

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

Appendix 2

Systematic literature search

2.1 Questions and PICO criteria

Data bases: Medline, Embase, Cochrane Library

Conference Abstracts:

- IAS Conference on HIV pathogenesis and treatment
- International AIDS conference
- Conference on retroviruses and opportunistic infections
- European conference on clinical aspects and treatment of HIV infection
- Interscience conference on antimicrobial agents and chemotherapy
- International congress on drug therapy in HIV infection
- British HIV Association and HIV/hepatitis conference
- European Association for the Study of Liver Diseases
- American Association for the Study of Liver Diseases
- British Association for the Study of Liver Diseases
- International Co-infection workshop

Date parameters:

- Data bases: January 2009–November 2012
- Conference abstracts: January 2009–November 2012

Screening, prevention and immunisation

Study design: Systematic reviews (SRs), randomised control trials (RCTs), Observational, risk economic

Screening for HCV:

Population: HIV-infected persons

Intervention: HCV screening 6m, diagnostic test HCV antigen/HCV PCR

Comparator: HCV screening 12m, anti-HCV

Outcome: missed HCV cases, cost and transmission rates

Questions

1. Should screening be performed for HCV in adults with HIV infection 6 monthly or 12 monthly?
2. Should the screening test be HCV antibody, HCV-PCR or HCV antigen?

Screening for liver fibrosis:

Population: HIV-infected persons

Intervention: Hepatitis fibrosis screening with hepatic elastometry

Comparator: Liver biopsy

Outcome: Distinction of mild/normal disease vs. established fibrosis, distinction of cirrhosis from non-cirrhosis, adverse effects, cost and patient satisfaction

Question

3. Is liver biopsy or hepatic elastometry the investigation of choice in the assessment of fibrosis?

Antiretroviral therapy and hepatotoxicity

Study design: SRs, RCTs, Observational

Antiretroviral therapy in HCV/HIV infected patients

Population: HCV/HIV infected, ART naive/experienced

Intervention: ARVs (all classes)

Comparator: no treatment

Outcome: severe adverse events, Grade 3/4 treatment-associated hepatitis, and HIV viral suppression <50 copies/mL

Question

4. When deciding ART for adults with HCV/HIV infection, is there a preferred combination which differs from those with HIV mono-infection?

Hepatitis B (HBV)

Study design: SRs, RCTs, Observational

Thresholds for ART treatment

Population: HBV/HIV infected, ART naive

Intervention: Starting ART early: i) at CD4 >350–500 cells/ μ L, ii) at CD4 >500 cells/ μ L, iii) immediately at diagnosis

Comparator: Starting ART count <350 cells/ μ L

Outcome: 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

Question

5. When is the optimum time to commence ART in chronic HBV/HIV co-infection?

HBV treatment: CD4 >500 cells/ μ L

Population: HBV/HIV infected, ART naïve, CD4 >500 cells/μL

Intervention: Adefovir, pegylated interferon

Comparator: no treatment, TDF/FTC containing ART

Outcome: Mortality, HIV disease progression, HBV disease progression (cirrhosis, HCC), HBV DNA decline on therapy, severe treatment-associated adverse events and patient acceptability

Question

6. Which is the anti-HBV treatment of choice when the CD4 count is >500 cells/μL?

ART treatment in HBV

Population: HBV/HIV infected, ART naïve

Intervention: FTC (emtricitabine)

Comparator: 3TC (lamivudine)

Outcome: HBV DNA decline on therapy, cost and adverse events

Question

7. Should FTC or 3TC be used in combination with tenofovir?

Hepatitis C (HCV)

Study design: SRs, RCTs, Observational

Population: HCV/HIV infected, genotype 1

Intervention: *IL28B* screening

Comparator: No screening for *IL28B*

Outcome: Sustained virological response (SVR) rates at 12 and 24 weeks, cost and need for triple therapy

Question:

8. Should *IL28B* be used routinely as a screening test in determining treatment strategies in adults with chronic HCV/HIV infection?

Thresholds for ART treatment

Population: HCV/HIV infected, ART naïve

Intervention: Starting ART early: i) at CD4 >350–500 cells, ii) at CD4 >500, iii) immediately at diagnosis; starting ART before HCV treatment

Comparator: Starting ART count <350 cells; starting HCV treatment before ART

Outcome: Mortality, non-hepatic HCV comorbidity, HCV disease progression (cirrhosis, hepatocellular carcinoma), ARV resistance development and severe treatment-associated adverse events

Question:

9. When is the optimum time to start ART in chronic HCV/HIV infection?

Acute HCV

Population: hepatitis C <6m, HCV treatment naive

Intervention: 24w treatment; PEG-IF/RBV therapy

Comparator: 48w treatment, PEG-RIB

Outcome: sustained virological response (SVR)

Questions

10. Are there benefits of treating with PEG-IF and ribavirin over giving PEG-IFN alone and are there benefits of 48 weeks of treatment as opposed to 24 weeks of treatment?

End Stage Liver Disease (ESLD)

ESLD

Population: chronic viral hepatitis/HIV co-infected patients, established cirrhosis

Intervention: Ultrasound screening for HCC 6m

Comparator: Ultrasound screening for HCC 12m

Outcome: HCC mortality, HCC missed diagnoses and cost of screening

Question

11. Should ultrasound scan (USS) surveillance testing be performed 6- or 12-monthly to detect early HCC in adults with chronic viral hepatitis/HIV infection?

Questions 1 and 3

BHIVA Hepatitis co-infection Guideline: SEARCH PROTOCOL: main databases search

Search 1: HBV diagnosis and screening

Component	Description
Review area	diagnosis and screening of HBV /HDV/HEV in HIV co-infected people
Objectives	To establish best diagnostic tests and screening methods for HBV in people with HIV
Populations	HIV All
Interventions	Diagnostic tests, viral load testing, Hepatitis B surface antigen, HBV-DNA, occult, HDV (delta) E Screening, monitoring tests, liver biopsy, elastography, biomarkers FibroScan, hepatic elasticity, liver fibrosis screening/monitoring AFP, alpha fetoprotein, ultrasound, hepatoma screening, hepatocellular/ liver cell carcinoma screening/testing
Comparisons/ aspects covered by search	With each other and placebo
Outcomes	To be decided by writing groups
Study designs	All studies
Exclusions	Animal studies, letters, editorials, comments, Non English studies.
How the information was searched	Databases: Medline, Embase, Cochrane Library Language: restrict to English only date parameters : 2009-current
Search terms and date	HIV + HEP B/D/E+ see above for interventions

searched	
Search results	Medline= 624 Embase= 797 Cochrane = 26 Total deduplicated/sifted = 848
The review strategy (The methods that will be used to review the evidence, outlining exceptions and subgroups.)	
Key papers	

Questions 1–3, 9, 10

BHIVA Hepatitis co-infection Guideline: SEARCH PROTOCOL: main databases search

Search 2: HCV diagnosis and screening

Component	Description
Review area	diagnosis and screening for Hepatitis C in people with HIV
Objectives	To establish best diagnostic tests for hepatitis and the best screening methods in co-infected people
Populations	HCV/HIV co-infected All
Interventions	Diagnostic tests, standard HCV antibody tests/ HCV antibody enzyme immunoassay/ELISA, HCV core antigen tests, HCV-RNA, viral load testing, AFP, alpha fetoprotein, ultrasound, hepatoma screening Genotype screening, IL28 / Interleukin 28B screening Screening, monitoring tests, liver biopsy, elastography, biomarkers
Comparisons/ aspects covered by search	With each other and placebo
Outcomes	To be decided by writing groups
Study designs	All studies
Exclusions	Animal studies, letters, editorials, comments, Non English studies.
How the information was searched	Databases: Medline, Embase, Cochrane Library Language: restrict to English only date parameters : 2009-current
Search terms and date searched	HIV + HCV+ see above for interventions

Search results	Medline= 845 Embase= 1079 Cochrane = 35 Total deduplicated/sifted = 1143
The review strategy (The methods that will be used to review the evidence, outlining exceptions and subgroups.)	
Key papers	

Questions 5–7

BHIVA Hepatitis co-infection Guideline: SEARCH PROTOCOL: main databases search

Search 3: Drug therapies for HBV

Component	Description
Review area	Drug therapies for people with HIV and HBV/HDV/HEV co- infection
Objectives	To establish best drug therapies and regimens for people with HIV and hepatitis B/D/E
Populations	HIV/ HEP B/D/E co-infected All
Interventions	ARVS, HAART, antiretrovirals, protease inhibitor, integrase inhibitor, NNRTI, NRTI, abacavir, atazanavir, cobicistat, darunavir, didanosine, efavirenz, elvitegravir, emtricitabine, enfuvirtide, etravirine, fosamprenavir, indinavir, lamivudine, lopinavir, maraviroc, nevirapine, raltegravir, rilpivirine, ritonavir, saquinavir, stavudine, tenofovir, zidovudine interferon, peginterferon, telbivudine, entecavir, adefovir
Comparisons/ aspects covered by search	With each other
Outcomes	To be decided by writing groups includes hepatotoxicity
Study designs	All studies
Exclusions	Animal studies, letters, editorials, comments, Non English studies.
How the information was searched	Databases: Medline, Embase, Cochrane Library Language: restrict to English only date parameters : 2009-current
Search terms and date searched	HIV + HBV/HDV/HEV+ drug therapies

Search results	Medline= 469 Embase= 580 Cochrane = 27 Total deduplicated/sifted = 664
The review strategy (The methods that will be used to review the evidence, outlining exceptions and subgroups.)	
Key papers	

Questions 4, 9, 10

BHIVA Hepatitis co-infection Guideline: SEARCH PROTOCOL: main databases search

Search 4: Therapies for HCV

Component	Description
Review area	Therapies for people with hepatitis C/HIV co-infection
Objectives	To establish best drug therapies and regimens for people with HIV/ hepatitis C
Populations	HIV/ HEPC co-infected All
Interventions	ARVS, HAART, antiretrovirals, protease inhibitor, integrase inhibitor, NNRTI, NRTI, abacavir, atazanavir, cobicistat, darunavir, didanosine, efavirenz, elvitegravir, emtricitabine, enfuvirtide, etravirine, fosamprenavir, indinavir, lamivudine, lopinavir, maraviroc, nevirapine, raltegravir, rilpivirine, ritonavir, saquinavir, stavudine, tenofovir, zidovudine ribavirin, interferon, peginterferon, PEG-RIB, DAA, direct-acting antivirals, telaprevir, boceprevir EPO, epoetin, erythropoietin, darbepoetin(for anaemia)
Comparisons/ aspects covered by search	With each other
Outcomes	To be decided by writing groups includes hepatotoxicity
Study designs	All studies
Exclusions	Animal studies, letters, editorials, comments, Non English studies.
How the information was searched	Databases: Medline, Embase, Cochrane Library Language: restrict to English only date parameters : 2009-current

Search terms and date searched	HIV + HCV+ drug therapies/ regimens for HIV and HCV
Search results	Medline= 848 Embase= 1145 Cochrane = 48 Total deduplicated/sifted = 1086
The review strategy (The methods that will be used to review the evidence, outlining exceptions and subgroups.)	
Key papers	

Question 11

BHIVA Hepatitis co-infection Guideline: SEARCH PROTOCOL: main databases search

Search 5: ESLD

Component	Description
Review area	Management of people with HIV and ESLD
Objectives	To establish best management methods for people with HIV and ESLD
Populations	HIV/ ESLD (including liver failure, cirrhosis, portal hypertension, hepatocellular carcinoma, liver transplantation) All
Interventions	All therapies/management methods No terms entered in search
Comparisons/ aspects covered by search	With each other and placebo
Outcomes	To be decided by writing groups
Study designs	All studies
Exclusions	Animal studies, letters, editorials, comments, Non English studies.
How the information was searched	Databases: Medline, Embase, Cochrane Library Language: restrict to English only date parameters : 2009-current
Search terms and date searched	HIV + ESLD (including all above population terms)
Search results	Medline= 354 Embase= 384

	Cochrane = 13 Total deduplicated/sifted = 497
The review strategy (The methods that will be used to review the evidence, outlining exceptions and subgroups.)	
Key papers	

BHIVA Hepatitis co-infection Guideline: SEARCH PROTOCOL: main databases search

Additional search: Immunisation

Component	Description
Review area	Immunisation against Hepatitis (A and B) in people with HIV
Objectives	To review methods/ effectiveness of the use of HAV and HBV vaccination in people with HIV
Populations	HIV All
Interventions	HAV/HBV Immunisation/ vaccination/ vaccine(s)/ booster Engerix B, Fendrix, HBvaxPro, Avaxim, Epaxal, Havrix, Ambirix, Twinrix
Comparisons/ aspects covered by search	All aspects including safety and efficacy, dosage, schedule, timing etc- to be decided by writing group
Outcomes	To be decided by writing groups
Study designs	All studies
Exclusions	Animal studies, letters, editorials, comments, Non English studies.
How the information was searched	Databases: Medline, Embase, Cochrane Library Language: restrict to English only date parameters : 2009-current
Search terms and date searched	HIV + interventions (see above) Searched 17 October 2012
Search results	Medline= 211 Embase= 280 Cochrane = 15 Total deduplicated/sifted = 323
The review strategy (The methods that will be used to review the	

evidence, outlining exceptions and subgroups.)	
Key papers	<i>Search validated against included papers in updating guideline</i>