

## **2010 European Guideline for the management of Hepatitis B and C virus infections**

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## **Hepatitis B virus infection**

### Introduction

Hepatitis B is caused by an hepadna (DNA) virus. Despite availability of a vaccine, HBV infection is endemic, estimated to affect 400million people worldwide, with very high carriage rates (up to 20%) particularly in South and East Asia. High carriage rates (up to 10%) are also found in some regions of Central and South America, Africa and parts of Asia. The reported incidence of acute hepatitis B in 2004 was 0-10/100,000 population in most of Europe but was 10-50/100,000 in Albania and most of Eastern Europe.<sup>1,2</sup> There has been a steady decline in incidence, particularly in West Europe, in the last two decades. Chronic carriage in the general population occurs in >8% in parts of Eastern Europe, 2-8% in Southern Europe and 0.1-2% in Northern and Western Europe<sup>3</sup>. However, much higher carriage rates are found in certain sub-groups including injecting drug users, homosexual men, female sex workers and immigrants from high endemicity countries<sup>4-7</sup>

### Transmission

- Sexual transmission occurs in unvaccinated homosexual men and correlates with multiple partners and unprotected anal sex.<sup>5,6,8-11</sup> Transmission also occurs after heterosexual contact (e.g. 18% infection rates for regular partners of patients with acute hepatitis B)<sup>12-14</sup>. Sex workers are also at higher risk<sup>7,15</sup>.



\*in very early infection the IgM anti-core can be negative and therefore so can the IgG

\*\* N=normal

*Other tests*

- Acute HBV infection - serum amino-transferases (ALT) raised: rarely >10,000 IU/l. Serum bilirubin: rarely >300  $\mu$ moles/l. Alkaline phosphatase generally <2x the upper limit of normal, except in cases complicated by cholestasis. Prothrombin time generally normal, although may be prolonged by up to 5 seconds; greater prolongation indicates developing hepatic failure.
- Chronic HBV infection - in most cases the only abnormality to be found will be mildly abnormal amino-transferase levels (usually <100 IU/l) and in many patients the liver function tests (LFT) will be normal, particularly in the immune tolerant and inactive carrier stages<sup>10, 23-27</sup>.

### Indications for HBV testing

1] Patient with acute icteric hepatitis: Test for Hepatitis B surface antigen (HBsAg) (and liver function test, prothrombin time, urea and electrolytes) [IIa, B]. If HBsAg positive, proceed to 'e' antigen (HBeAg), anti-core IgM and hepatitis B virus DNA (HBV-DNA) [IIA, B]. Interpretation: see table. Also test for hepatitis A and C.

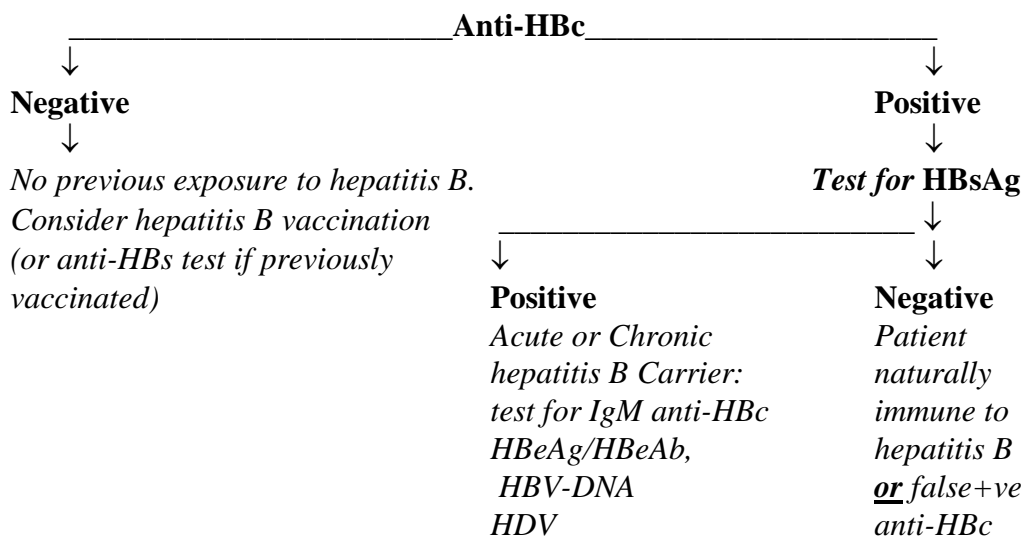
2] Part of Screening: If local prevalence of hepatitis B carriage is <1% consider screening high risk groups only (patients from highly endemic areas, homosexual men, sex workers, heterosexual people with multiple partners, injecting drug users, HIV-positive patients, sexual assault victims and sexual partners of HBsAg positive patients or those in these risk groups) <sup>5-20</sup>. [IIa, B]. If local prevalence of hepatitis B carriage is >1% consider testing all those attending for a STD screen.

3) All HIV patients, especially prior to initiation of HAART

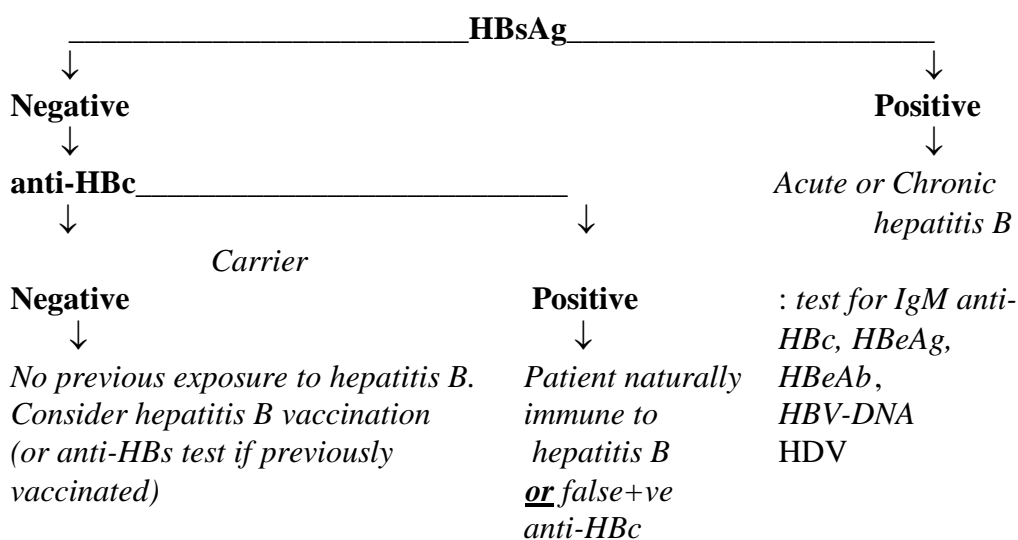
4) All patients commencing immunomodulatory therapies and chemotherapy

*Screening tests in asymptomatic patients:* Initial screening for hepatitis B can be achieved by using either the anti-hepatitis B core antibody (anti-HBc) or HBsAg tests or both, followed by further tests accordingly (see flow charts and table for interpretation). Anti-HBc as the first test has the advantage that it will detect evidence of current or past infection allowing decisions to be made about the need for vaccination or treatment <sup>28-33</sup>. However, this test is prone to false-positives and people who are anti-HBc+ve, anti-HBs -ve may be considered as possibly non-immune (see below). An alternative screening strategy is to test for HBsAg initially which detects active infection but does not allow vaccination decisions to be made unless the anti-HBc test is also used. [IIa, B]

Flow chart for hepatitis B screening using serum anti-HBc



*Flow chart for hepatitis B screening using serum HBsAg*



If after screening, the patient is found to be non-immune, consider vaccination (see below) <sup>16,17,34,35</sup> [Ia, A]. If found to be a chronic HBV carrier, consider referral for further assessment and possible antiviral therapy <sup>26, 36,37</sup>. [Ia, A].

*Primary Prevention/Vaccination*

- Hepatitis B transmission can be reduced by avoiding unprotected penetrative anal and vaginal sex and oro-anal contact, or by using condoms if the partner is HBsAg positive or their status is unknown <sup>38</sup>. [IIa, B]
- The World Health Organisation recommends universal HBV vaccination <sup>38</sup>.
- If universal vaccination is not pursued it should be offered to non-immune patients in most of the high risk groups (see above) <sup>16, 17, 34, 35</sup>. [Ia, A] The main exception is people born in countries of high endemicity but not at continuing risk who are being screened primarily to detect chronic HBV carriage <sup>29,30</sup>. [IIa, B]
- HIV positive patients show a reduced response rate to the vaccine (approximately 40%) and initial responders can become anti-HBs-negative within a year <sup>40-42</sup>. [IIa, B].
- There are three possible vaccination schedules for both the monovalent and the combined hepatitis A+B vaccines: 0, 1, 6 months, 0, 1, 2 and 12 months ('rapid course') or 0, 1, 3 weeks, and 12 months ('ultra-rapid course') <sup>17, 30, 31, 34, 35</sup>. [IIa, B] Non- or poor responders usually respond to further doses (up to three injections normal or double dose), ideally given as a repeat course <sup>44, 45</sup> [IIa, B]. Some newer vaccines are more immunogenic including Fendrix™, which has a novel adjuvant and the pre-S-antigen-containing vaccines. Currently Fendrix is only licensed for use in patients with renal insufficiency and pre-S vaccines have not been launched commercially <sup>46-50</sup>.

- If the primary course of vaccination is incomplete, the missing doses of vaccine needed to complete the course can be given up to four years later without the need to restart the full course<sup>51, 52</sup> [III, B]
- Some patients test anti-HBc positive but negative for anti-HBs and HBsAg. This could be due to either past infection or may be a false-positive test. A single hepatitis B vaccine dose will induce anti-HBs if there has been past natural HBV exposure (amnestic response, measured 4 weeks after single dose of HBV vaccine). If anti-HBs is still negative after a single booster, regard as non-infectious and give a full course of HBV vaccine [III.B]<sup>53</sup>
- Recent evidence suggests that immuno-competent adults and children who have responded to a primary course of HBV vaccine (>10 IU/l) do not require booster doses for at least fifteen years<sup>43, 54-56</sup> [III, B] although a booster after five years is still recommended by some national bodies<sup>16</sup>. However, immuno-compromised patients, such as those with HIV or renal failure, require booster doses of vaccine when the anti-HBs level falls below 100 IU/l<sup>42, 43, 55</sup> [IIa, B].

### Management of HBsAg-positive patients

#### General

- Patients should be advised to avoid unprotected sexual intercourse, including oro-anal contact until they have become non-infectious or their partners have been successfully vaccinated (see below)<sup>9, 10, 12, 16, 29</sup>. [IIa, B]
- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s), routes of transmission of infection (see below) and advised not to donate blood<sup>16</sup> [III, B]
- Hepatitis B is a notifiable disease in many European countries<sup>1,2</sup>.
- If not performed already, screen for other sexually transmitted diseases in cases thought to have been sexually acquired or if otherwise appropriate<sup>8, 12</sup> [III,B]
- Other tests such as liver biopsy or assessment of liver fibrosis (for assessment of chronic disease) should be performed by specialists in this field<sup>10, 23-26</sup> [IV, C]

#### Indications for therapy of Chronic Infection

- Treatment should normally be given in collaboration with a hepatologist or physician experienced in the management of chronic viral hepatitis [IV, C]. The decision to treat depends on pattern of disease, HBV-DNA level, and presence or absence of significant necro-inflammation and hepatic fibrosis. HBV-DNA thresholds of  $2 \times 10^4$ ,  $2 \times 10^3$  and  $2 \times 10^3$  IU/ml, are often used for HBeAg+ve chronic hepatitis, HBeAg –ve chronic hepatitis and cirrhosis respectively, for initiating therapy<sup>26,57</sup>
- Patients should be considered for therapy with lamivudine, adefovir, tenofovir, telbivudine, entecavir (or combinations of nucleos(t)ide analogues) or pegylated interferon [Ib, A]<sup>26,57-62</sup>. Additional treatments that may soon be licensed in HBV mono-infection include emtricitabine (FTC) [Ib,A], clevudine [IIa,B] and valtorcitabine [III,C]<sup>63-65</sup>. Treatment responders have long-term

benefits in terms of reduced liver damage and decreased risk of liver cancer<sup>26,56-64</sup>.

- All patients should have an HIV test prior to starting HBV therapy because of the different treatment strategies required and the significant risk of anti-retroviral-resistant HIV developing if lamivudine, tenofovir or entecavir are used as monotherapy [Ib,A]<sup>26, 57, 64, 66</sup>.
- Lamivudine, emtricitabine and tenofovir will suppress hepatitis B viral replication during therapy of HIV<sup>67-69</sup> and may delay liver damage if given as part of combination antiretroviral therapy. [Ib, A]<sup>67-69</sup>.
- Lamivudine and emtricitabine should only be given to HIV+ patients in combination with tenofovir as part of HAART because of the high rate of resistance that occurs to these drugs if given as the only HBV-active agent (Ib,A)<sup>67-69</sup>. Entecavir should not be used in HIV+ patients without adequately suppressed HIV as it causes the M184V (lamivudine/emtricitabine) resistant mutation<sup>66</sup> and there is some evidence that telbivudine may also have HIV activity<sup>70</sup> [III,B]
- Adefovir can be used alone in HIV+ patients<sup>71</sup> [IIa,B]
- Specific therapy may not be indicated, based on the HBV-DNA viral load, unless de-compensated liver disease has ensued, but all HBsAg+ve patients should receive long-term follow-up due to the risk of liver cancer.<sup>10</sup> Hepatitis A vaccination should be offered if non-immune, due to the worse prognosis of dual infection<sup>72</sup> [III,B]

### Special situations

#### *Pregnancy and Breastfeeding*

- Vertical transmission (mother to infant) of infection occurs in 65-90% of pregnancies where the mother is HBeAg positive and in about ten percent of HBsAg positive, HBeAg negative mothers. Most (>90%) of infected infants become chronic carriers<sup>18, 20, 73</sup>.
- Infants born to HBsAg positive mothers are vaccinated from birth, sometimes in combination with Hepatitis B specific Immunoglobulin (HBSIg) 200 i.u. intramuscularly<sup>18, 73</sup> [IIa,B]. This reduces vertical transmission by approximately ninety percent. There is some evidence that lamivudine may further reduce vertical transmission if given to women with a high HBV-DNA viral load in the third trimester<sup>74</sup> [Ib, A]. However, if HBSIg is not available, vaccination alone prevents vertical transmission in 66-100%<sup>73</sup> [IIa, B]. Infants should be tested for hepatitis B (HBsAg and anti-HBs) 4-6 weeks after the final dose of vaccine [IV, C].
- Infected mothers should continue to breast feed as there is no additional risk of transmission.

#### Management of partners and other contacts

- Partner notification should be performed and documented and the outcome documented at subsequent follow-up. Contact tracing to include any sexual contact (penetrative vaginal or anal sex or oro/anal sex) or needle sharing partners during the period in which the index case is thought to have been infectious<sup>29-31, 75</sup> [IIa, A]. The infectious period is from two weeks before

the onset of jaundice until the patient becomes HBsAg negative. In cases of chronic infection trace contacts as far back as any episode of jaundice or to the time when the infection is thought to have been acquired although this may be impractical for periods of longer than two or three years [IV, C]. Arrange screening for hepatitis B of children who have been born to infectious women if the child was not vaccinated at birth<sup>16</sup> [IV, C].

- If available, HBSIg 500 i.u. intramuscularly may be administered to a non-immune contact after a single unprotected sexual exposure or parenteral exposure or needle-stick injury if the donor is known to be infectious. This works best within 48 hours and is of no use after more than seven days<sup>16, 76</sup> [IIa,A]
- An accelerated course of recombinant vaccine should be offered to those given HBSIg plus all sexual and household contacts (at 0, 1, 2, 12 months or 0, 1, 3 weeks, 12 months)<sup>16, 17, 30, 31, 34</sup> [IIa, B]
- Avoid sexual contact, especially unprotected penetrative sex, until vaccination has been successful (anti-HBs titres >10i.u./l.)<sup>16, 30, 31, 43</sup> [IIa, B]. Condoms will reduce the rate of transmission of hepatitis B if the patient and partner continue to have sex<sup>38</sup> [III, B].

#### Follow-up.

- Acute infection: regular Liver function tests (1-4 weekly) until normal. In view of the possibility of chronic infection, serum HBsAg should be repeated after six months even if the LFT is normal<sup>10, 22, 23</sup> [III, B]
- Chronic infection: If untreated, patients should be regularly reviewed at intervals of one year or less, ideally by a physician with expertise in this disease<sup>10, 25, 26</sup> [IV, C]
- Immunity after recovery from infection (surface antigen negative) is lifelong in all but a very tiny minority<sup>25</sup> [III, B]

### Hepatitis D (Delta virus infection, HDV)

This is an incomplete RNA virus that requires the hepatitis B virus outer coat. It is only found in patients with hepatitis B. It is largely an infection of injecting drug users (IDUs) and their sexual partners but also in female sex-workers, and sporadically in other groups<sup>77</sup>. Suspect HDV in hepatitis B particularly if the acute hepatitis is severe, if chronic hepatitis B carriers get a further attack of acute hepatitis or if the liver disease in chronic HBV is rapidly progressive<sup>10, 21, 23, 78</sup> [III, B] There is an increased rate of fulminant hepatitis and progression of chronic hepatitis to cirrhosis<sup>21, 22, 78</sup> [III, B]. Diagnosis is confirmed by a positive anti-HDV antibody or HDV-RNA test<sup>23, 28</sup> [III,B]

### **Hepatitis C virus infection**

#### Introduction

A RNA virus in the flaviviridae family. It is endemic world-wide with high prevalence rates (>10%) in Mongolia, Egypt, Cameroon, Guinea and Bolivia<sup>4, 79</sup>. The WHO estimates that 3% of the world's population is infected, with 4

million carriers in Europe. The prevalence in most European countries is 1-2.5% with the highest rates in Moldova and Romania (2.5-10%)<sup>80</sup>. Within most countries the highest rates are in injecting drug users (IDUs) and men with haemophilia<sup>4, 80</sup>.

### *Transmission*

- Parenteral spread accounts for the majority of cases through shared needles/syringes and other drug paraphernalia (e.g filters, water) in IDUs, transfusion of contaminated blood or blood products (pre-1990s), renal dialysis, sharing razors with infected individuals or needle-stick injury<sup>80-86</sup>.
- Sexual transmission occurs at a low rate (approximately 0.2 - 2% per year of relationship) but this rate increases if the index patient and/or the recipient or both are HIV infected<sup>87-93</sup>. There has been a steady rise in acute HCV throughout Europe in men who have sex with men (MSM) over the last ten years, mostly associated with HIV-co-infection<sup>11,88,89,91</sup>. Other factors linked to HCV in MSM include ulcerative STIs such as syphilis and lymphogranuloma venereum, traumatic anal sex and recreational drugs such as cocaine snorting<sup>11,88,89,91</sup>. There is also evidence of slightly increased risk of HCV infection in female sex workers former prisoners, tattoo recipients and alcoholics<sup>7, 94-97</sup>.
- Vertical (mother to infant) spread also occurs at a low rate (5% or less) in HCV-RNA positive women<sup>87, 98-102</sup>. Higher rates (up to 40%) are seen if the woman is both HIV and HCV positive, most likely associated with high serum HCV-RNA levels in these carriers<sup>98-102</sup>.
- Amongst blood donors, 50% of those with HCV infection do not admit to having recognisable risk factors (sporadic cases)<sup>103</sup>.

## Diagnosis

### Clinical

Incubation period: 4-20 weeks for symptomatic acute hepatitis C.

- The majority of patients (>80%) undergo asymptomatic acute infection<sup>82, 83, 104</sup>.
- <20% have acute icteric hepatitis<sup>82, 83, 104</sup> but fulminant hepatitis is particularly common after hepatitis A super-infection of chronic hepatitis C carriers<sup>105</sup>.
- Approximately 70-85% of individuals with acute hepatitis C become chronic carriers - a state which is generally asymptomatic but may cause non-specific ill health<sup>104, 106-107</sup>. Some reports suggest that HCV genotype 1 could clear spontaneously more often but leads to more severe liver disease<sup>106</sup>. Once established, the rate of progression of the liver disease varies from patient to patient (0.02%/year)<sup>82-83</sup>. Liver cirrhosis and decompensated liver disease appears earlier if there is a high alcohol intake or other liver disease, including steatohepatitis<sup>108-111</sup>. Significant liver disease can be present in up to 35% of carriers who have normal serum aminotransferase levels<sup>82, 83, 112, 113</sup>.

### Laboratory

- A screening antibody test such as an Enzyme immuno-assay (EIA) or other immunoassay is initially performed and RT-PCR for RNA is used to confirm active infection (IIa, B) <sup>114-117</sup>. In HIV+ patients with a low CD4 count (<200 cells/mm<sup>3</sup>) the EIA may occasionally be negative and an RT-PCR may be needed for definitive diagnosis (IIb, B) <sup>118</sup>. An antibody test may not become positive for three or more months after acute HCV infection but a test for HCV-RNA will be positive after only two weeks (IIb, B) <sup>114-117</sup>. Chronic infection is confirmed if an HCV-RNA assay is positive six months after the first positive test. Patients with low-level viraemia may require HCV-RNA levels testing on two or more occasions to confirm infection (IIb, B) <sup>114-117</sup>. All patients being considered for therapy should have a viral RNA test to confirm viraemia and be genotyped. A positive antibody test with persistently negative RNA test indicates resolved infection (IIb, B) <sup>114-117</sup>.
- Acute HCV infection - serum amino-transferase (ALT) levels are raised but rarely >1,000 IU/l. Serum bilirubin: rarely >300 µmoles/l. Alkaline phosphatase is generally < 2x the upper limit of normal, except in cases complicated by cholestasis. Prothrombin time is rarely prolonged by up to 5 seconds; greater prolongation indicates developing hepatic failure.
- Chronic HCV infection - in most cases the only abnormality to be found will be mildly abnormal amino-transferase levels (usually <100 IU/l) and in a third of patients the liver function tests (LFT) will be normal.

### Indications for HCV Testing

1. *Patient with acute icteric hepatitis:* also measure LFT, prothrombin time, urea and electrolytes. If HCV antibody test negative, consider re-testing three and nine months after onset of jaundice or test immediately using RT-PCR if available (IIb, B) <sup>114-117</sup>. Also test for hepatitis A and B (and HEV in native travellers or immigrants from endemic areas) (see below).

#### *2. Part of Screening*

- Consider testing for hepatitis C in all injecting drug users, especially if equipment has been shared, in men with haemophilia or other patients who received blood or blood products pre-1991 and in people sustaining a needle-stick injury if the donor HCV status was positive or unknown (IIb, B) <sup>81-85</sup>
  - Other groups to be considered for testing are sexual partners of HCV positive individuals, homosexual men, especially if HIV infected, female sex workers, tattoo recipients, alcoholics and ex-prisoners (III, B) <sup>7, 11, 88, 89, 91 94-97</sup>. It may take three months or more for the anti-HCV test to become positive after exposure (see “diagnosis”).
3. All HIV infected persons, especially from the countries where HIV epidemic has been driven by IDUs and especially prior to HAART

### *Primary Prevention/Vaccination*

- Needle and syringe exchange schemes for drug users have led to a fall in parenterally transmitted infections including HCV, HBV and HIV in most studies (IIb, B) <sup>120-123</sup>. Harm reduction strategies around injecting drug use should also be discussed.
- It seems likely that if condoms are used consistently, then sexual transmission of HCV will be avoided (III, B) <sup>38</sup>.
- Since 1991 donated blood has been screened for HCV and blood products rendered almost incapable of transmitting infection in most European countries (III, B) <sup>104, 119</sup>.
- There is no effective HCV vaccine currently available.

### Management of HCV-positive patients.

#### General

- Patients should be clearly advised not to donate blood, semen or organs and given advice on other routes of transmission, including unprotected anal and vaginal sex (IIb, B) <sup>7, 11, 88, 89, 91 94-97</sup>.
- Patients should be given a detailed explanation of their condition with particular emphasis on the long-term implications for the health of themselves and their partner(s). This should be reinforced by giving them clear and accurate written information (IV, C).
- Acute hepatitis C infection is a notifiable disease in many countries <sup>79, 80</sup>.
- If not performed already, screen for other sexually transmitted diseases in cases thought to have been sexually acquired or if otherwise appropriate (III, B) <sup>8, 16</sup>.
- Other tests for assessing chronic liver disease should be performed by specialists in this field (III, B) <sup>82, 124, 125</sup>. Among others, assessment of liver synthetic function (albumin, prothrombin time), disclosure of portal hypertension (platelets, ultrasonography) and liver fibrosis estimation using non-invasive markers (serum fibrosis indexes or imaging techniques such as elastometry) are warranted. Liver biopsy may be considered in patients in whom other hepatic diseases want to be excluded or when required by treatment protocols. Otherwise, liver biopsy is no longer mandatory as part of regular chronic hepatitis C assessment.

#### Indications for therapy

- Acute icteric hepatitis: There is firm evidence that pegylated interferon (with or without ribavirin) given during the acute phase will reduce the rate of chronicity to only 10% or less (Ia, A) <sup>126-128</sup>. Spontaneous resolution of acute hepatitis C is presumed when there is a loss of HCV-RNA within the first 12 weeks, although fluctuations are not rare during the first year following acute HCV exposure. Only those HCV-RNA positive for more than 12 weeks need to be treated <sup>127</sup>. HCV genotype 1 and 4 infections require 24 weeks therapy whereas HCV genotypes 2 or 3 need only 12 weeks treatment <sup>127</sup> (Ia, A)
- Chronic HCV infection: Peginterferon alfa with ribavirin will cure chronic infection in approximately 50% of patients (Ia, A) <sup>129-134</sup>. However, the

treatment required will vary according to the genotype, initial treatment response and other factors. Treatment should be for 12-24 weeks for patients with genotypes 2 or 3<sup>132, 134</sup> although HCV genotype 3 patients with advanced liver fibrosis and detectable HCV-RNA at week 4 of therapy may benefit from longer treatment duration (12 months). All other HCV genotypes (including 1 and 4) should be treated for 12-18 months.

Treatment should be discontinued if there has not been a reduction in HCV viral load >2 log at week 12 of therapy or undetectable levels at week 24.

Patients achieving undetectable viral load at week 4 (rapid virological responders) have the greatest chances of cure and may benefit from shorter courses of therapy<sup>133</sup>. Patients are more likely to respond if they have less advanced liver fibrosis low serum HCV-RNA levels (<500,000 IU/ml), if they are infected with certain HCV genotypes (types 2 and 3) (Ib, A)<sup>129-134</sup>

- HIV-positive patients respond to treatment, although not as well as HIV-negative patients (Ib, A)<sup>135-138</sup>. Sustained virological response in those completing therapy is 11-29% for genotypes 1 or 4 and 43-73% for genotypes 2 or 3 (Ib, A)<sup>135-138</sup>.
- Patient selection for therapy depends mainly on HCV genotype and viral load. A liver biopsy is not necessary for making treatment decisions (Ib, A)<sup>124,125,129-138</sup>.
- Hepatitis A and B vaccination should be offered to hepatitis C carriers due to the worse prognosis of dual infection (III, B)<sup>105, 139</sup>. They should be informed of the increased risk of liver damage related to alcohol abuse (III, B)<sup>108-111</sup>.

### Special situations

#### *Pregnancy and Breast feeding*

- There is at present no clear knowledge about how to reduce the risk of vertical transmission. However, minimizing blood exposure from the mother to the child is expected to be beneficial, as in HIV infection. Women should be informed of the potential risk of transmission in pregnancy (see transmission) (Iib, B)<sup>87, 98-102</sup>
- Breast feeding: there is no evidence of additional risk of transmission, but caution warrants the avoidance of breastfeeding when possible in women who harbour a high HCV viral load (III,B)<sup>98-102, 140</sup>

#### Management of partners

- Partner notification should be performed and the outcome documented at subsequent follow-up (IV, C). Contact tracing to include needle sharing partners and any sexual contact (penetrative vaginal or anal sex) or during the period in which the index case is thought to have been infectious<sup>11, 80, 81, 87-93</sup>. The infectious period is from 4 weeks before the onset of jaundice in acute infection. If there was no acute infection, trace back to the likely time of infection (e.g. blood transfusion, first needle sharing) although this may be impractical for periods longer than two or three years (IV, C). Consider

testing children born to infectious women (III, B) <sup>87, 98-102</sup>. For other non-sexual contacts thought to be at risk, discuss with the public health physician.

- There is currently no available vaccine or immunoglobulin preparation that will prevent HCV acquisition.
- Sexual transmission should be discussed. It seems likely that if condoms are used consistently then sexual transmission will be avoided (III, B) <sup>38</sup>, but given the very low rate of transmission outside of HIV co-infection (III, B) <sup>87-93</sup>, monogamous partners may choose not to use them.

#### Follow-up

- Acute infection: regular LFT (1-4 weekly) until normal. In view of the possibility of chronic infection, serum RT-PCR should be repeated after six months even if the LFT is normal (III, B) <sup>114-117</sup>.
- Chronic infection: If untreated, patients should be regularly reviewed at intervals of 6-12 months, ideally by a physician with expertise in this disease (IV, C).
- There is no protective HCV immunity. Infection with another HCV variant, belonging to the same genotype or another, is well documented, among patients engaged in risk practices (III, B) <sup>114-117, 141</sup>.

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#### References

1. European commission health and consumers directorate general. Hepatitis B Overview of epidemiology and disease burden of hepatitis B in the European region. [http://ec.europa.eu/health/ph\\_information/dissemination/echi/docs/hepatitisB\\_en.pdf](http://ec.europa.eu/health/ph_information/dissemination/echi/docs/hepatitisB_en.pdf) Accessed April 2009
2. WHO regional office for Europe. Hepatitis B in the WHO European region 1990-2004. <http://data.euro.who.int/cisid/?TabID=201612>. Accessed April 2009
3. World Health Organisation. Hepatitis B. [http://www.who.int/csr/disease/hepatitis/HepatitisB\\_who.cdscr.lyo2002\\_2.pdf](http://www.who.int/csr/disease/hepatitis/HepatitisB_who.cdscr.lyo2002_2.pdf) Accessed April 2009.
4. Rantala M, van de Laar MJ. Surveillance and epidemiology of hepatitis B and C in Europe - a review. Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin, 2008;13:1560
5. Urbanus AT, van Houdt R, van de Laar TJ, Coutinho RA. Viral hepatitis among men who have sex with men, epidemiology and public health consequences. Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin, 2009 ;14 :1560
6. Gilson RJ, de Ruiter A, Waite J et al. Hepatitis B virus infection in patients attending a genitourinary medicine clinic: risk factors and vaccination coverage. Sex Trans Inf 1998;74:110-5
7. Ward H, Day S, Weber J. Risky business: health and safety in the sex industry over a 9 year period. Sex Trans Infect 1999;75:340-3

8. Hart GJ, Dawson J, Fitzpatrick RM et al. Risk behaviour, anti-HIV and anti-hepatitis B core prevalence in clinic and non-clinic samples of gay men in England, 1991-1992. *AIDS* 1993;7:863-9
  9. Davis LG, Weber DJ, Lemon SM. Horizontal transmission of hepatitis B virus. *Lancet* 1989;i:889-93
  10. Hoofnagle JH. Chronic hepatitis B. *N Engl J Med* 1990;323:337-9
  11. Osella AR, Massa MA, Joekes S et al. Hepatitis B and C virus transmission among homosexual men. *Am J Gastroenterol* 1998;93:49-52
  12. Struve J, Giesecke J, Lindh G et al. Heterosexual contact as a major route for transmission of acute hepatitis B amongst adults. *J Infect.* 1990;20:111-21
  13. Balogun MA, Ramsay ME, Fairley CK, Collins M, Heptonstall J. Acute hepatitis B infection in England and Wales: 1985-96. *Epidemiol Infect* 1999;122:125-31
  14. Huo TI, Wu JC, Huang YH et al. Evidence of transmission of hepatitis B to spouses from sequence analysis of the viral genome. *J Gastroenterol Hepatol* 1998;13:1138-42
  15. Hyams KC, Phillips IA, Tejada A, Hepatitis B in a highly active prostitute population: evidence for a low risk of antigenaemia. *J Infect Dis* 1990;162:295-8
  16. Department of Health. Hepatitis B. In: Immunisation against infectious disease - 'The Green Book'.
- [http://www.dh.gov.uk/en/PublicHealth/HealthProtection/Immunisation/Greenbook/DH\\_4097254](http://www.dh.gov.uk/en/PublicHealth/HealthProtection/Immunisation/Greenbook/DH_4097254) Accessed April 2009
17. Palmovich D, Crnjakovic-Palmovic J et al. Prevention of hepatitis B virus (HBV) infection in health-care workers after accidental exposure: a comparison of two prophylactic schedules. *Infection* 1993;21:42-5
  18. Brook MG, Lever AML, Griffiths P, et al. Antenatal screening for hepatitis B is medically and economically effective in the prevention of vertical transmission: Three years experience in a London hospital. *Quart.J.Med.* 1989; 264:313-317.
  19. Cramp ME, Grundy HC, Perinpanayagam RM et al. Seroprevalence of hepatitis B and C virus in two institutions caring for mentally handicapped adults. *J Roy Soc Med* 1996;89:401-2
  20. Kiire CF. The epidemiology and prophylaxis of hepatitis B in sub-Saharan Africa: a view from tropical and sub-tropical Africa. *Gut* 1996;38(suppl 2):S5-12
  21. McIntyre N. Clinical presentation of acute viral hepatitis. *Brit Med Bull* 1990;46:533-47
  22. Hyams KC. Risks of chronicity following acute hepatitis B virus infection: a review. *Clin Infect Dis* 1995;20:992-1000
  23. Gitlin N. Hepatitis B: diagnosis, prevention and treatment. *Clin Chem* 1997;43:1500-6
  24. Hann HW, Han SH, Block TM et al. Symptomatology and health attitudes of chronic hepatitis B patients in the USA. *J Viral Hepat* 2008;15:42-51,
  25. Pungpapong S, Kim WR, Poterucha JJ. Natural history of hepatitis B virus infection: an update for clinicians. *Mayo Clin Proc* 2007;82:967-75.
  26. Thomas HC. Best practice in the treatment of chronic hepatitis B: a summary of the European Viral Hepatitis Educational Initiative (EVHEI). *J Hepatol* 2007;47:588-97
  27. Kumar M, Chauhan R, Gupta N et al. Spontaneous increases in alanine aminotransferase levels in asymptomatic chronic hepatitis B virus-infected patients. *Gastroenterol* 2009;136:1272-80
  28. Krajden M, McNabb G, Petric M. The laboratory diagnosis of hepatitis B virus.

- Can J Infect Dis Med Microbiol 2005;16:65-72
29. Weinbaum CM, Williams I, Mast E et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recommendations & Reports* 2008;57/RR-8:1-20
  30. Sturrock CJ, Currie MJ, Vally H et al. Community-based sexual health care works: a review of the ACT outreach program. *Sex Health* 2007;4:201-4
  31. Sethi G, Holden BM, Greene L, Gaffney J, Ward H. Hepatitis B vaccination for male sex workers: the experience of a specialist GUM service. *Sex Trans Infect* 2006;82:84-5
  32. Koene RP, Gotz HM, Van Den Hoek JA et al. Significance of isolated antibody to hepatitis B core antigen in Dutch national vaccination campaign of behavioural high-risk groups. *Epidemiol Infect*, 2009;137:495-503
  33. Thio CL. Diagnosis, diagnostic tests and monitoring of hepatitis B virus in monoinfected and HIV-coinfected patients. *Antivir Ther Lond* 2007;12 Suppl 3:H25-31
  - \*34. Mathew JL, El Dib R, Mathew PJ, Boxall EH, Brok J. Hepatitis B immunisation in persons not previously exposed to hepatitis B or with unknown exposure status. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No.: CD006481. DOI: 10.1002/14651858.CD006481.pub2
  35. DY, Lai CL, Lim WL, Fung J, Wong DK, Yuen MF. Twenty-two years follow-up of a prospective randomized trial of hepatitis B vaccines without booster dose in children: final report. *Vaccine* 2008;26:6587-91
  36. Keeffe EB, Dieterich DT, Han SHB et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: an update. *Clin Gastroenterol Hepatol* 2006;4:936-62
  37. Papatheodoridis GV, Manolakopoulos S, Dusheiko G, Archimandritis AJ. Therapeutic strategies in the management of patients with chronic hepatitis B virus infection. *Lancet Infect Dis* 2008;8:167-78,
  38. Sanchez J, Gotuzzo E, Escamilla J et al. Sexually transmitted infections in female sex workers: reduced by condom use but not by a limited periodic examination program. *Sex Trans Dis* 1998;25:82-9
  39. Van Damme P, Kane M, Meheus A et al. Integration of hepatitis B vaccination into national immunisation programmes. *Viral Hepatitis Prevention Board. BMJ* 1997;314:1033-6
  40. Paitoonpong L, Suankratay C. Immunological response to hepatitis B vaccination in patients with AIDS and virological response to highly active antiretroviral therapy. *Scand J Infect Dis* 2008;40:54-8
  - 41 de-Vries-Sluijs TEMS, Hansen BE, van-Doornum GJJ, *et al.* A prospective open study of the efficacy of high-dose recombinant hepatitis B rechallenge vaccination in HIV-infected patients. *J Infect Dis* 2008;197:292-4
  - 42 Fonseca MO, Pang LW, de Paula Cavalheiro N et al Randomized trial of recombinant hepatitis B vaccine in HIV-infected adult patients comparing a standard dose to a double dose. *Vaccine* 2005;23:2902-8
  43. European consensus group on hepatitis B immunity. Are booster immunisations needed for lifelong hepatitis B immunity? *Lancet* 2000;355:561-65
  44. Nystrom J, Cardell K, Bjornsdottir TB, Fryden A, Hultgren C, Sallberg M Improved cell mediated immune responses after successful re-vaccination of non-responders to the hepatitis B virus surface antigen (HBsAg) vaccine using the combined hepatitis A and B vaccine. *Vaccine* 2008;26:5967-72

45. Cardell K, Akerlind B, Sallberg M, Fryden A. Excellent response rate to a double dose of the combined hepatitis A and B vaccine in previous nonresponders to hepatitis B vaccine. *J Infect Dis* 2008;198:299-304
46. Lo CM, Lau GK, Chan SC, Fan ST, Wong J. Efficacy of a pre-S containing vaccine in patients receiving lamivudine prophylaxis after liver transplantation for chronic hepatitis B. *Am J Transplant* 2007;7:434-9.
47. Pichichero ME. Improving Vaccine Delivery Using Novel Adjuvant Systems. *Hum Vaccin* 2008;4:1554-8619
48. Rendi WP, Shouval D, Genton B et al. Comparative immunogenicity of a PreS/S hepatitis B vaccine in non- and low responders to conventional vaccine. *Vaccine* 2006;24:2781-9
49. Kundi M. New hepatitis B vaccine formulated with an improved adjuvant system. *Expert Rev Vaccines* 2007;6:133-40
50. Beran J. Safety and immunogenicity of a new hepatitis B vaccine for the protection of patients with renal insufficiency including pre-haemodialysis and haemodialysis patients. *Exp Opin Biol Ther* 2008;8:235-47
51. van-der-Sande MAB, Mendy M, Waight P et al. Similar long-term vaccine efficacy of two versus three doses of HBV vaccine in early life. *Vaccine* 2007;25:1509-12
52. Marsano LS, West DJ, Chan I et al. A two dose hepatitis B vaccine regimen: proof of priming and memory responses in young adults, *Vaccine* 1998;16:624-9
53. Ural O, Findik D. The response of isolated anti-HBc positive subjects to recombinant hepatitis B vaccine. *J Infect* 2001;43:187-90
54. Van-Damme P, Van HK. A review of the long-term protection after hepatitis A and B vaccination. *Travel Med Infect Dis* 2007;5:79-84
55. Jack AD, Hall AJ, Maine N, Mendy M, Whittle HC. What level of hepatitis B antibody is protective? *J Infect Dis* 1999;179:489-92
56. Alfaleh F, Alshehri S, Alansari S, et al. Long-term protection of hepatitis B vaccine 18 years after vaccination. *J Infect* 2008;57:404-9
57. Keeffe EB, Dieterich DT, Han SH et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2008 update. *Clin Gastroenterol Hepatol* 2008;6:1315-41
58. Papatheodoridis GV, Manolakopoulos S, Dusheiko G, Archimandritis AJ. Therapeutic strategies in the management of patients with chronic hepatitis B virus infection. *Lancet Infect Dis* 2008;8:167-78,
59. Lai CL, Gane E, Liaw YF et al. Telbivudine versus lamivudine in patients with chronic hepatitis B. *N Engl J Med* 2007;357:2576-88
60. Chan HLY, Heathcote EJ, Marcellin P et al. Treatment of hepatitis B e antigen positive chronic hepatitis with telbivudine or adefovir: a randomized trial. *Ann Intern Med* 2007;147:745-54
61. McMahon MA, Jilek BL, Brennan TP. The HBV drug entecavir - effects on HIV-1 replication and resistance. *N Engl J Med* 2007;356:2614-21
62. Tan J, Degertekin B, Wong SN et al. Tenofovir monotherapy is effective in hepatitis B patients with antiviral treatment failure to adefovir in the absence of adefovir-resistant mutations. *J Hepatol* 2008;48:391-8,
63. Lim SG, Leung N, Hann HW et al. Clinical trial: a phase II, randomized study evaluating the safety, pharmacokinetics and anti-viral activity of clevudine for 12 weeks in patients with chronic hepatitis B. *Aliment Pharmacol Therapeut*, 2008;27:1282-92
64. Keeffe EB, Marcellin P. New and emerging treatment of chronic hepatitis B.

Clin Gastroenterol Hepatol 2007;5:285-94

65. Hui CK, Zhang HY, Bowden S et al. 96 weeks combination of adefovir dipivoxil plus emtricitabine vs. adefovir dipivoxil monotherapy in the treatment of chronic hepatitis B. *J Hepatol* 2008;48:714-20
66. McMahon M, Jilek B, Brennan T et al. The HBV drug entecavir – effects on HIV replication and resistance. *N Engl J Med* 2007;356:2614-2621
67. Gazzard BG, BHIVA Treatment Guidelines Writing Group. British HIV Association Guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008. *HIV Medicine* 2008;9:563-608
68. Nuesch R, Ananworanich J, Srasuebkul P et al. Interruptions of tenofovir/emtricitabine-based antiretroviral therapy in patients with HIV/hepatitis B virus co-infection. *AIDS* 2008;22:152-4
69. Soriano V, Vispo E, Bottecchia M et al. Management of hepatitis B virus co-infection on and off antiretroviral therapy. *Curr HIV/AIDS Rep* 2008;5:86-93
70. Low E, Cox A, Atkins M, Nelson M. Telbivudine has activity against HIV-1. *AIDS* 2009;23:546-7
71. Peters MG, Andersen J, Lynch P, et al. Randomized controlled study of tenofovir and adefovir in chronic hepatitis B virus and HIV infection: ACTG A5127. *Hepatology*. 2006;44:1110–1116
72. Pramoolsinsap C. Acute hepatitis A and immunity to hepatitis A virus in hepatitis B virus carriers and in HBV- or hepatitis C virus-related chronic liver diseases in Thailand. *J Viral Hepat* 2000;7:11-12
73. Gambarin GM. Hepatitis B in pregnancy. *Clin Liver Dis* 2007;11:945-63
74. Xu WM, Cui YT, Wang L, Yang H et al. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled study. *J Viral Hep* 2009;16:94-103
75. Veldhuijzen IK, Mes TH, Mostert MC et al. An improved approach to identify epidemiological and phylogenetic transmission pairs of source and contact tracing of hepatitis B. *J Med Virol*, 2009;81:425-34
76. Zuckerman JN. Review: hepatitis B immune globulin for prevention of hepatitis B infection. *J Med Virol* 2007;79:919-21
77. Cross TJS, Rizzi P, Horner M et al. The increasing prevalence of hepatitis delta virus (HDV) infection in South London. *J Med Virol* 2008;80:277-82
78. Farci P, Chessa L, Balestrieri C, Serra G, Lai ME. Treatment of chronic hepatitis D. *J Viral Hepat* 2007;14 Suppl 1:58-63
79. WHO. Hepatitis C prevalence 2007. <http://www.who.int/ith/maps/hepatitisc2007.jpg> Accessed April 2009.
80. WHO. Hepatitis C. <http://www.who.int/csr/disease/hepatitis/whocdscsrlyo2003/en/index1.html> Accessed April 2009.
81. De P, Roy E, Boivin JF, Cox J, Morissette C. Risk of hepatitis C virus transmission through drug preparation equipment: a systematic and methodological review. *J Viral Hepat* 2008;15:279-92
82. Persico M, Perrotta S, Persico E et al. Hepatitis C virus carriers with persistently normal ALT levels: biological peculiarities and update of the natural history of liver disease at 10 years. *J Viral Hepat* 2006;13:290-6
83. Massard J, Ratziu V, Thabut D et al. Natural history and predictors of disease severity in chronic hepatitis C. *J Hepatol* 2006;44Suppl:S19-24

84. Esteban JI, Sauleda S, Quer J. The changing epidemiology of hepatitis C virus infection in Europe. *J Hepatol* 2008;48:148-62
85. Elder A, Paterson C. Sharps injuries in UK health care: a review of injury rates, viral transmission and potential efficacy of safety devices. *Occup Med Lond* 2006;56:566-74
86. Sawayama Y, Hayashi J, Kakuda K et al. Hepatitis C virus infection in institutionalized psychiatric patients: possible role of transmission by razor sharing. *Digest Dis Sci* 2000;45:351-6
87. McMahon JM, Pouget ER, Tortu S. Individual and couple-level risk factors for hepatitis C infection among heterosexual drug users: a multilevel dyadic analysis. *J Infect Dis* 2007;195:1572-81
88. Jebbari H, Alexander S, Ward H et al. Update on lymphogranuloma venereum in the United Kingdom. *Sex Transm Infect* 2007;83:324-6
89. Danta M, Dusheiko GM. Acute HCV in HIV-positive individuals - a review. *Curr Pharm Des* 2008;14:1690-7
90. Akahane Y, Kojima M, Sugai Y et al. Hepatitis C virus infection in spouses of patients with type C chronic liver disease. *Ann Intern Med* 1994;120:748-52
91. Giraudon I, Ruf M, Maguire H et al. Increase in newly acquired hepatitis C in HIV-positive men who have sex with men across London and Brighton 2002-2006: is this an outbreak? *Sex Trans Infect* 2008;84:111-115
92. Kao JH, Liu CJ, Chen PJ et al. Low incidence of hepatitis C virus transmission between spouses: a prospective study. *J Gastroenterol Hepatol* 2000;15:391-5
93. Marinovich B, Castilla J, del-Romero J et al. Absence of hepatitis C virus transmission in a prospective cohort of heterosexual serodiscordant couples. *Sex Transm Infect* 2003;79:160-2
94. Taylor A, Hutchinson SJ, Gilchrist G, Cameron S, Carr S, Goldberg DJ. Prevalence and determinants of hepatitis C virus infection among female drug injecting sex workers in Glasgow. *Harm Reduct J* 2008;5:11
95. Vescio MF, Longo B, Babudieri S et al. Correlates of hepatitis C virus seropositivity in prison inmates: a meta-analysis. *J Epidemiol Community Health* 2008;62:305-13
96. Macías J, Palacios RB, Claro E et al. High prevalence of hepatitis C virus infection among non-injecting drug users: association with sharing the inhalation implements of crack. *Liver Int* epub: 26 2 2008
97. Zhang T, Li Y, Ho WZ. Drug abuse, innate immunity and hepatitis C virus. *Rev Med Virol* 2006;16:311-27
98. Indolfi G, Resti M. Perinatal transmission of hepatitis C virus infection. *J Med Virol* 2009;81:836-43
- \* 99 McIntyre PG, Tosh K, McGuire W. Caesarean section versus vaginal delivery for preventing mother to infant hepatitis C virus transmission. *Cochrane Database of Systematic Reviews* 2006, Issue 4. Art. No.: CD005546. DOI: 10.1002/14651858.CD005546.pub2.
- 100 Mast EE, Hwang LY, Seto DSY, et al. Risk factors for prenatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. *J Infect Dis* 2005;192:1880-9.
- 101 Mok J, Pembrey L, Tovo PA, Newell ML for the European Paediatric Hepatitis C Virus Network. When does mother to child transmission of hepatitis C virus occur? *Arch Dis Child* 2005;90:F156-F160

- 102 Azzari C, Moriond -M, Indolfi G et al. Higher risk of hepatitis C virus perinatal transmission from drug user mothers is mediated by peripheral blood mononuclear cell infection. *J Med Virol* 2008;80:65-71
103. Pellicano R, Mladenova I, Dimitrova SM, Bruno CM, Sciacca C, Rizzetto M  
The epidemiology of hepatitis C virus infection. An update for clinicians.  
*Minerva Gastroenterologica e Dietologica* 2004;50:1-7
104. Wang CC, Krantz E, Klarquist J et al. Acute hepatitis C in a contemporary US cohort: modes of acquisition and factors influencing viral clearance. *J Infect Dis* 2007;196:1474-82
105. Lefilliatre P, Villeneuve JP. Fulminant hepatitis A in patients with chronic liver disease. *Can J Public Health* 2000;91:168-70
106. Harris HE, Eldridge KP, Harbour S, Alexander G, Teo CG, Ramsay ME.,  
Does the clinical outcome of hepatitis C infection vary with the infecting hepatitis C virus type? *J Viral Hepat* 2007;14:213-20
- 107 Kallman J, O-Neil MM, Larive B et al. Fatigue and health-related quality of life (HRQL) in chronic hepatitis C virus infection. *Dig Dis Sci* 2007;52:2531-9
- 108 Singal AK, Anand BS. Mechanisms of synergy between alcohol and hepatitis C virus. *J Clin Gastroenterol* 2007;41:761-72
- 109 Stroffolini T, Sagnelli E, Mariano A, Craxí A, Almasio P. Characteristics of HCV positive subjects referring to hospitals in Italy: a multicentre prevalence study on 6,999 cases. *J Viral Hepat* 2006;13:351-4
- 110 Bruno S, Crosignani A, Maisonneuve P et al. Hepatitis C virus genotype 1b as a major risk factor associated with hepatocellular carcinoma in patients with cirrhosis: a seventeen-year prospective cohort study. *Hepatology* 2007;46:1350-6
- 111 Ke WM, Li XJ, Yu LN et al. Etiological investigation of fatal liver failure during the course of chronic hepatitis B in southeast China. *J Gastroenterol* 2006;41:347-51
- 112 Hui CK, Zhang HY, Shek T et al. Disease progression in Chinese chronic hepatitis C patients with persistently normal alanine aminotransaminase levels. *Aliment Pharmacol Ther* 2007;25:1283-92
- 113 Zeuzem S, Alberti A, Rosenberg W et al. Review article: management of patients with chronic hepatitis C virus infection and normal alanine aminotransferase activity. *Aliment Pharmacol Ther* 2006;24:1133-49
114. Scott JD, Gretch DR. Molecular diagnostics of hepatitis C virus infection: a systematic review. *JAMA* 2007;297:724-32
- 115 Abdel-Hamid M, El-Daly M, El-Kafrawy S et al. Comparison of second- and third-generation enzyme immunoassays for detecting antibodies to hepatitis C virus. *J Clin Microbiol* 2002;40:1656-9
- 116 Schutzbank TE, Sefers SE, Kahmann N, Li H, Tang YW. Comparative evaluation of three commercially available methodologies for hepatitis C virus genotyping. *J Clin Microbiol* 2006;44:3797-8.
117. Contreras AM, Tinoco E, Celis A et al. Hepatitis C antibody intra-assay correlation: is retest in duplicate necessary? *Transfusion* 2007;47:1686-90
118. Hadlich E, Alvares-Da-Silva MR Dal-Molin RK, Zenker R, Goldani LZ. Hepatitis C virus (HCV) viremia in HIV-infected patients without HCV antibodies detectable by third-generation enzyme immunoassay. *J Gastroenterol Hepatol* 2007;22:1506-9
119. Horowitz B, Busch M. Estimating the pathogen safety of manufactured human plasma products: application to fibrin sealants and to thrombin. *Transfusion* 2008;48:1739-53

120. Prati D. Transmission of hepatitis C virus by blood transfusions and other medical procedures: a global review. *J Hepatol* 2006;45:607-16
- 121 Van-Den-Berg C, Smit C, Van-Brussel G, Coutinho I, Prins M. Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C virus: evidence from the Amsterdam Cohort Studies among drug users. *Addiction* 2007;102:1454-62
- 122 Mateu GP, Treloar C, Calatayud VA et al. How can hepatitis C be prevented in the long term? *Int J Drug Policy* 2007;18:338-40
- 123 Wright NMJ, Tompkins CNE. A review of the evidence for the effectiveness of primary prevention interventions for hepatitis C among injecting drug users. *Harm Reduct J* 2006;3:27
124. Friedrich–Rust M, Ong M, Performance of Transient Elastography for the Staging of Liver Fibrosis: A Meta-Analysis *Gastroenterol* 2008;134:960–974
- 125 Paggi S, Colli A, Fraquelli M et al. A non-invasive algorithm accurately predicts advanced fibrosis in hepatitis C: a comparison using histology with internal-external validation. *J Hepatol* 2008;49:564-71
126. Calleri G , Cariti G, Gaiottino F et al. A short course of pegylated interferon-alpha in acute HCV hepatitis. *J Viral Hepat* 2007;14:116-21
- 127 Kamal SM, Moustafa KN, Chen J et al. Duration of peginterferon therapy in acute hepatitis C: a randomized trial. *Hepatology* 2006;43:923-31
128. Matthews GV, Hellard M, Haber Pet al. Characteristics and treatment outcomes among HIV-infected individuals in the Australian Trial in Acute Hepatitis C. *Clin Infect Dis* 2009;48:650-8
- \* 129. Brok J, Gluud LL, Gluud C. Ribavirin plus interferon versus interferon for chronic hepatitis C. *Cochrane Database of Systematic Reviews* 2005, Issue 2. Art. No.: CD005445. DOI: 10.1002/14651858.CD005445.
- 130 Deutsch M, Hadziyannis SJ. Old and emerging therapies in chronic hepatitis C: an update. *J Viral Hepat* 2008;15:2-11
- 131 Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N. Interferon alpha (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation. *Health Technol Assess* 2007;11:1-205
- 132 Dalgard O, Bjøro K, Ring LH et al. Pegylated interferon alfa and ribavirin for 14 versus 24 weeks in patients with hepatitis C virus genotype 2 or 3 and rapid virological response. *Hepatology* 2008;47:35-42
- 133 Mangia A, Minerva N, Bacca D et al. Individualized treatment duration for hepatitis C genotype 1 patients: A randomized controlled trial. *Hepatology* 2008;47:43-50
134. Mangia A, Minerva N, Bacca D et al. Determinants of relapse after a short (12 weeks) course of antiviral therapy and re-treatment efficacy of a prolonged course in patients with chronic hepatitis C virus genotype 2 or 3 infection. *Hepatology* 2009; 49:358-63
- 135 Kim AI, Dorn A, Bouajram R, Saab S. The treatment of chronic hepatitis C in HIV-infected patients: a meta-analysis. *HIV Med* 2007;8:312-21
- 136 Soriano V, Barreiro P, Martin-Carbonero L. Update on the treatment of chronic hepatitis C in HIV-infected patients. *AIDS Rev* 2007;999-113
- 137 Shire NJ, Welge JA, Sherman KE. Response rates to pegylated interferon and ribavirin in HCV/HIV coinfection: a research synthesis. *J Viral Hepat* 2007;14:239-48

- 138 Laguno M, Cifuentes C, Murillas J et al. Randomized trial comparing pegylated interferon alpha-2b versus pegylated interferon alpha-2a, both plus ribavirin, to treat chronic hepatitis C in human immunodeficiency virus patients. *Hepatology* 2009;49:22-31
- 139 Liaw YF. Hepatitis C virus superinfection in patients with chronic hepatitis B virus infection. *Journal of Gastroenterology*. 2002;37Suppl 13:65-8
- 140 Bhola K, McGuire W. Does avoidance of breast feeding reduce mother-to-infant transmission of hepatitis C virus infection? *Arch Dis Child* 2007;92:365-6
- 141 Arrais TC, Van Dooren S, Vandamme AM et al. Change in hepatitis C virus genotype in hemodialysis patients after end-of-treatment response to interferon monotherapy--relapse or re-infection? *J Med Virol* 2008;80:80-6

\* These references are from the Cochrane Database of Systematic Reviews

## Appendix 1

### Evidence Base

#### Medline

For each type of hepatitis, a medline search was performed for the years 1966-2009 (May) for hepatitis type B and 1990-2009 (May) for hepatitis C. From the MeSH terms “hepatitis B”, and “hepatitis C”, the following sub-headings were used: Complications, Drug Therapy, Diagnosis, Epidemiology, Etiology, Mortality, Prevention and Control, Therapy, Transmission, Virology. The searches were limited to “human” for all searches. For Drug Therapy, Prevention & Control, and Therapy searches were limited initially to “randomized controlled trials” but in the absence of enough publications this was changed to “controlled clinical trials”, “clinical trials” or “reviews” in that order. For the sub-headings other than these three the search was limited to “reviews”. Textword searches for “hepatitis B”, and “hepatitis C” were combined, as appropriate, with textword searches for “ complication\$”, “diagnosis”, “prevention”, “transmission”, “immunoglobulin”, “vaccine”, “non-response”, “non-responders”, “HIV”, “randomized controlled trial”, “lamivudine”, “telbivudine”, “entecavir” “tenofovir” “pegylated” “adefovir” “ribavirin” “ribavirin”

#### Cochrane Library

The Cochrane Library Database of Systematic Reviews was searched for all relevant articles using the textword “hepatitis”.

## Appendix 2

### Levels of Evidence

- Ia Evidence obtained from meta-analysis of randomised controlled trials.
- Ib Evidence obtained from at least one randomised controlled trial.
- IIa Evidence obtained from at least one well designed study without randomisation.
- IIb Evidence obtained from at least one other type of well designed quasi-experimental study.
- III Evidence obtained from well designed non-experimental descriptive studies such as comparative studies, correlation studies, and case control studies.
- IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

### *Grading of Recommendations*

- A (Evidence levels Ia, Ib) Requires at least one randomised control trial as part of the body of literature of overall good quality and consistency addressing the specific recommendation.
- B (Evidence levels IIa, IIb, III) Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.
- C (Evidence IV) Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.

### Appendix 3

#### Declarations of interest

Some authors and the lead editor have on behalf of national educational societies been provided with educational grants from a number of organisations making drugs in this area