhosis and other common causes excluded
Behavioural modification counselling

- Important to reinforce message of condoms
- Counselling should be given at HIV diagnosis and on an ongoing basis on relevant risk factors for HCV:
  - UPSI
  - Concurrent STI
  - High-risk sexual practices (fisting, sex toys etc.)
  - Recreational drug usage/sharing injecting equipment
- Risk-reduction advice should be given to all patients with HBV or HCV co-infection
Assessment of liver disease

- Liver disease staging and grading is essential:
  - For antiviral treatment decisions
  - To identify advanced fibrosis and need for monitoring
- All patients with chronic HBV or HCV co-infection should have a fibrosis assessment
  - Non-invasive test recommended: transient elastography (FibroScan)
  - If unavailable then panel of biochemical tests (e.g. APRI, ELF)
  - Liver biopsy investigation of choice in certain situations (e.g. aetiology of liver disease unclear, discordance between results)
Immunisation

- All non-immune patients should be immunised against HAV and HBV.
- A schedule of four 40-μg (double dose) vaccinations at 0, 1, 2 and 6 months is recommended.
  - Anti-HBs should be measured 4–8 weeks after last vaccine dose.
  - If anti-HBs <10 IU/L, offer 40-μg vaccination monthly for 3 months, check anti-HBs 4–8 weeks afterwards.
  - If anti-HBs between >10 and <100 IU/L, offer one 40-μg vaccination, check anti-HBs 4–8 weeks afterwards.
Immunisation

- If anti-HBs declines to <10 IU/L after initial satisfactory response, one 40-μg (double dose) booster should be given.
- If the patient is unable to develop an antibody response to vaccine or anti-HBs <10 IU/L, post vaccine annual HBsAg screening should continue.
- Anti-HBs levels should be checked regularly after successful vaccination:
  - Annually if between >10 and <100 IU/L
  - Every 2 years if >100 IU/L
Initiation of ART should be considered in all co-infected patients irrespective of CD4 cell count.

- Choice should take into consideration pre-existing liver disease
- ART should not be delayed because of a risk of drug-induced liver injury
- Where direct-acting antivirals (DAAs) are used for HCV treatment, careful consideration should be given to potential drug–drug interactions

All patients should have baseline LFTs checked before initiating a new ARV, at 1 month, and then 3–6 monthly
ARV therapy in hepatitis co-infection

- ART should be discontinued if grade 4 hepatotoxicity (transaminases >10 times ULN) develops
- In patients with ESLD (Child–Pugh B/C):
  - Close monitoring is imperative
  - Consideration should be given to performing plasma level monitoring of ART agents, 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
HBV

- The prevalence of HBV/HIV in the UK is 6.9%
  - Highest rates in those of Black/‘other’ ethnicity and those with a history of injection drug use (IDU)
- The 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
- HBV does not impact on HIV progression
- HIV affects all phases of HBV natural history with:
  - Lower rate of natural clearance and higher HBV-DNA levels
  - Faster progression to fibrosis, ESLD, and HCC
HBV

- 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.
- Patients should be treated if they have:
  - An HBV DNA ≥2000 IU/mL
  - Anything more than minimal fibrosis (Metavir ≥F2 or Ishak ≥S2 on liver biopsy or indicative fibrosis ≥F2 by TE – FibroScan ≥9.0 kPa)
- 6-monthly transaminases and HBV DNA measurements should be performed for routine monitoring of therapy
HBV

- Those with a CD4 cell count ≥500 cells/μL, an HBV DNA of <2000 IU/mL, minimal or no evidence of fibrosis (Metavir ≤F1 or Ishak ≤S1 or FibroScan <6.0 kPa) and a repeatedly normal ALT can be given the option to:
  - Commence treatment or
  - Be monitored not less than 6 monthly with HBV DNA and ALT and at least yearly for evidence of fibrosis

- Patients with a CD4 cell count <500 cells/μL should be treated with fully suppressive ART inclusive of anti-HBV-active antivirals
HBV treatment CD4 cell count $>500$ cells/$\mu$L

- TDF/FTC or TDF/3TC as part of a fully suppressive is recommended for all patients
- Adefovir or 48 weeks of PEG-IFN are alternative options in patients unwilling or unable to receive TDF/FTC
- PEG-IFN should be used in HBsAg-positive patients with:
  - Repeatedly raised ALT, low HBV DNA ($<2 \times 10^6$ IU/mL), minimal fibrosis and irrespective of HBeAg antigen status
  - A lack of HBV DNA response (reduction to $<2000$ IU/mL at 12 weeks) prompting discontinuation.
  - Repeat testing performed 3-monthly to observe the presence of seroconversion
HBV treatment CD4 cell count <500 cells/μL

- All patients should receive TDF/FTC or TDF/3TC as part of a fully suppressive combination ART regimen
- Within the context of ART:
  - Where TDF is not currently being given as a component of ART it should be added or substituted for another agent within the regimen unless there is a contraindication
  - 3TC/FTC should not be used as the sole anti-HBV agent due to the rapid emergence of HBV resistant to these agents
  - 3TC/FTC may be omitted and tenofovir be given as the sole anti-HBV active agent if there is clinical/genotypic evidence of 3TC/FTC- resistant HBV or HIV
HBV treatment CD4 cell count <500 cells/μL

- Where wild-type HBV exists, either FTC or 3TC can be given with tenofovir
- If tenofovir is contraindicated, entecavir should be used if retaining activity. This must be used in addition to fully suppressive ART
- Patients with severe/fulminant HBV in the context of HIV should be treated with:
  - ART inclusive of tenofovir and 3TC or FTC or
  - Entecavir given with ART
HDV

- HDV has a prevalence of 2.6–6.0% in the UK
  - All patients who are HBsAg positive should be screened for HDV with anti-HDV
  - Repeat testing is only required where there is continued risk
  - If anti-HDV positive, an HDV-RNA should be performed
- All patients with HDV/HBV/HIV should be treated with TDF in the context of ART
- Ideally patients should be managed in a centre used to managing HDV infection
- 1 year of PEG-IFN has been effective in achieving an SVR in:
  - 28–41% of monoinfected patients with similar results reported from small series in co-infected
HCV – when to start ART

Where a decision has been made not to start anti-HCV therapy immediately:

- If the CD4 count is ≥500 cells/μL ART is advised
- If the CD4 count is <500 cells/μL ART should be started

Where anti-HCV therapy is going to be started

- ART should be started first if the CD4 count is <350 cells/μL
- ART is advisable first when the CD4 count is 350–500 cells/μL

If there is an urgent indication for anti-HCV treatment, ART should be started:

- As soon as the patient has been stabilised on HCV therapy
HCV treatment – before starting

- All patients should be:
  - Considered for HCV treatment
  - Have a baseline fibrosis assessment
  - Be managed in a joint clinic or by a physician with hepatitis and HIV expertise
  - Pre-treatment, have referrals made to appropriate services if drug or alcohol dependency, or mental health disease input required
  - Be jointly managed with a hepatologist if advanced cirrhosis
HCV – using current DAAs

- If boceprevir is to be used, raltegravir (RAL) is the treatment of choice
- If telaprevir is to be used, either RAL or standard-dose atazanavir/r is the treatment of choice
  - Efavirenz may be used but the telaprevir dose needs to be increased to 1125 mg tds
- PCK data supports etravirine, rilpivirine and maraviroc as alternatives with either of these DAAs
HCV treatment – genotype 1

- Patients should be treated with triple therapy (PEG-IFN, ribavirin and either boceprevir or telaprevir) if:
  - Cirrhosis (Metavir F4)
  - The patient wishes to start
- Patients should receive 48w of treatment if they have cirrhosis or fail to achieve an RVR
- Non-cirrhotic patients (null/partial/rebound) are advised to wait for newer DAAs
  - Close monitoring with at least annual fibrosis assessments by FibroScan is recommended
- Patients with ESLD must be managed in a tertiary centre
HCV treatment – genotype 2/3/4

- Patients should be treated with PEG-IFN and ribavirin if:
  - Cirrhosis (Metavir F4)
  - The patient wishes to start
- Patients should receive 48w of treatment if they have cirrhosis, fail to achieve an RVR, or have GT4:
  - If RVR achieved and no cirrhosis, duration can be reduced to 24w for GT 2 and 3
- Non-cirrhotic patients are advised to wait for newer DAAs
  - Close monitoring with at least annual fibrosis assessments by FibroScan is recommended
Acute hepatitis C

- Patients with acute HCV (AHC) should be treated:
  - If $<2 \log_{10}$ decrease in HCV RNA at 4w or with a positive HCV RNA at 12w
  - With PEG-IFN and ribavirin for 24w
- Patients should be managed as for chronic HCV if:
  - They have not commenced treatment by 24w
  - They do not achieve an EVR or relapse after treatment
- Patients who have been re-infected should be managed as for AHC
Hepatitis E

- Patients need only be screened for HEV if:
  - Raised LFTs and/or liver cirrhosis when other causes have been excluded
- Screening should be with anti-HEV
  - If the CD4 count is <200 cells/μL, HEV-RNA should be performed as well
- Acute HEV in the context of HIV does not require treatment
- Patients with confirmed chronic HEV/HIV (RNA positive for more than 6 months) should:
  - Receive optimised ART
  - Be considered for ribavirin with additional or switch to PEG-IFN if no response
Cirrhosis/ESLD

- Patients with cirrhosis/ESLD should be screened for:
  - Complications of cirrhosis and portal hypertension in accordance with national guidelines for monoinfection
  - HCC with 6-monthly ultrasound and serum AFP
- Management should be:
  - Jointly with hepatologists or gastroenterologists with knowledge of ESLD preferably within a specialist centre
  - All patients with hepatitis virus/HIV with cirrhosis should be referred early, and no later than after first decompensation, to be assessed for liver transplantation.
- All non-cirrhotic patients with HBV/HIV should be screened for HCC 6 monthly