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Management of hepatitis C

A national clinical guideline

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December 2006

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

- 1⁺⁺ High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
- 1⁺ Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
- 1⁻ Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
- 2⁺⁺ High quality systematic reviews of case control or cohort studies
High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
- 2⁺ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
- 2⁻ Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
- 3 Non-analytic studies, eg case reports, case series
- 4 Expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

- A** At least one meta-analysis, systematic review of RCTs, or RCT rated as 1⁺⁺ and directly applicable to the target population; *or*
A body of evidence consisting principally of studies rated as 1⁺, directly applicable to the target population, and demonstrating overall consistency of results
- B** A body of evidence including studies rated as 2⁺⁺, directly applicable to the target population, and demonstrating overall consistency of results; *or*
Extrapolated evidence from studies rated as 1⁺⁺ or 1⁺
- C** A body of evidence including studies rated as 2⁺, directly applicable to the target population and demonstrating overall consistency of results; *or*
Extrapolated evidence from studies rated as 2⁺⁺
- D** Evidence level 3 or 4; *or*
Extrapolated evidence from studies rated as 2⁺

GOOD PRACTICE POINTS

- Recommended best practice based on the clinical experience of the guideline development group

Scottish Intercollegiate Guidelines Network

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1 Introduction

1.1 THE NEED FOR A GUIDELINE

The hepatitis C virus (HCV) was first identified in 1989¹ and HCV infection has become a major health problem worldwide. Approximately 0.8% of the Scottish population are thought to be chronically infected with HCV (around 37,500 individuals). The prevalence of infection varies between population groups ranging from 50% in injecting drug users (IDU) to less than 0.04% among new blood donors.¹

Up to 80% of patients infected with HCV become chronically infected and most of these patients will show evidence of chronic hepatitis.²

Hepatitis C is usually slowly progressive over a period of many years. Five to 15% of patients with chronic hepatitis may progress to liver cirrhosis over 20 years.³ Four to nine per cent of patients with cirrhosis will develop liver failure, and two to five per cent of patients with cirrhosis will develop primary hepatocellular carcinoma.

In the UK the two major routes of transmission of HCV have been sharing of drug injecting equipment by IDU and transfusion of infected blood or blood products. Virus inactivation treatment of blood products began in 1987 and from 1991 blood has been screened for hepatitis C, eliminating blood products as a source of HCV infection.

HCV infection can be effectively treated with combination drug therapy (pegylated alpha interferon and ribavirin) with sustained viral response rates in 50-80% of patients. Although there are existing guidelines around the selection of patients for treatment⁴⁻⁷ there are no national guidelines for screening, testing, diagnosis, service configuration, care during treatment nor post-treatment follow up in adults or children. Presently wide variation exists across Scotland in the delivery of services to individuals infected with HCV.

1.2 REMIT OF THE GUIDELINE

The guideline provides evidence based recommendations covering all stages of the patient care pathway; screening, testing, diagnosis, referral, treatment, care and follow up of infants, children and adults with, or exposed to, HCV infection. The remit encompasses prevention of secondary transmission of the virus but specifically excludes primary prevention of HCV infection. Primary prevention of hepatitis C infection is an important public health concern but is a difficult topic for an evidence based guideline to cover. The principles and evidence for the prevention of all blood borne viruses are generic and reviewing all of this evidence would have been beyond the capacity of any guideline development group, whilst reviewing the HCV evidence alone would have produced a distorted view.

This guideline will be of interest to all health professionals in primary and secondary care involved in the management of people with hepatitis C infection.

1.3 DEFINITIONS

Acute hepatitis C

There is no generally accepted definition of acute hepatitis C infection but for purposes of investigations and treatment of acute hepatitis C, the following criteria have been used; a clear point of exposure and a positive HCV RNA within six months or a significant rise in serum alanine aminotransferase or seroconversion in which antibody and/or HCV RNA is absent from a first and present in a second sample.

Chronic hepatitis C

Ongoing infection with hepatitis C virus beyond the acute phase.

Mild disease is present when inflammation of the liver tissue is absent or largely confined to the portal tracts with no evidence of fibrous tissue extending between the portal tracts.

Moderate liver disease is described when there is significant inflammation and/or liver cell damage associated with increased fibrous tissue extending beyond the portal tracts but not resulting in nodule formation.

Severe disease occurs when patients have developed bridging fibrosis or cirrhosis (histologically proven or otherwise) of the liver, whether there are clinical signs of liver dysfunction or not.

Genotypes

Many different strains of HCV have been recognised by virological testing. These have been grouped into six categories known as genotypes 1 to 6. There are significant geographical variations in the prevalence of the different genotypes in different parts of the world. In the UK genotype 1 is the most common, followed by genotype 3 and then genotype 2. There are small numbers of patients in the UK infected with hepatitis C virus of genotypes 4, 5 and 6, most of whom acquired the infection overseas.

Sustained viral response

Sustained viral response (SVR) is defined as undetectable HCV RNA in the patient's serum using sensitive nucleic acid detection techniques, six months after the end of a period of antiviral therapy.

Early viral response

Early viral response (EVR) is either a negative HCV RNA or a two log drop in quantitative HCV RNA levels after starting antiviral treatment. It is measured at 12 weeks for patients with genotype 1.⁸⁻¹⁰

Rapid viral response

Rapid viral response (RVR) is a negative qualitative HCV RNA measured four weeks after antiviral treatment for patients with genotype 2 or 3.

Non-responder

A non-responder is a patient who after antiviral treatment for HCV has detectable HCV RNA at the end of treatment.

Relapser

A relapser is a patient who after antiviral treatment for HCV has no detectable HCV RNA at the end of treatment, but who does have detectable HCV RNA six months after the end of a period of antiviral therapy.

Current and former injecting drug users

Definitions of current and former injecting drug users vary between different therapeutic environments. Any definition must be considered in the continuum of a chronic, relapsing disease. Precise definition of former injecting drug users is for the most part arbitrary, and in the context of hepatitis C the issue is the potential risk of re-infection with HCV after successful treatment. For the purpose of this guideline an individual infected with HCV may be considered as not at risk of reinfection if they have been non-injecting for six months.

Exposure prone procedures

Exposure prone procedures (EPP) are those where there is a risk that injury to a healthcare worker may result in the exposure of a patient's open tissues to the blood of the worker. These procedures include those where the worker's gloved hands may be in contact with sharp instruments, needle tips and sharp tissues (spicules of bone or teeth) inside a patient's open body cavity, wound or confined anatomical space where the hand or fingertips may not be completely visible at all times.

1.4 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

1.5 REVIEW AND UPDATING

This guideline was issued in 2006 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website: www.sign.ac.uk.

2 Testing

2.1 CLINICAL AND COST-EFFECTIVE TESTING FOR HCV

National and international guidelines recommend that individuals who have an excess risk of being infected and might benefit from knowing their HCV status should be offered an HCV test.^{5, 11-13} This recommendation is based primarily on the need to diagnose an often silent infection, allowing the initiation of prompt antiviral treatment if appropriate.¹⁴ Since treatment cannot be offered unless a diagnosis of chronic HCV infection is made, the offering, and uptake, of testing among populations at risk of HCV will convey a degree of clinical benefit.

Further benefits of diagnosing people infected with HCV include the opportunity to convey information aimed at slowing the rate of HCV disease progression (such as advice about the dangers of excess alcohol consumption) and reducing the chances of infection being transmitted to others. No robust, consistent evidence to indicate the effectiveness of these interventions was identified.

UK guidelines consistently recommend that people who may convey an HCV risk to patients in the healthcare setting should undergo HCV testing.^{5, 11-13} Several instances of healthcare worker to patient and blood/organ donor to recipient transmission of HCV have been recorded.^{15, 16}

Controlled trials or cohort studies to gauge the cost effectiveness of offering an HCV test to different population groups have not been undertaken. Limited evidence from economic modelling work, indicates that offering an HCV test to former injecting drug users in drug treatment and perhaps other settings would convey cost-effective clinical benefits.¹⁷ Former IDU are more likely to have a higher prevalence of HCV and comply with therapy than current IDU. Models of best practice for the identification and testing of former IDU have not been developed and evaluated. Expert opinion suggests that general practices, particularly those that serve areas with a high prevalence of drug use, may constitute environments where focused, well supported testing initiatives might be successful. Prisons may also offer similar opportunities.¹⁸ Targeted and generalised HCV awareness/testing campaigns have been conducted but no evaluations of their success in encouraging people (including former IDU) at high risk of HCV to engage with services have been reported.

In populations where the prevalence of HCV is low (eg genitourinary medicine clinic attendees), economic modelling indicates that universal testing does not convey cost-effective clinical benefit.¹⁷

D The following groups should be tested for HCV:

- **blood/tissue donors**
- **patients on haemodialysis**
- **healthcare workers who intend to pursue a career in a specialty that requires them to perform exposure prone procedures.**

D The following groups should be offered an HCV test:

- **patients with an otherwise unexplained persistently elevated alanine aminotransferase**
- **people with a history of injecting drug use**
- **people who are human immunodeficiency virus (HIV) positive**
- **recipients of blood clotting factor concentrates prior to 1987**
- **recipients of blood and blood components before September 1991 and organ/tissue transplants in the UK before 1992**
- **children whose mother is known to be infected with HCV**
- **healthcare workers following percutaneous or mucous membrane exposure to blood which is, or is suspected to be, infected with HCV**
- **people who have received medical or dental treatment in countries where HCV is common and infection control may be poor**
- **people who have had tattoos or body piercing in circumstances where infection control procedure is, or is suspected to be, suboptimal**
- **people who have had a sexual partner/household contact who is HCV infected.**

2.2 HCV DIAGNOSTIC TESTING

2.2.1 PRINCIPLES OF TESTING

Detection of viral RNA by nucleic acid tests (NAT, usually using reverse transcription polymerase chain reaction; RT PCR) indicates current infection. Detection of antibodies indicates resolved or current infection. The testing algorithm suggested in Figure 1 is based on the following key principles:

- diagnostic assays are most reliable when used on plasma or serum¹⁹ 2⁺⁺
- assays for antibody in saliva are very sensitive if optimum salivary collection devices and modified enzyme linked immunosorbent assays (ELISA) are used, but NAT for viral RNA is unreliable¹⁹⁻²¹ 2⁺⁺
- limited testing of dried blood spots for detecting antibody has suggested it may be useful but further evaluation is needed for the detection of viral RNA¹⁹ 2⁺⁺
- nucleic acid testing sensitive enough to detect 50-100 IU/ml of virus must be performed to detect current infection²² 2⁺
- viral RNA can be detected as early as one to two weeks after infection, whereas antibody can be detected at seven to eight weeks after infection²³ 4
- antibody to infection may not be generated particularly if the individual is immunosuppressed²⁴ 4
- following acute infection, HCV RNA may oscillate between positive and negative for several months. Results from samples taken at this time may be misleading.²³ In an individual positive for HCV antibody, but negative for HCV RNA, a second sample should be tested to confirm the initial diagnosis, especially as the date of infection is unknown in most cases 4
- individuals with a positive HCV antibody test and repeatedly negative RNA do not require further active management of hepatitis C infection²⁴ 4
- since hepatitis C is a serious communicable disease, after an initial laboratory diagnosis, a second sample should be taken from the patient to confirm correct identification of the original sample²⁵ 4
- genotyping of individuals with proven HCV infection is required to determine likely response to treatment. Those with genotype 1 infection require longer duration of treatment than those with genotype 2 and 3 (see section 9.1.2)⁷ 1⁺⁺
- expert guidance suggests that healthcare workers who have, or might have, sustained an occupational exposure to HCV should be offered RNA testing at six, 12 and 24 weeks, with anti-HCV testing at 12 and 24 weeks.²⁶ 4

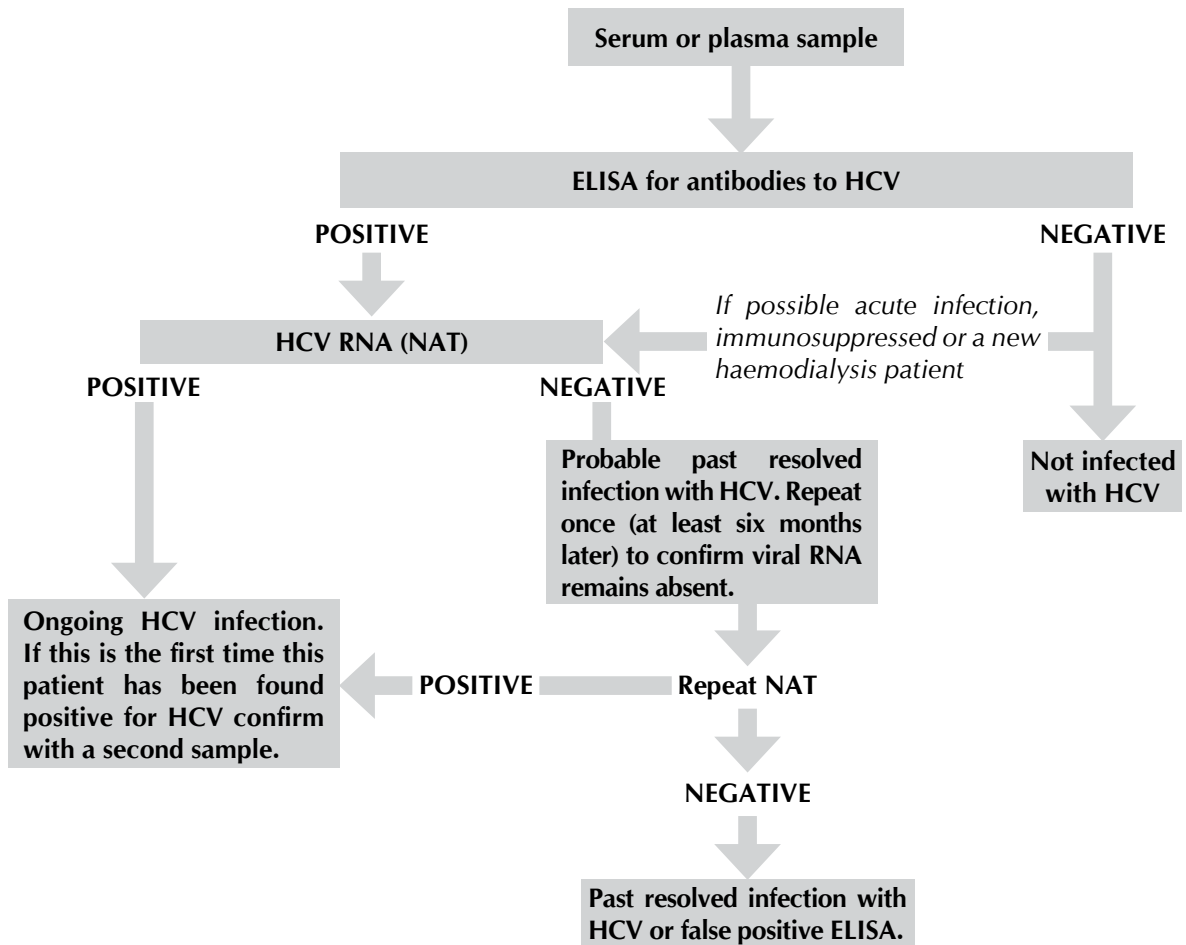
B Diagnostic testing for HCV should be performed on serum or plasma where possible.

D HCV genotyping should be undertaken if antiviral therapy is being considered.

D Following an isolated acute percutaneous exposure to blood infected, or strongly suspected of being infected, with HCV, healthcare workers should be offered HCV RNA testing at six, 12 and 24 weeks and anti-HCV testing at 12 and 24 weeks.

The testing procedure outlined in Figure 1 should be followed.

Figure 1: Initial laboratory diagnosis of hepatitis C infection (except infants)



3 Prevention of secondary transmission

Secondary transmission is defined as the onward transmission of infection from individuals who are known to be HCV infected.

3.1 TRANSMISSION THROUGH SEXUAL AND HOUSEHOLD CONTACT

Observational studies indicate that there is a very small risk of people with diagnosed HCV infection transmitting infection to their family, or close contacts, and sexual partners. Cohort studies of couples discordant for HCV indicated an HCV incidence of 0-2 per 1,000 years of sexual contact.²⁷⁻²⁹ Those with HIV co-infection, particularly gay men, may be more likely to transmit HCV to their sexual partners.^{30, 31} The findings suggest that transmission may occur through exposure to blood as a consequence of, for example, the sharing of razors and toothbrushes (ie activities which might result in percutaneous or mucous membrane exposure to infected blood), and through unprotected sexual intercourse.

2+
1-

No studies were identified to ascertain if interventions such as educational initiatives, including the promotion of condom use, aimed at people diagnosed with HCV infection, are effective in reducing the frequency of such risk behaviours and/or preventing associated secondary transmission of HCV. Expert opinion suggests that people infected with HCV should be advised that the use of condoms and the avoidance of activities which could lead to percutaneous or mucous membrane exposure to infected blood will eliminate the albeit very small risk of them transmitting the virus to others.^{13, 32}

4

After being advised of the low risk of HCV being transmitted sexually, individuals infected with HCV should be asked to consider using condoms for sexual intercourse.

D Individuals co-infected with HIV/HCV should be advised always to practise safe sex and use condoms.

D Individuals infected with HCV should be advised to avoid activities which could result in percutaneous or mucous membrane exposure to their infected blood, such as the sharing of razors and toothbrushes.

3.2 TRANSMISSION THROUGH INJECTING DRUG USE

The sharing of injecting equipment by drug users is the principal means through which infection is transmitted in developed countries.^{13, 32} Observational data demonstrate that interventions such as needle and syringe exchange and methadone maintenance therapy, are likely to have reduced, though not controlled, HCV transmission among IDU in a number of countries including Scotland.³³ Studies of interventions aimed specifically at preventing IDU known to be infected with HCV transmitting their infection to others through the sharing of injecting equipment, were not identified.

2+

No robust consistent evidence on the influence of knowledge of HCV infection status among IDU on their injecting risk behaviour was identified. Expert opinion suggests that advising current IDU with chronic HCV on how to prevent transmission of their infection to other IDU, through for example safe injecting practice, may be an effective intervention.^{13, 32}

4

D Injecting drug users known to be infected with HCV should be given advice on how they can prevent transmission of infection to other injecting drug users.

3.3 TRANSMISSION BETWEEN HEALTHCARE WORKERS AND PATIENTS

3.3.1 RISK OF HEALTHCARE WORKER INFECTION

Expert opinion suggests that infection control precautions should be standard and universal and not determined by knowledge of patients' blood borne virus status.³⁴

4

Estimates of transmission risk following needlestick injury vary, with one large prospective study of 4,403 exposed healthcare workers finding an overall transmission rate of 0.31%, whilst a review of 25 smaller studies reported a combined rate of 1.9% from 2,357 exposures.^{15, 35} The relative risk is higher when injuries are deep and from blood-filled needles. Risk arising from superficial or mucocutaneous exposures is likely to be much lower, though difficult to quantify, while transmission from solid needles is extremely unlikely.³⁵ Transmission occurs only from RNA positive sources.

2+
4

- Standard infection control precautions against blood borne virus transmission should be undertaken by all healthcare workers regardless of the patient's known or suspected infective status.
- Healthcare workers sustaining needlestick injuries from HCV infected sources should be advised that:
 - the overall risk of transmission is probably less than 2% and may be much lower
 - the risk is higher from deep injuries and from blood-filled needles
 - transmission from solid needles is very unlikely.

3.3.2 RISK OF PATIENT INFECTION

Several reports have shown that HCV can be transmitted from healthcare workers to patients.¹⁶ Most of these occurred after exposure prone procedures, usually after deep-cavity surgery. Estimates of transmission rates to patients in two retrospective analyses involving infected cardiothoracic surgeons were 2.3% and 0.36%, whilst the risk of transmission from an infected gynaecologist was only 0.04%.³⁶⁻³⁸ UK health departments advise that healthcare workers who are HCV RNA positive should not undertake EPP.^{16, 39}

3
4

- D Healthcare workers who are aware they are HCV RNA positive should not undertake exposure prone procedures.**

4 Referral

Referral to specialist care should be considered for all patients with active HCV infection (HCV RNA positive) and not restricted to potential candidates for antiviral therapy. Specialist clinics are often a source of information for patients and relatives, including health promotion and methods of avoiding secondary transmission of the virus.

Recent modelling suggests that 90% of individuals with HCV in Scotland are current or former IDU.¹ Factors associated with injecting drug use (eg poverty, chaotic lifestyle, comorbidity, including alcohol dependence) can be obstacles to individuals navigating their way through and remaining in investigation, referral and treatment pathways.^{14, 18} Expert consensus suggests that uptake of services may be improved by integrated multidisciplinary care which also addresses, for example, individuals' alcohol and drug use problems simultaneously with their HCV specialist care.¹⁴

4

No evidence was identified supporting the prevailing view that the investigation and treatment of current IDU with HCV infection should not be promoted because they are unlikely to have progressed to at least moderate hepatitis, or are unlikely to adhere to such care.

Two observational studies and one five year follow-up study have shown that IDU, described as "active" at the time of enrolment and undergoing management of their drug problem, complied with antiviral treatment to the same degree as those who had never injected drugs.⁴⁰⁻⁴² These studies were small and no details of participants' injecting behaviour were provided.

2-

All patients with acute HCV should be referred to specialist care immediately as treatment given during the acute phase is more likely to be successful (see section 6.3).⁴³

1++

Ideally the specialist clinic should be integrated with other services by means of outreach clinics so that the patient journey is seamless, especially for those who find it difficult to access medical care. Such integration should encourage agencies such as drug problems services and prison medical services to positively and repeatedly address the issue of HCV infection.

D Individuals, including injecting drug users, diagnosed with chronic HCV should be offered integrated multidisciplinary care as it can maximise their uptake of, and retention in, services.

A Patients with acute HCV infection should be referred to specialist care immediately.

Current injecting drug users infected with HCV should not be excluded from consideration for HCV clinical management, including antiviral therapy, on the basis of their injecting status.

All patients should be referred to a setting that periodically reassesses the state of infection and the progression of liver disease, to determine if further interventions or therapies are needed.

5 Children and hepatitis C

5.1 MOTHER TO CHILD TRANSMISSION

Pregnant women who are HCV RNA negative do not pose a risk of transmission to their child.^{44,45} | 2+

The risk of women who are HCV infected and RNA positive transmitting infection to their babies in utero or during parturition is approximately five per cent; the rate is twice as high for those co-infected with HIV.⁴⁶ The baby's risk of acquiring HCV from a mother infected with HCV is not increased by mode of delivery or breast feeding.⁴⁶ One prospective study has indicated that fetal scalp monitoring may increase the risk of mother to child transmission.⁴⁷ A large retrospective study did not demonstrate any excess risk.⁴⁶ Vaginal delivery may increase the risk of HCV transmission if the mother is co-infected with detectable HIV viral load.⁴⁶ | 2++

B In pregnant women knowledge of HCV RNA positive status should not influence obstetric management or standard advice regarding breast feeding.

5.2 HCV TESTING IN CHILDREN AND INFANTS

The aim of testing infants born to women with hepatitis C is not primarily to identify all children to whom the virus has been transmitted, but to identify those at risk of persistent infection and its long term consequences.

Infants born to women who are HCV antibody positive will test positive for HCV antibody at birth.⁴⁸ Infants who are not infected become negative for HCV antibody between six and 20 months of age. Around 80% will be negative by 12 months of age.^{44, 49} Positive results for viral RNA by NAT may be obtained in the early months of life in children who subsequently become negative and lose HCV antibody.⁴⁸⁻⁵¹ Some infected infants may not become HCV RNA positive until 12 months of age or thereafter.⁵¹ A recent study indicates that the sensitivity of a positive RT PCR result obtained on two occasions between two and six months of life in predicting infection is 81% (confidence interval; CI 58-97%).⁵² | 2+
| 2+

In HIV co-infection, infants consistently positive by RNA may have negative HCV antibody tests between 12 and 18 months of age.⁵³ | 3

B Infants born to women who are HCV antibody positive and HCV RNA negative do not need to be tested.

B In children born to women infected with HCV, an HCV antibody test should be performed at 12 months of age or thereafter to identify the majority of children who are not infected.

B In children whose mothers are co-infected with HIV, and in infants found to be HCV antibody positive after 12 months, an HCV RNA test should be performed, and if positive, confirmed on a second sample.

B If information regarding the risk of HCV infection in an individual child is required before 12 months of age, an HCV RNA test and retest can be performed after two months of age. Further testing is still required to make a definitive diagnosis.

5.3 NATURAL HISTORY OF HCV INFECTION IN CHILDREN

Cross-sectional studies indicate that 20-40% of children who are HCV antibody positive after 18 months of age have undetectable HCV RNA, suggesting spontaneous clearance.^{54, 55} In those with chronic infection who remain HCV RNA positive, subsequent spontaneous clearance is rare (3.5%).⁵⁶

3

Levels of transaminases (ALT) twice the upper limit of normal are found in 50% of infected children.⁵⁶

3

Progression to severe hepatitis or cirrhosis in childhood is rare (<5%).^{54, 56-58} There is a slow, non-linear progression of fibrosis with age.^{56, 57} The mean time to development of cirrhosis in individuals infected as infants is estimated at 28 years.⁵⁷

3

D Children infected with HCV should be monitored to identify the minority who are at risk of progressive fibrosis during childhood, and who may be candidates for treatment.

Children infected with HCV should be assessed clinically every 6-12 months, and have blood taken for tests of liver function. Those with clinical or ultrasound abnormalities, or with serum ALT persistently twice the upper limit of normal should be considered for liver biopsy.

5.4 TREATMENT OF CHILDREN WITH HEPATITIS C

Response rates to treatment in children are of a similar magnitude, and show the same influences of genotype, to adults.⁵⁹ Combination treatment with interferon (IFN) and ribavirin gives an overall SVR of 50-60%.⁵⁹⁻⁶² Data on the use of pegylated interferon, as opposed to standard interferon, and on optimal dosage and adverse sequelae in children are limited. There is a potential for effects on thyroid function and growth problems.^{61, 62}

3

D Children with evidence of moderate or severe liver disease should be considered for treatment with pegylated IFN and ribavirin.

D In children who are asymptomatic with mild or no liver disease, benefits of treatment need to be weighed against the risk of side effects.

Children infected with HCV should be managed in consultation with a paediatric service with specialist expertise in hepatitis C.

6 Acute hepatitis C

6.1 NATURAL HISTORY

The incidence of acute hepatitis C is unknown but can be estimated from the prevalence of chronic hepatitis C (CHC).⁶³ Acute hepatitis C infection is usually asymptomatic.⁶⁴ The full clinical spectrum of acute hepatitis C symptoms can occur but is rare (< 15% patients).⁶⁵ The mortality of acute hepatitis C is very low (0.1% or less) and chronic infection is the most common outcome.^{63, 65, 66}

3

Laboratory diagnosis should start with testing for anti-HCV but in early cases HCV RNA may be the only marker of infection (see section 2.2).⁶⁷

2+

Spontaneous recovery occurs in 30-50% of patients with symptomatic infection, usually within three months of diagnosis. This is most common in females with an icteric illness.^{63, 64, 68, 69}

3

D Patients with acute hepatitis C virus infection require clinical and laboratory monitoring (looking for spontaneous viral clearance) for the initial three months following diagnosis as they will often have a self limiting illness.

6.2 POST-EXPOSURE PROPHYLAXIS

No trials were identified that show whether or not immunoglobulin, IFN based therapies or antiviral agents are effective at preventing transmission when given immediately post-exposure. Two reviews which considered older studies of immunoglobulin did not establish efficacy and concluded that immunoglobulin and IFN based therapies are not recommended after HCV exposure.^{26, 70}

4

6.3 TREATMENT OF PATIENTS WITH ACUTE HEPATITIS C

6.3.1 TIMING OF TREATMENT

Most patients who spontaneously clear hepatitis C do so within 12 weeks of diagnosis.^{63, 69} There are no data to suggest that delaying treatment from three to six months post-diagnosis compromises treatment response, whilst allowing for spontaneous clearance to occur.⁴³ Delaying treatment to one year post-acquisition compromises a sustained viral response.⁴³

3

1++

D Treatment should start between three and six months after diagnosis of acute hepatitis C, if the infection has not resolved spontaneously.

6.3.2 CHOICE AND DURATION OF TREATMENT

Two systematic reviews examined the effectiveness of non-pegylated IFN for the treatment of patients with acute hepatitis C.^{71, 72} In one study participants in the treatment groups had higher sustained viral response rates (62%) than those in untreated groups (12%).⁷¹ A Cochrane review demonstrated that increasing the dose of non-pegylated IFN during the induction phase of treatment was associated with higher sustained viral response.⁷² There are no data on the influence of genotype on response to treatment for acute hepatitis C infection.

1+

No randomised controlled trials (RCTs) of pegylated IFN versus conventional IFN for patients with acute hepatitis C were identified. A case series treated 16 patients, who had not seroconverted by three months, with pegylated IFN alone for 24 weeks, and reported a sustained viral response of 94%.⁶³

3

A Patients with acute HCV infection should be treated with IFN therapy if the infection does not resolve spontaneously.

D Patients can be treated with either pegylated IFN or non-pegylated IFN.

D Patients with acute HCV infection should be treated with IFN therapy for 24 weeks irrespective of genotype.

7 Assessment of liver disease

7.1 CLINICAL ASSESSMENT

Clinical assessment of the severity of liver disease in patients with chronic hepatitis C is inaccurate and tends to underestimate the severity of change seen on liver biopsy.⁷³

3

7.2 FIBROSIS MARKERS

Studies of non-invasive prediction of the severity of liver disease using combinations of clinical and biochemical scores have found that it may be possible to distinguish patients with cirrhosis from those with mild disease. Intermediate stages are not distinguishable.⁷⁴

2⁺⁺

A systematic review demonstrated that surrogate markers of fibrosis either reflecting disordered liver function (alanine aminotransferase, platelets) or fibrosis metabolism (eg tissue inhibitor of matrix metalloproteinase 1, hyaluronic acid) cannot be used individually to predict fibrosis. In individual patients such markers used alone cannot differentiate the stage of fibrosis reliably. Used in panels they are able to determine whether an individual has high or low levels of fibrosis. The 14 studies in the systematic review used 10 different panels of markers, none of which was superior to any other in statistical comparisons. The tests were compared against the gold standard of liver biopsy as part of their validation, though liver biopsy may potentially be inaccurate due to sampling error. Comparison of surrogate markers and liver biopsy to clinical outcomes would be more relevant.⁷⁵

2⁺⁺

Other methods for assessing liver fibrosis, such as measuring liver stiffness, show promise in pilot studies.^{76, 77}

B Biochemical markers should not be used as an alternative to liver biopsy for staging of intermediate grades of fibrosis.

B Biochemical tests may be used as an alternative to liver biopsy to diagnose cirrhosis or to direct screening for complications of fibrosis.

7.3 LIVER BIOPSY

Liver biopsy needs to be at least 25 mm long in order to report stage of fibrosis with 75% accuracy.⁷⁸ The mortality of liver biopsy is between 0.13-0.33% and the rate of significant morbidity is about 5.9%.⁷⁹

3

7.3.1 WHEN TO BIOPSY

Liver biopsy of patients with CHC infection can reveal additional diagnoses such as alcoholic liver disease or steatosis (10% patients) and may influence management decisions in five per cent of patients.⁸⁰ Repeat liver biopsies may be useful for the identification of individuals for treatment; one third of patients with mild CHC show one stage of fibrosis progression on the Ishak scale (0-6) at a median of 30 months.⁸¹ The frequency and timing of liver biopsy should be tailored to individual patients as progression of fibrosis is non-linear.

3

Advanced fibrosis or cirrhosis on liver biopsy compared with milder disease predicts a modest reduction in SVR after antiviral therapy.⁸²

1⁺⁺

Liver biopsy before and after successful antiviral therapy (median 20 months interval) has shown both improvement in fibrosis (277 out of 1,094 patients) and downgrading of stage in cirrhosis (75 out of 153 patients).⁸³

1⁺

D Liver biopsy should be performed if there is concern about additional causes of liver disease.

D Repeat liver biopsies should be considered in patients with mild disease who remain untreated, if progression of liver fibrosis would influence the decision to opt for antiviral therapy.

In patients with congenital bleeding disorders liver biopsy should be performed in consultation with a haemophilia specialist.

7.3.2 BIOPSY AND GENOTYPE

The sustained viral response rate after pegylated IFN and ribavirin therapy for patients with genotype 2 and 3 infection is 76-82% and 41-51% for patients with genotype 1 infection.⁷ The UK Health Technology Assessment Centre has recommended that pre-treatment liver biopsy in patients with genotype 2 and 3 infection may not be required.⁷

4

D Liver biopsy should not be considered an essential test prior to using antiviral therapy, especially in patients with genotype 2 and 3 disease.

8 Progression of untreated disease

Chronic hepatitis C infection is associated with a significant risk of progression to cirrhosis and hepatocellular carcinoma (HCC).^{3, 84} Quantifying the magnitude of risk of progression to cirrhosis and HCC with time is difficult as outcomes are strongly influenced by study design and the characteristics of the population sampled.^{3, 84}

2++

A systematic review of 57 studies (both cross-sectional and longitudinal) which included liver clinic, post-transfusion, blood donor and community based patients, calculated the following estimates for the risk of progressing to cirrhosis after 20 years:³

2++

- liver clinic: 22% (95% CI 18-26%)
- post-transfusion: 24% (95% CI 11-37%)
- blood donor: 4% (95% CI 1-7%)
- community based: 7% (95% CI 4-10%).

Due to the selection biases inherent in the cross-sectional liver clinic data, the community based cohort studies may be the most representative of true disease progression at a population level. The community based cohorts indicate that in those who acquire HCV infection in young adulthood, less than 10% will develop cirrhosis within 20 years. Older age at HCV acquisition, male gender and heavy alcohol consumption were associated with more rapid disease progression.³

2++

The mean time from HCV infection to the development of HCC also shows considerable variation between studies, ranging from nine to 31 years in one systematic review.⁸⁴ Virtually no cases of HCC occur during the first decade after HCV infection, most are detected after 20 years of infection.⁸⁴

2++

Patients with established HCV related cirrhosis have a seven per cent risk of developing HCC, by five years follow up.^{85, 86}

2+

Patients with established CHC related cirrhosis are also at risk of complications such as ascites, gastrointestinal bleeding and hepatic encephalopathy.^{85, 86} The cumulative probability of all forms of decompensation in cirrhotic patients who remained tumour free was 18% at five years in one study, with an overall five year survival rate of 91%.⁸⁶

2+

8.1 AGE, GENDER AND ETHNICITY

Increasing age at time of infection with HCV is associated with more rapid progression of liver fibrosis and reduced time from infection to cirrhosis.⁸⁷⁻⁸⁹ Age over 40 years at time of infection is particularly associated with more rapid progression.^{88, 89}

3

Three cohort studies reported that men infected with HCV are more likely to progress to advanced stages of hepatic fibrosis than women.^{88, 90, 91}

3

Variations in disease progression have been observed in patients of different race. Two cohort studies demonstrated that disease progressed less rapidly in African-American than non African-American patients.^{92, 93} The likely rate of progression in these patients should be considered when deciding whether to proceed with antiviral therapy.

2+

D When estimating the likely rate of progression of liver disease age at infection, gender and ethnicity should be considered.

8.2 BODY WEIGHT

Studies have identified body mass index (BMI) > 25 as being associated with hepatic steatosis (see section 11.1.3).

8.3 TOBACCO SMOKING

Smoking is an independent risk factor for the progression of hepatic inflammation and fibrosis in patients with CHC.^{94, 95} No data were identified on the impact of stopping smoking.

3

D Patients with CHC should be advised that smoking tobacco can accelerate progression of liver disease.

8.4 ALCOHOL

Heavy alcohol consumption in patients infected with CHC is associated with more severe liver disease including cirrhosis, endstage liver disease and hepatocellular cancer.^{96, 97} Average alcohol intake of more than six UK units per day is associated with more rapid progression of liver fibrosis.^{87, 88, 91} Even moderate amounts of alcohol (within government recommended guidelines) have been associated with increased liver fibrosis compared to those who abstain.^{88, 98}

2+
2++

Patients who are aware of their HCV status are more likely to heed advice on reducing alcohol intake than those who perceive themselves to be uninfected.⁹⁹

2++

B Patients with CHC should be advised that drinking alcohol (even in moderation) can accelerate progression of liver disease.

8.5 ALANINE AMINOTRANSFERASE

Approximately 25% (range 10-40%) of patients with CHC have persistently normal serum alanine aminotransferase (PNALT). Such patients are more likely to be female and have mild disease.¹⁰⁰ Although there is a substantial overlap between patients with PNALT and patients with mild liver disease, the terms are not synonymous and the groups are regarded separately for treatment purposes (see sections 9.2.1 and 9.2.3). The definition of 'persistently normal' varies in the literature with ALT measurements made every two to three months for time periods ranging between six and 18 months.¹⁰⁰ Flares in ALT can still occur in 21.5% of patients after being normal for 12 months.¹⁰¹ There is no association with hepatitis C genotype or viral load.¹⁰⁰

1-
2-

Progression of liver fibrosis is slower in patients with PNALT than in patients with elevated ALT.¹⁰² In patients with untreated mild liver disease the progression to moderate or severe disease during follow up of 5.6 years is five per cent in patients with PNALT and 24% in patients with elevated ALT.

2++

Routine liver biopsy is not believed to be indicated unless specific information is required in selected patients.¹⁰⁰

1-

D When defining PNALT serum ALT measurement should be undertaken every two to three months to ensure that flares in ALT are not missed.

The duration of follow up to define PNALT should be 12 months.

Liver biopsy should only be considered if there are clinical or other concerns about the individual patient.

8.6 HIV CO-INFECTION

There is an increased rate of progression to endstage liver disease in patients with HIV and HCV co-infection compared to those with HCV mono-infection (relative risk; RR 6.14, 95% CI 2.86 to 13.2).¹⁰³ Median time to cirrhosis in patients with co-infection is 26 years, compared to 38 years in those with HCV mono-infection.¹⁰³ Patients with HCV infection with mild immunodepression as a result of HIV also have more severe liver disease than those with HCV mono-infection.¹⁰⁴ There is a marked increase in liver related mortality in patients with CHC and HIV co-infection (RR 17.5).¹⁰⁵

1+
2+

Effective anti-HIV therapy and the associated immune recovery may limit HCV liver disease progression.¹⁰⁶ | 2++

B The increased rate of progression to decompensated liver disease in patients with HCV and HIV co-infection should prompt early consideration of antiviral therapy.

8.7 CO-INFECTION WITH HEPATITIS A OR B VIRUSES

Vaccination against hepatitis A and B is recommended in people with HCV.¹⁰⁷ A consensus report on the treatment of hepatitis recommended vaccination for hepatitis B but not hepatitis A.¹⁰⁸ One case study of patients with HCV who contracted hepatitis A reported a very high level of fulminant hepatitis.¹⁰⁹ | 4

Antibody response to hepatitis B vaccination is reduced in patients with chronic HCV.¹¹⁰ | 3

D Vaccination against hepatitis A and B should be considered for patients infected with hepatitis C.

Patients who are infected with HCV who have serological evidence of current or past infection with hepatitis B virus (HBV) are more likely to have advanced liver disease.^{90, 111, 112} | 3

D When estimating the likely rate of progression of liver disease as a result of hepatitis C infection, active or previous HBV infection should be considered.

Patients infected with HCV should be tested for evidence of active or previous HBV infection.

8.8 IRON STATUS

Patients with CHC can have elevated iron stores, but there is debate over whether this has any influence on the disease. Serum ferritin and transferrin saturation are increased in 20-60% of patients and correlate with serum ALT, suggesting they are markers of inflammation. There is a poor correlation with hepatic iron concentration (HIC).¹¹³ HIC is rarely significantly elevated in pre-cirrhotic patients. Twenty to fifty per cent of patients with cirrhosis will have elevated HIC but this is also a common finding in patients with cirrhosis due to hepatitis B and alcoholic liver disease.¹¹³ | 4

It is uncertain whether hepatic iron excess as a single factor has any influence on response to treatment with IFN alone.¹¹³ | 4

No evidence was found that iron depletion (by venesection) has any influence on the virus or the activity of liver disease.¹¹³ There is preliminary evidence from four small RCTs that venesection on selected patients with markers of iron excess prior to IFN monotherapy may improve the SVR.^{113, 114} | 4
1-

D Modest iron loading does not justify specific intervention prior to antiviral therapy as it is unlikely to be of clinical importance.

D Patients with significant iron retention require further investigation for additional conditions known to result in iron overload.

8.9 HCV GENOTYPE

No consistent link between HCV genotype and disease progression has been demonstrated in several cohort studies.^{87, 90, 91, 115, 116} | 2+

8.10 CRYOGLOBULINAEMIA

A poor quality meta-analysis of the influence of cryoglobulinaemia suggested that cirrhosis is diagnosed more frequently in patients with cryoglobulinaemia.¹¹⁷ | 1-

9 Treatment of chronic hepatitis C

9.1 ANTIVIRAL THERAPY

Several meta-analyses and systematic reviews confirm that a combination of pegylated IFN with ribavirin is effective in treating patients with CHC, leading to high levels of SVR.^{7, 118-120} Two commercial brands of pegylated IFN and ribavirin are available but they have not been directly compared in an RCT. All patients should be considered as candidates for treatment. A summary of results is illustrated in Table 1.

1⁺⁺

Table 1: Results from randomised controlled trials of therapy with combination peginterferon and ribavirin in naive patients*¹²¹

Study	Results	Genotype 1		Genotype 2/3	
		No. treated	SVR	No. treated	SVR
Manns et al, 2001	IFN alfa-2b, 3 mU 3 times/wk + ribavirin (1000 mg < 75 kg, 1200 mg ≥ 75 kg) X 48 wk	343	33%	146	79%
	Peg-IFN alfa-2b 1.5 (4 wk) → .5 ug/kg/wk (44 wk) + ribavirin (1000mg < 75 kg, 1200 mg ≥ 75 kg) X 48 wk	349	34%	153	80%
	Peg-IFN alfa-2b 1.5 ug/kg/wk + ribavirin (800 mg/dly) X 48 wk	348	42%	147	82%
Fried et al, 2002	IFN alfa-2b 3 mU TIW + ribavirin (1000 mg < 75 kg, 1200 mg ≥ 75kg) X 48 wk	285	36%	145	61%
	Peg-IFN alfa-2a 180 ug/wk + ribavirin (1000 mg < 75 kg, 1200 mg ≥ 75 kg) X 48 wk	298	46%	140	76%
	Peg-IFN alfa-2a 180 ug/wk X 48 wk	145	21%	69	45%
Hadziyannis et al, 2004	Peg-IFN alfa-2a 180 ug/wk + ribavirin (800 mg/dly) X 24 wk	101	29%	106	78%
	Peg-IFN alfa-2a 180 ug/wk + ribavirin (1000 mg < 75 kg, 1200 mg ≥ 75 kg) X 24 wk	118	41%	162	78%
	Peg-IFN alfa-2a 180 ug/wk + ribavirin (800 mg/dly) X 48 wk	250	40%	111	73%
	Peg-IFN alfa-2a 180 ug/wk + ribavirin (1000 mg < 75 kg, 1200 mg ≥ kg) X 48 wk	271	51%	165	77%

* Reprinted from Clinical Gastroenterology & Hepatology, 3, Wong W, Update on Chronic Hepatitis C, 507–20, Copyright (2005), with permission from American Gastroenterological Association.

A

A combination of pegylated IFN and ribavirin is the treatment of choice for patients with hepatitis C.

9.1.1 SUSTAINED VIRAL RESPONSE

Sustained viral response has become the accepted objective of treatment programmes for CHC and is currently achieved in 41-51% of patients with genotype 1 disease and 73-82% of patients with genotype 2 and 3 disease who have received a course of combination therapy with pegylated IFN and ribavirin.^{122, 123} Data are available on long term outcomes after SVR but are limited in number, quality and length of follow up:

- | | |
|---|---|
| <ul style="list-style-type: none"> ▪ viral relapse is uncommon after SVR (1-13% of patients)¹²⁴⁻¹²⁶ ▪ mortality is reduced after SVR¹²⁷ ▪ patients with an SVR have a reduced risk of developing cirrhosis and primary hepatocellular carcinoma^{124, 128} ▪ occult hepatitis C may persist in macrophages, lymphocytes or hepatocytes in some patients who have achieved an SVR. There may be a small risk of future relapse in this event.^{129, 130} | <p>1+</p> <p>2+</p> <p>2++</p> <p>3</p> |
|---|---|

B Sustained viral response should be used as a marker for viral clearance.

<p>An SVR of 80% is achieved in patients who take 80% of the dose of both pegylated IFN and ribavirin for more than 80% of the duration. This compares with 33% in less compliant patients.¹³¹</p>	<p>2+</p>
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9.1.2 GENOTYPE AND DURATION OF TREATMENT

<p>The optimal duration of treatment for patients with genotype 1 or 4 is 48 weeks. For patients with genotype 2 or 3, 24 weeks has been the standard.^{7, 118, 119}</p>	<p>1++</p>
--	------------

<p>Patients with genotype 1 infection who fail to achieve an early viral response at 12 weeks have a less than five per cent chance of achieving a sustained viral response.⁸ Of those genotype 1 patients who failed to achieve an EVR but continued on therapy and were still HCV RNA positive at 24 weeks, none had an SVR.¹³²</p>	<p>1+</p>
---	-----------

<p>Patients with genotype 2 and 3 infection who achieve a rapid viral response (HCV RNA negative) at four weeks can receive 12 or 16 weeks of pegylated IFN and ribavirin therapy with similar results to 24 weeks of treatment.^{9, 10}</p>	<p>1+</p>
--	-----------

B The duration of treatment with a combination of pegylated IFN with ribavirin, should be 12-24 weeks for patients with genotype 2 or 3 and 48 weeks for patients with genotype 1 or 4.

- | | |
|--|--|
| <p>A</p> <ul style="list-style-type: none"> ▪ Patients with genotype 1 infection should be tested for an early viral response at 12 weeks. ▪ Patients with genotype 1 infection who fail to achieve an EVR at 12 weeks should be considered for cessation of treatment. ▪ Patients with genotype 1 infection with an EVR at 12 weeks should continue treatment for 48 weeks. Those who are still HCV RNA positive at 24 weeks should be considered for cessation of treatment. | |
|--|--|

B Patients with genotype 2 or 3 infection should have an HCV RNA test performed four weeks after starting antiviral therapy, and if this is negative, may be considered for a reduced duration of therapy of 12 or 16 weeks.

9.2 PATIENT SUBGROUPS

9.2.1 PATIENTS WITH MILD CHRONIC HEPATITIS

In patients with mild CHC the efficacy and safety of non-pegylated IFN alfa-2a and ribavirin combination therapy is similar to that in other patients with hepatitis C. Liver biopsy to exclude patients with mild disease is therefore not required prior to considering antiviral treatment.¹³³

1⁺⁺

B Patients with mild CHC should be considered for treatment with a combination of pegylated IFN with ribavirin.

9.2.2 PATIENTS WITH CIRRHOSIS

See section 10.1.1 for information on patients with cirrhosis.

9.2.3 PATIENTS WITH PERSISTENTLY NORMAL ALT LEVELS

The efficacy and safety of pegylated IFN alfa-2a and ribavirin combination therapy in patients with CHC and persistently normal ALT level is similar to that seen in patients with elevated ALT levels.¹³⁴ See also section 8.5.

1⁺

A Patients with chronic hepatitis C and normal ALT should be considered for treatment with pegylated IFN and ribavirin.

9.2.4 PATIENTS WITH HIV CO-INFECTION

Pegylated IFN and ribavirin for 48 weeks is effective in treating patients with HCV and HIV co-infection, leading to sustained viral response in 60% of patients with genotype 2 and 3 and 14-29% in patients with genotype 1. For patients with genotype 1 infection and low HCV viral load (<800,000 IU/ml), the sustained viral response rate is around 60%.¹³⁵⁻¹³⁷

1⁺

98% of patients with HIV/HCV co-infection who did not have an EVR at week 12 did not achieve an SVR at week 48.¹³⁷

1⁺

A Patients with CHC and HIV should be considered for treatment with a combination of pegylated IFN and ribavirin for 48 weeks irrespective of genotype.

A For patients with HCV genotype 1 infection and HIV, the lack of an early viral response at week 12 predicts those who are unlikely to obtain an SVR, and treatment can be stopped.

9.2.5 PATIENTS WITH HEPATITIS B CO-INFECTION

Treatment outcomes with a combination of non-pegylated interferon and ribavirin in co-infected patients with chronic hepatitis B and C are similar to those achieved in patients with HCV mono-infection.^{138, 139} No trials were found examining pegylated interferon and ribavirin in patients co-infected with chronic hepatitis B and C.

2⁺⁺

C Patients with chronic hepatitis B and C co-infection should be considered for combination treatment with pegylated IFN and ribavirin.

9.2.6 PATIENTS IN DRUG TREATMENT PROGRAMMES

In patients with CHC who are on a stable drug treatment programme, management with a combination of pegylated IFN and ribavirin is effective, leading to high levels of sustained viral response. Whilst drop-out rates are higher than in other cohorts, the drop-outs occur early, within the first eight weeks. After eight weeks compliance is similar to other groups.^{42, 140}

2⁺

C Patients with CHC who are on a drug treatment programme can be considered for treatment with a combination of pegylated IFN and ribavirin.

Active drug users should be engaged in efforts to address their healthcare needs and in harm reduction.

Active drugs users should have a comprehensive assessment of their psychological needs and of their likely adherence to antiviral treatment.

9.3 FACTORS INFLUENCING EFFECTIVENESS

9.3.1 AGE, GENDER AND ETHNICITY

Antiviral therapy is less effective in patients over the age of 40 and men are less likely than women to achieve a sustained viral response.^{7, 118, 119} Variations have been observed in the response of patients of different race to antiviral therapy. A meta-analysis of ethnic differences showed that patients of African-American or Hispanic origin had lower SVRs than Caucasian or Asian groups (16% and 24% vs 32% and 59% with genotype 1 achieved SVR).¹⁴¹

1+

A Patients should be advised that older age at the time of treatment leads to a lower sustained viral response.

B Patients should be advised about the likelihood of sustained viral response according to their ethnic origin.

9.3.2 BODY WEIGHT

Three systematic reviews report that in patients with CHC whose weight is greater than 75 kg, treatment with a combination of pegylated IFN and ribavirin leads to a lower SVR than in patients weighing less than 75 kg.^{7, 118, 119} Dosage of pegylated IFN and ribavirin in these studies was given at a cut-off point of 75 kg and not weight related, therefore caution should be taken when extrapolating results. Weight and diet issues are discussed in section 11.

1+

9.3.3 ALCOHOL

Treatment studies in patients continuing to use alcohol are limited. Two cohort studies have shown that response rate to standard IFN treatment was inversely proportional to the amount of alcohol ingested.^{142, 143} A six month abstinence from alcohol did not offset previous lifetime alcohol intake.¹⁴⁴

2+

Patients should be advised that drinking alcohol (even in moderation) can reduce the response to treatment with pegylated IFN and ribavirin.

9.4 CONTRAINDICATIONS

9.4.1 PREGNANCY AND RISK OF PREGNANCY

There are no studies on the effects of antiviral therapy on human pregnancy. Studies in animals have shown that ribavirin therapy, at well below the recommended human dose, causes malformations in the fetus. The incidence and severity of the teratogenic effects increased with escalation of the ribavirin dose. Survival of the fetus and the offspring was reduced.¹⁴⁵ Further animal studies have shown abnormalities in sperm.¹⁴⁵

There are no data on the use of pegylated IFN in pregnant women and it is not known whether pegylated IFN or ribavirin are excreted in human milk.

Pegylated IFN and ribavirin must not be prescribed to women who are pregnant.

Treatment with pegylated IFN and ribavirin should not be initiated until pregnancy has been excluded.

Couples, with one partner receiving pegylated IFN and ribavirin, should use two forms of contraception during treatment and for seven months after therapy has ended.

9.4.2 PATIENTS WITH RENAL FAILURE

Ribavirin causes a dose-dependent haemolytic anaemia and the degree of haemolysis is dependent on the severity of the renal failure.¹⁴⁶ Treatment with pegylated IFN2a monotherapy at a dose of 135 mcg subcutaneously per week for patients on haemodialysis may be considered but patients need to be closely monitored.¹⁴⁷

1+
3

D Patients with CHC and renal failure may be treated with IFN monotherapy, with careful monitoring required.

9.4.3 PATIENTS WITH MENTAL HEALTH PROBLEMS

Patients with mental health problems respond equally well to interferon and ribavirin therapy but their psychiatric symptoms should be managed carefully, particularly in the first four weeks of treatment.^{148, 149}

2+
3

B Patients with stable mental health problems should not be excluded from treatment for CHC.

B Patients with mental health problems should have their psychiatric symptoms monitored prior to and throughout IFN treatment.

Formal psychiatric assessment should be considered for selected patients if necessary.

9.5 MANAGEMENT OF ADVERSE EFFECTS

9.5.1 FLU-LIKE SYMPTOMS

Virtually all patients taking pegylated IFN and ribavirin will experience flu-like symptoms such as fever, myalgia, rigors, arthralgia and headache. These tend to become less severe after the first month of treatment.¹⁵⁰ Simple interventions such as paracetamol use, increased fluid intake and rest can minimise these effects.^{150, 151}

4

D Patients experiencing flu-like side effects from pegylated IFN and ribavirin can be advised to use paracetamol within manufacturers' guidelines.

D Patients should be advised to maintain an adequate fluid intake throughout treatment with pegylated IFN and ribavirin.

D Patients should be advised to coordinate their injections of pegylated IFN and ribavirin with periods of reduced activity, such as weekends and holidays.

9.5.2 ANAEMIA AND NEUTROPENIA

Haemoglobin levels should be maintained at a level that prevents a need for dose reduction or discontinuation of pegylated IFN and ribavirin therapy as this can cause a reduction in SVR.¹³¹ Up to a third of patients receiving combination therapy develop anaemia and 13% progress to a haemoglobin of less than 100 g/l.

2+

In clinical trials the use of erythropoietin in patients who developed anaemia (haemoglobin level \leq 120 g/l) while on pegylated IFN and ribavirin therapy improved the anaemia and lessened the need to reduce the dose of ribavirin. It also improved quality of life.^{152, 153} There is no direct evidence that this results in an increase in the SVR. None of the erythropoietins are currently licensed for this indication.

1+

Granulocyte-colony stimulating factor (G-CSF) may relieve drug-induced neutropenia in patients receiving pegylated IFN and ribavirin therapy. It is most commonly needed in patients given antiviral therapy post liver transplant.¹⁵⁴

3

B Erythropoietin should be considered in CHC patients receiving pegylated IFN and ribavirin therapy who develop anaemia, to prevent curtailment or dose reduction of ribavirin.

D G-CSF should be considered on a case-by-case basis for patients who develop significant neutropenia while receiving treatment with pegylated IFN and ribavirin for CHC infection, to prevent curtailment or dose reduction of pegylated IFN.

9.5.3 DEPRESSION

Depression is a commonly reported side effect of pegylated IFN and ribavirin therapy in both patients who have previously experienced depression and those who have not.¹⁵⁵ Antidepressants can be successfully used for treatment related depression and as a preventative measure prior to exposure to antiviral treatment.^{148, 156}

1++
1-
3

B All patients receiving pegylated IFN and ribavirin should be monitored for signs of depression before, during and immediately post-treatment.

B Patients treated with pegylated IFN and ribavirin who experience depression should be considered for treatment with antidepressants and for referral to a specialist, if necessary.

A validated assessment tool (eg Hospital Anxiety and Depression score) should be used for monitoring depression.

9.5.4 SKIN REACTIONS

Severe skin reactions are uncommon during pegylated IFN or ribavirin therapy but dry skin, pruritus and diffuse eczematous lesions occur in approximately 20% of patients.¹⁵⁰ Psoriasis may also be exacerbated by treatment for CHC. Injection site reactions occur in over 50% of treated patients.¹⁵¹ Skin lesions appear most commonly on the distal limbs and head and neck region, suggesting a predominance in sun-exposed areas.¹⁵⁷ Patients respond well to antihistamines, emollients and topical steroids, allowing continuation of treatment.¹⁵⁷ Discontinuation rates for dermatological side effects are approximately 3-4%.¹⁵⁸

4
3

D All patients on pegylated IFN and ribavirin should be advised to ensure appropriate skin hygiene and hydration.

D Patients should be advised to avoid overexposure to sun.

D Patients should be advised to rotate injection sites.

D The use of emollients and topical corticosteroids can be considered for non-specific rashes.

The use of antihistamines can be considered for pruritus.

Severe dermatological reactions or those that do not respond to first line treatment should be referred for dermatological opinion.

9.5.5	<p>THYROID DYSFUNCTION</p> <p>IFN therapy is associated with the development of thyroid dysfunction (both hypothyroid and hyperthyroid) in up to six per cent of those treated.¹⁵⁰ Females are more at risk, especially those with thyroid autoantibodies before treatment.¹⁵⁹ IFN is associated with the induction and enhancement of thyroid autoimmunity, which is not always reversible.^{160, 161} Pre-treatment autoantibodies are not universally predictive of thyroid dysfunction during treatment.¹⁵⁰</p> <p>D Thyroid function should be monitored at baseline before IFN therapy, at week 12 of treatment and at any time where there is a suspicion of thyroid dysfunction.</p> <p><input checked="" type="checkbox"/> Patients developing thyroid dysfunction should be referred to an endocrinologist.</p>	4 1- 2+
9.5.6	<p>WEIGHT LOSS</p> <p>Chronic hepatitis C infection causes increased basal metabolic rate in non-cirrhotic patients.¹⁶² Weight loss is commonly reported in patients on antiviral treatment.^{150, 151, 163} Nutritional therapy of patients with HCV is discussed in section 11.1.</p>	2- 4
9.5.7	<p>DYSPNOEA</p> <p>Dyspnoea is a rarely reported side effect of pegylated interferon and ribavirin therapy. It may occur as a result of treatment related anaemia but may also be caused by more serious cardiovascular or respiratory conditions.^{150, 151, 164}</p> <p>D Patients treated with pegylated IFN or ribavirin who report dyspnoea that is not related to anaemia should be urgently assessed medically for cardiopulmonary problems.</p>	2- 4
9.5.8	<p>RETINOPATHY</p> <p>Retinopathy during pegylated IFN therapy is common but generally mild and transient. It resolves spontaneously on discontinuing IFN and treatment is seldom required. The long term consequences are unknown.¹⁶⁵ Patients with hypertension or diabetes are at greater risk of developing retinopathy.¹⁵¹ Other ophthalmic side effects are uncommon.</p> <p>D Patients with CHC and hypertension or diabetes should have an ophthalmic examination prior to commencing treatment, paying particular attention to cotton wool spots and retinal haemorrhage.</p> <p>D Any patient reporting visual disturbance during treatment should be examined further by an ophthalmologist.</p> <p>D IFN should be discontinued in any patient with visual disturbance until it has resolved or an ophthalmologist has confirmed there is no retinal injury.</p>	1+ 4
9.5.9	<p>ALOPECIA</p> <p>Alopecia is a relatively common reported side effect of IFN and ribavirin therapy. Hair will grow again on cessation of treatment.^{150, 151}</p> <p>D Patients should be advised that treatment related hair loss is reversible on cessation of treatment.</p>	4
9.5.10	<p>OTHER SIDE EFFECTS</p> <p>Other reported side effects include insomnia, poor concentration, oral disease, nausea, and post-treatment withdrawal symptoms. No evidence on their effective management was identified.</p> <p>Fatigue is one of the most commonly reported side effects of IFN or ribavirin treatment and may be multifactorial with anaemia, hypothyroidism, sleep disturbance and depression all contributing.^{150, 151}</p>	4

9.6 RELAPSE OR FAILED TREATMENT

9.6.1 IFN AND RIBAVIRIN

Retreatment with a combination of pegylated IFN and ribavirin is effective in patients with CHC who have had unsuccessful treatment with non-pegylated IFN with or without ribavirin, and leads to sustained viral response in a proportion of patients. The SVR is highest in patients who had received prior treatment with non-pegylated IFN monotherapy, those infected with genotypes 2 or 3, those who had relapsed rather than not responded to previous treatment, and those who were not cirrhotic at time of retreatment.¹⁶⁶

3

D Patients with CHC who have had unsuccessful treatment with non-pegylated IFN and ribavirin should be considered for pegylated IFN and ribavirin retreatment.

9.6.2 OTHER THERAPIES

Meta-analysis of three studies of viral relapsers after IFN based treatment (304 patients) found no significant increase in SVR with the addition of amantadine to IFN plus ribavirin therapy.¹⁶⁷ Non-responders to IFN based treatment showed a significant increase in SVR (12.7%, 95% CI 3.8-21.6%) with the addition of amantadine to IFN plus ribavirin therapy.¹⁶⁷

1-

Three open label studies of IFN and ribavirin plus amantadine for the retreatment of non-responders to IFN based treatment found an SVR rate between zero and ten per cent.¹⁶⁸ In another small study the addition of amantadine to pegylated IFN and ribavirin did not lead to an increase in the SVR or biochemical response.¹⁶⁹

1+

IFN in combination with ribavirin is superior to IFN in combination with amantadine.¹⁶⁸

1+

A small randomised placebo controlled trial demonstrated that 48 weeks of ribavirin monotherapy is not superior to placebo with regard to HCV RNA levels or histological change in patients who are non-responders to standard IFN and ribavirin therapy.¹⁷⁰

1+

In patients with chronic hepatitis C who did not respond to previous therapy, interleukin 12 (500 mg/kg twice weekly for eight weeks) was shown to produce a sustained viral response in one per cent of patients and severe adverse reactions in three per cent.¹⁷¹

2+

C The following therapies are not recommended for the treatment of patients infected with CHC, whether they are being treated for the first time, previously relapsed, or have never responded to treatment:

- amantadine in addition to pegylated IFN alone or in combination with ribavirin
- ribavirin monotherapy
- interleukin 12.

9.7 MONITORING PATIENTS WHO ARE NOT RECEIVING TREATMENT

9.7.1 CLINICAL REVIEW

No evidence was identified regarding effective practice in monitoring and advising patients who are not candidates for treatment or who have received unsuccessful treatment.

Patients should be encouraged to continue attending follow-up clinics for review in order to monitor their condition and discuss new therapies as they emerge.

Patients should have access to counselling and specialist nurse services to provide support on lifestyle issues relating to hepatitis C.

9.7.2 ROLE OF LIVER BIOPSY

Routine liver biopsy during or after antiviral treatment is not indicated unless specific information is required in selected patients.¹⁰⁰

1-

10 Treatment of advanced infection

10.1 ANTIVIRAL THERAPY

10.1.1 PATIENTS WITH CIRRHOSIS

Patients with cirrhosis are defined as having compensated or decompensated cirrhosis. Those with decompensation have deterioration with development of one or more of the following: jaundice, ascites, variceal bleeding or encephalopathy.

There are several large well conducted RCTs of interferon and ribavirin, pegylated IFN and ribavirin, and pegylated interferon monotherapy in patients with chronic HCV who have a high likelihood of progressing to endstage liver disease.^{122, 123, 172, 173} Subgroups within these trials had cirrhosis or advanced fibrosis. Randomisation distributed them evenly between the interventions so that subgroup analysis was possible. Therapy appeared no more toxic to the patients with cirrhosis compared to those without cirrhosis, but was less effective. The SVRs achieved were 50-70% for genotype 2 and 3, and 20-30% for genotype 1.

1+

No head-to-head trials of the different pegylated IFNs were identified. Long term therapy for patients with cirrhosis is under investigation but there are no results published to date.

A Patients with compensated cirrhosis should be considered for therapy with pegylated IFN and ribavirin, unless contraindicated.

In patients with cirrhosis who obtain SVR with IFN treatments there is a significant reduction in the incidence of hepatocellular carcinoma compared to controls (number needed to treat = 5).¹⁷⁴ In those who fail to obtain an SVR with IFN treatment there is still a significant reduction in incidence of HCC compared to controls.¹⁷⁵

1++

A Patients with compensated HCV cirrhosis may benefit from IFN treatment to reduce the risk of development of HCC. The duration of therapy required to achieve this is not clear.

There was insufficient evidence on the treatment of patients with HCV and decompensated cirrhosis to make a recommendation.

10.1.2 PATIENTS REFERRED FOR LIVER TRANSPLANT

Several studies have addressed the benefits of antiviral therapy given in the period leading up to, or following, orthotopic liver transplantation (OLT).^{154, 176-179} In the period before transplantation many are excluded from therapy because of contraindications. SVR rates are low. There is little evidence for treatment in the peri-transplant period (the time period immediately pre-, during and post-transplantation). Post-transplant therapy is poorly tolerated, due to anaemia and leucopenia, but appears safe in regard to graft failure. In those patients able to tolerate full dose therapy, high SVRs are achieved.

3
1+

D Patients in whom transplant is planned should not receive antiviral therapy in the pre-transplant or peri-transplant stages, except as part of clinical trials.

D Patients should be considered for antiviral therapy post liver transplant to achieve HCV clearance in cases of recurrence of HCV related liver disease.

10.2 LIVER TRANSPLANTATION

In early studies of patients transplanted for HCV cirrhosis, the five and 10 year survival rates were equivalent to patients post OLT for non-HCV causes (68% and 60%).¹⁷⁹ In a more recent analysis of the United Network for Organ Sharing (UNOS) database outcomes were studied in HCV positive (5,640, 43%) and HCV negative recipients (7,386, 56.7%). In the HCV negative and the HCV positive recipient populations, five year patient survival rates were 83.5% vs. 74.6% ($P < 0.00001$) and five year graft survival rates 80.6% vs. 69.9% ($P < 0.00001$), respectively. HCV infection reduces outcome following transplantation but this effect is not sufficient to deny an individual patient transplantation.¹⁸⁰

2+

Patients with HCV and transplantable hepatocellular carcinoma (one lesion < 5cm or fewer than three lesions < 3 cm, on cross-sectional imaging) have no decrease in survival benefit up to 48 months post orthotopic liver transplantation when compared to patients with HCV alone.^{179, 181} 2+

Quality of life in patients post OLT for HCV is equivalent to patients with non-HCV at three years.¹⁸² 3

C Patients with hepatitis C virus and concurrent operable hepatocellular carcinoma should be offered liver transplantation.

C Patients with HCV associated chronic liver failure should be offered liver transplantation.

No studies were found on the effectiveness of retransplantation in patients with graft loss due to HCV recurrence.

10.3 SCREENING FOR HEPATOCELLULAR CARCINOMA

The results of studies evaluating the sensitivity and specificity of serum alpha fetoprotein for detection of HCC in individuals with HCV indicate that in isolation this marker is of limited value only.¹⁸³ 1+

Annual ultrasound scanning of patients with cirrhosis and HCV does not detect tumours at a stage that permits likely curative treatment.¹⁸⁴ Scanning on a six monthly basis may result in the detection of tumours at a stage that permits curative therapy.¹⁸⁵ 2+

Methods of screening and surveillance other than alpha fetoprotein and ultrasound remain experimental.

The rate of development of HCC in patients with HCV who are non-cirrhotic is extremely low (7.6% vs 92.4%).¹⁸⁶ 2+

A The measurement of alpha fetoprotein should not be used in isolation for screening or surveillance of the development of HCC in patients with hepatitis C.

D Surveillance using ultrasound should take place at six monthly intervals.

C Surveillance should be confined to patients with cirrhosis.

11 Nutrition, supportive care and complementary therapies

11.1 NUTRITIONAL INTERVENTIONS

11.1.1 DIETARY INTERVENTIONS

Protein energy malnutrition is common in all patients with chronic liver disease and can lead to weight loss. Chronic hepatitis C infection increases basal metabolic rate in non-cirrhotic patients.¹⁶² Malnutrition (either under- or overweight) negatively affects nutritional status, quality of life and survival. Nutritional assessment to identify patients at risk and provision of nutritional support (enteral and parenteral) to improve clinical outcome should play an important role in patient care.¹⁸⁷

2⁻
4

Weight loss is commonly reported in patients on antiviral therapy.^{150, 151, 163} This is possibly a result of other side effects, such as fatigue and depression, which may have a negative impact on appetite.^{150, 151}

2⁻
3

- D**
- **Nutritional care for people infected with hepatitis C should involve promotion of optimal nutrition and prevention or treatment of malnutrition or deficiencies of specific nutrients.**
 - **Patients should have a nutritional screen and if needed a nutritional assessment and appropriate advice by a dietitian.**

D **Patients with advanced liver disease should be given nutritional support to minimise malnutrition.**

- Antiviral therapy represents a high risk period for weight loss so patients should be monitored closely and given nutritional support, as required, during treatment.

A systematic review of 11 RCTs found no conclusive evidence to support any benefit of branched chain amino acids (BCCA) in patients with cirrhosis and hepatic encephalopathy.¹⁸⁸ It was unclear how many of the patients included in the study were HCV positive. BCCA improve serum albumin levels in the compensated stage of cirrhosis in patients with a branch chain tyrosine ratio (BTR) <4 and serum albumin level between 35-39 g/l.^{189, 190} The methodology used in these studies gave little consideration to confounding variables.

1⁺⁺
1⁻

Coffee may have a protective effect against the development of hepatocellular carcinoma in patients with liver disease when consumed in quantities of three or more cups per day. It is unclear which compound in coffee causes the effect.^{191, 192}

2⁺

11.1.2 VITAMINS AND MINERALS

There is little evidence that individual vitamins and minerals may influence the natural history of CHC.

Zinc supplementation of 34 mg/day may have some beneficial effect on sustained viral response in patients taking interferon therapy; with genotype 1b; with viral load lower than 5x10⁵ copies/ml.¹⁹³

2⁻

Vitamin K² may be beneficial in the prevention of development of HCC in patients with hepatitis C.¹⁹⁴

2⁻

Vitamin E supplementation had no beneficial effect in patients taking pegylated interferon and ribavirin. It does not appear to prevent ribavirin haemolysis or enhance virological clearance.¹⁹⁵

1⁻

Iron restricted to <7 mg/day in conjunction with a controlled calorie intake of 30 Kcals/kg, protein intake of 1.1-1.2 g/kg, and fat at 15% of dietary intake, reduces aminotransferase levels.¹⁹⁶

4

Vitamin C supplementation of 600 mg/day is not beneficial in the prevention of retinopathy associated with interferon therapy.¹⁶⁵

1⁻

- ☑ Patients with chronic hepatitis C should be encouraged to achieve the UK recommended nutrient intake of vitamins and minerals.¹⁹⁷ They should be advised that there is no identified evidence to support amounts in excess of this.
- ☑ Patients whose serum ferritin levels are consistently high should not be advised to reduce dietary iron intake.

11.1.3 OVERWEIGHT

Studies have identified BMI > 25 as being associated with hepatic steatosis, which leads to more severe fibrosis.^{88, 198} Liver fibrosis, steatosis and ALT level decrease with supervised weight loss programmes of diet and regular exercise, aiming at 0.5 kg weight loss weekly.¹⁹⁹

2+
3

C Patients who are overweight should be advised to lose weight, within a realistic weight loss target, as this may have a beneficial effect on the degree of liver damage associated with hepatitis C infection.

- ☑ Weight loss should only be considered if the patient is stable in their management of hepatitis C. Interventions aimed at weight reduction during antiviral treatment are not recommended, as side effects may lead to excessive unintentional weight loss.
- ☑ Patients on weight loss programmes should receive regular follow up and support.

11.2 SPECIALIST NURSE INTERVENTIONS

Specialist nursing support is key to maintaining adherence to treatment in patients with neuropsychiatric conditions.²⁰⁰ Specialist hepatology nursing has a significant role to play in helping patients to attain and maintain SVR.²⁰¹

2-

- ☑ Clinical nurse specialists should be an integral member of the clinical team caring for patients with chronic hepatitis C.

11.3 PSYCHOSOCIAL INTERVENTIONS

Two studies on psychological interventions for patients with hepatitis C showed no evidence for a benefit. One small non-randomised trial showed some benefit, but the other, an RCT which tested individually tailored interventions, showed no difference in outcome from standard care.^{202, 203}

2-
1+

11.4 EXERCISE

Light to moderate exercise programmes have been recommended for patients receiving treatment for hepatitis C.¹⁵⁰ A small cohort study shows that patients on antiviral therapy have a reduced exercise tolerance.²⁰⁴

4
2-

D Patients with hepatitis C should be encouraged to take mild to moderate exercise. Those on antiviral therapy should be advised that they may find their capacity for exercise reduced.

11.5 COMPLEMENTARY THERAPIES

Two meta-analyses have concluded that there is no evidence to support the use of complementary or alternative medicines in the treatment of patients with hepatitis C.^{205, 206}

1++

None of the trials identified ran for a long enough period to show the long term safety or harm of herbal remedies.

No trials were found which specifically examined the use of silymarin (milk thistle) in patients with chronic hepatitis C.

- Patients should be made aware that there is a potential for harm associated with some complementary preparations.

11.6 PALLIATIVE CARE

No evidence was identified looking specifically at palliative care for patients with HCV.

12 Information for discussion with patients and carers

12.1 PATIENT INFORMATION LEAFLET

To find out patients' main information needs, interviews and focus groups were held with patients, and questionnaires sent to people with hepatitis C across the UK by the Scottish Hepatitis C support network and the UK Hepatitis C resource centre. The results have been translated into questions and suggested answers, which could be used to encourage discussions between patients and health professionals. Several of the organisations listed in section 12.2 produce good-quality patient leaflets which could be used alongside the information below.

12.2 SOURCES OF FURTHER INFORMATION

Anam Cara

Ardoch House
25 Ardoch Street
Glasgow
G22 5QG

Tel: 0141 336 8093 • Email: anam-cara@btconnect.com

A confidential advice and support service for individuals living with hepatitis C in Greater Glasgow.

Body Positive Tayside

11-15 Princes Street
Dundee
DD4 6BY

Tel: 01382 461555 • Fax: 01382 461424

Email: admin@bptayside.sol.co.uk • www.bodypositivetayside.org

Offers a full range of literature on hepatitis C and provides a one to one counselling service and drop-in centre. Information and support is available for people affected by HIV and hepatitis C.

The British Liver Trust

Portman House
44 High Street
Ringwood
BH24 1AG

Tel: 01425 463080 • Fax: 01425 470706 • www.britishlivertrust.org.uk

Provides a range of publications on individual liver conditions and offers support to patients with liver disease and those who care for them.

C Level

268 Bath Street
Glasgow
G2 4JR

Tel: 0141 332 2520 • www.c-level.org.uk

Information, advice and support service offering confidential testing, group support, one to one support, complementary therapies, volunteer opportunities, peer education and staff training.

C Plus

17 Academy St
(First Floor)
Edinburgh
EH6 7EE

Tel: 0131 478 7929 • Fax: 0131 478 7928 • Email: cplus@hepccentre.org.uk

Support and information service for people living with or affected by Hepatitis C in the Lothians.

Fife Positive Support

Social Work Offices
70 Stenhouse Street
Cowdenbeath
Fife
KY4 9DD

Tel: 01383 313320 • Fax: 01383 313293

Email: lan.robertson@fife.gov.uk or Janice.kenny@fife.gov.uk

Offers flexible support and information to individuals and families living in Fife affected by hepatitis C, hepatitis B or HIV.

The Hepatitis C Trust

27 Crosby Row
London
SE1 3YD

Tel: 020 7089 6220 • Fax : 020 7089 6201 • Helpline: 0870 2001200

Email: info@hepctrust.org.uk • www.hepcuk.info

The Hepatitis C Trust was set up by people with the illness and runs a range of services that provide support, information and representation for people with hepatitis C.

Haemophilia Society UK

First Floor
Petersham House
57a Hatton Garden
London
EC1N 8JG

Tel: 020 7831 1020 • Fax: 020 7405 4824 • Freephone helpline: 0800 018 6068

Email: info@haemophilia.org.uk • www.haemophilia.org.uk

Provides services for people with haemophilia and von willebrand's affected by HIV and viral hepatitis.

UK Hepatitis C Resource Centre

276 Bath Street
Glasgow
G2 4JR

UK Hepatitis C Information Line: 0870 242 2467

Email: info@hepccentre.org.uk • www.hepccentre.org.uk

UK Hepatitis C Services Directory: www.hepccentre.org.uk/resources

The UK Hepatitis C Resource Centre provides a range of services and resources to help anyone in the UK affected by, or at risk from, hepatitis C.

Information about **hepatitis C** for patients and carers

What is hepatitis C?

Hepatitis C is an illness caused by a virus which can be passed through blood from one person to another. It mainly affects the liver, causing swelling (inflammation) and scarring (fibrosis and cirrhosis), sometimes leading to cancer of the liver (hepatocellular carcinoma). You can have the hepatitis C virus for 20 to 30 years before the liver is seriously damaged and symptoms begin to show. A liver transplant may be an option for people who develop advanced liver disease.

How does it affect people?

It is a potentially life-threatening condition that can affect you physically and emotionally. It can affect your quality of life. Treatment is available which can cure hepatitis C in many cases.

What are the symptoms of hepatitis C?

Some people have no symptoms at all for many years while others may feel extreme tiredness, have sweats (especially at night), aches and pains, loss of appetite and concentration problems. People may even be thought to have myalgic encephalomyelitis (**ME**) or chronic fatigue syndrome. Symptoms may come and go. In the later stages of the infection when the liver is more seriously damaged, there may be symptoms such as jaundice, itchiness and a swollen abdomen.

Have I been at risk?

Risk factors where blood from someone infected with hepatitis C may get into the bloodstream of another person include:

- injecting or snorting drugs while sharing any equipment;
- sharing items such as razors, toothbrushes or any item that can scratch the skin;
- piercing or tattooing if any equipment is reused;
- sexual activity, although the risk is low except where there is a risk of bleeding;
- being exposed to blood at work, for example, a needlestick injury, cuts, cleaning up blood, and dealing with violent incidents where blood is involved;
- transmission from mother to child around the time of birth (this is quite rare and happens about five times in 100);
- receiving a blood transfusion or surgical treatment abroad or in the UK before 1991, or blood products in the UK before about 1987 (transfusions and blood products are now safe from HCV infection in the UK); and
- receiving medical or dental treatment in countries where hepatitis C is common and infection control may be poor.

What happens during testing?

If you decide to go ahead with testing, you will be asked to give blood samples which will be sent to a laboratory for testing. Anyone who has recently been exposed to hepatitis C will need to repeat the test to make sure any negative result is accurate. This is because there is a 'window period' immediately after exposure until the test becomes positive.

If you are not infected, the healthcare team will explain how to take precautions so you don't put yourself at risk again. If you do have hepatitis C, they will explain what this means and refer you to a specialist clinic for more help and liver assessment.

To find out how your liver is being affected by hepatitis C, you will need to go to a specialist clinic. Assessment will include blood tests such as liver function tests (LFT), a genotype (strain of hepatitis C virus) test, an examination, discussions about lifestyle, other medical conditions and medicines you take, ultrasound scan, and possibly a liver biopsy. A liver biopsy means taking a small piece of the liver for laboratory analysis. This is done under local anaesthetic.

What happens during treatment?

When these results are available, your doctor and nurse will be able to discuss treatment with you. The treatment involves an injection of a drug called pegylated interferon once a week, and ribavirin capsules or tablets taken every morning and night. Treatment lasts for either six months or a year. You will be given lots of information and advice to help you through the treatment.

Treatment is not suitable for everyone and depends on other medical conditions or complications. Avoid pregnancy while you or your partner is on treatment, and for seven to 12 months afterwards, because these drugs may be harmful to an unborn baby.

Treatment can be very effective but the drugs can have side effects. These can be managed with appropriate care and support. Your clinic should help you to access support as part of your care while on treatment. You will be expected to avoid alcohol or drugs (except prescribed drugs) for the whole time you are on treatment.

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Treatment can be very effective but the drugs can have side effects. These can be managed with appropriate care and support. Your clinic should help you to access support as part of your care while on treatment. You will be expected to avoid alcohol or drugs (except prescribed drugs) for the whole time you are on treatment.

What can I do to help myself?

- There are a number of lifestyle factors that can make living with chronic hepatitis C easier.
- Drink lots of water and replace alcohol with water or fruit juices.
- A balanced diet is crucial. Cut down on rich, fatty and sugary foods. Losing excess weight puts less strain on your liver. Professional guidance on achieving a healthy balanced diet is helpful.
- If you have a poor appetite, try and eat smaller meals more often.
- Regular moderate exercise can reduce stress or depression, increase energy levels and help boost your immune system.
- It is strongly recommended that you do not drink alcohol. Alcohol and hepatitis C damage the liver, and in combination cause damage at a faster rate. Professional support is available to help you reduce and stop drinking.

Stop smoking if you have hepatitis C. Help is available to stop smoking.

There is very little evidence for the benefits of complementary medicines, but many patients find them helpful in dealing with the many different symptoms associated with this disease. It is important to get professional advice before starting these.

There are various specialist support services for people with hepatitis C, such as counselling, peer support with other people with hepatitis C, and advocacy support to help with making decisions.

Hepatitis C can make people feel very isolated and emotional, and support for managing stress is important. Patients should have efficient and effective routes to treatment options, with access to:

- multidisciplinary team services providing good communication with the patient;
- good-quality information services;
- patient involvement at all stages of care and treatment;
- a smooth transition to palliative care if needed; and
- regular needs assessment.

13 Implementation, resource implications and audit

13.1 LOCAL IMPLEMENTATION

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. It is acknowledged that every Board cannot implement every guideline immediately on publication, but mechanisms should be in place to ensure that the care provided is reviewed against the guideline recommendations and the reasons for any differences assessed and, where appropriate, addressed. These discussions should involve both clinical staff and management. Local arrangements may then be made to implement the national guideline in individual hospitals, units and practices, and to monitor compliance. This may be done by a variety of means including patient-specific reminders, continuing education and training, and clinical audit.

13.2 RESOURCE IMPLICATIONS

This section is based on discussions with the guideline development group regarding current resource use in Scotland and the likely impact of implementing the recommendations made in the guideline. Where current practice will not change as a result of the recommendations it is unlikely there will be resource implications.

- Increased numbers of people being offered testing, along with the inclusion of current injecting drug users and patients with mild chronic hepatitis C being considered for antiviral therapy, could result in more people requiring treatment.
- There may be extra resourcing required for patients who need treatment with erythropoietin and G-CSF. Erythropoietin currently costs around £350 per week, and G-CSF about £130 per week. This will be in addition to the cost of HCV treatment.

The good practice point advising that clinical nurse specialists should be an integral member of the clinical team may have staffing implications.

13.3 KEY POINTS FOR AUDIT

The following key clinical indicators could be used to gauge the performance of clinical services in managing people with HCV through the referral, investigation and treatment pathway:

- the proportion of people diagnosed with chronic HCV who enter specialist care
- the number of people with chronic HCV in specialist care who are eligible for antiviral therapy; for those considered ineligible for treatment, the reasons for their ineligibility
- the number of people with chronic HCV who receive antiviral therapy
- the proportion of people with chronic HCV who complete their course of antiviral therapy; for those who do not complete the course, the reasons for non-completion
- the proportion of those administered therapy who achieve a sustained viral response (categorised into those completing the course and those who do not).

13.4 RECOMMENDATIONS FOR RESEARCH

The following areas for further research were identified by the guideline development group:

- a study into whether testing and knowledge of HCV status changes behaviour to slow down disease progression, or reduce transmission to others
- an initiative to identify former injecting drug users should be developed, implemented and evaluated
- a prospective study to clarify the long term prognosis of individuals with chronic HCV infection, including treated and untreated participants, ideally as part of an ongoing national clinical audit in Scotland
- long term follow up of outcomes after the use of pegylated IFN in children
- the effectiveness of pegylated interferon and ribavirin therapy in Caucasian patients with chronic hepatitis B and chronic hepatitis C co-infection
- an RCT on antiviral therapy for patients with genotypes 2 and 3 with cirrhosis for 24 or 48 weeks
- the role of coffee and its derivatives in the prevention of hepatocellular carcinoma
- the effectiveness of long term weight reduction programmes on delayed progression in hepatitis C
- the role of haematopoietic growth factor support in post OLT patients
- the development of strategies to eradicate HCV post transplant
- the effectiveness of specialist nurse intervention in the care and management of patients with HCV
- a review of the specific palliative care needs of patients with HCV.

13.5 FURTHER PUBLICATIONS

The following reports have been approved by NHS Quality Improvement Scotland:

- NICE technology appraisal guidance no.106. Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C, 2006²⁰⁷
- NICE technology appraisal guidance no.75. Interferon alfa (peylated and non-peylated) and ribavirin for the treatment of chronic hepatitis C, 2004.²⁰⁸

The Scottish Medicines Consortium has issued advice on the use of pegylated IFN and ribavirin, for the treatment of children from three years of age, adolescents and adults with chronic hepatitis C. Further details are available from the website: www.scottishmedicines.org.uk

14 Development of the guideline

14.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of NHS Quality Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in “SIGN 50: A Guideline Developer’s Handbook”, available at www.sign.ac.uk

14.2 THE GUIDELINE DEVELOPMENT GROUP

Dr John Dillon (Chair)	<i>Consultant Hepatologist, Ninewells Hospital, Dundee</i>
Dr Philip Newsome (Secretary)	<i>Specialist Registrar in Hepatology, Royal Infirmary of Edinburgh</i>
Professor Jeremy Bagg	<i>Professor of Clinical Microbiology, Glasgow University Dental School</i>
Dr Peter Bramley	<i>Consultant Gastroenterologist, Stirling Royal Infirmary</i>
Dr Sandy Elder	<i>Consultant Occupational Health Physician, SALUS, Coatbridge</i>
Dr Andrew Fraser	<i>Consultant Gastroenterologist, Aberdeen Royal Infirmary</i>
Mr Jeff Frew	<i>Patient Representative, Edinburgh</i>
Professor David Goldberg	<i>Consultant Epidemiologist, Scottish Centre for Infection and Environmental Health, Glasgow</i>
Ms Ysobel Gourlay	<i>Senior Pharmacist, Gartnavel General Hospital, Glasgow</i>
Dr Rosie Hague	<i>Consultant in Paediatric Infectious Diseases and Immunology, Royal Hospital for Sick Children, Glasgow</i>
Dr Janina Harvey	<i>Consultant in Genitourinary Medicine, Falkirk and District Royal Infirmary</i>
Dr Mary Hepburn	<i>Honorary Consultant Obstetrician and Gynaecologist, Princess Royal Maternity Hospital, Glasgow</i>
Dr Nick Kennedy	<i>Consultant in Infectious Diseases, Monklands Hospital, Airdrie</i>
Dr Clifford Leen	<i>Consultant in Infectious Diseases, Western General Hospital, Edinburgh</i>
Mr Krishnakumar Madhavan	<i>Transplant Surgeon, Royal Infirmary of Edinburgh</i>
Ms May McCreaddie	<i>Research Associate, Department of Nursing Studies, University of Edinburgh</i>
Dr Elizabeth McCrudden	<i>Senior Lecturer and Honorary Consultant in Virology, Institute of Virology, Glasgow</i>
Ms Margot Miller	<i>Clinical Nurse Practitioner (Gastrointestinal/Liver), Royal Infirmary of Edinburgh</i>
Dr Peter Mills	<i>Consultant Gastroenterologist, Gartnavel General Hospital, Glasgow</i>
Mrs Margaret Neilson	<i>Clinical Nurse Specialist (Liver Disease), Glasgow Royal Infirmary</i>
Dr J J Kennedy Roberts	<i>General Practitioner and Lead Specialist Senior Medical Officer, Glasgow Addiction Service</i>
Mrs Kay Roberts	<i>Pharmacy Consultant, Glasgow</i>
Mr Ian Robertson	<i>Social Worker, Fife Positive Support, Rosyth</i>

Dr Nicola Rowan	<i>Director of Blood Borne Viruses, UK Hepatitis C Resource Centre, Glasgow</i>
Ms Ailsa Stein	<i>Information Officer/Programme Manager, SIGN</i>
Dr Lorna Thompson	<i>Programme Manager, SIGN</i>
Dr Henry Watson	<i>Consultant Haematologist, Aberdeen Royal Infirmary</i>
Ms Tracy Wilson	<i>Senior Dietitian, Western General Hospital, Edinburgh</i>
Dr Steven Yule	<i>Consultant Radiologist, Aberdeen Royal Infirmary</i>

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest and further details of these are available on request from the SIGN Executive. Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive.

14.3 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic literature review was carried out using an explicit search strategy devised by the SIGN Information Officer in collaboration with members of the guideline development group. Literature searches were initially conducted in Medline, Embase, Cinahl and the Cochrane Library, using the year range 2000-2005. Key websites on the Internet were also used, such as the National Guidelines Clearinghouse. The literature search was updated with new material during the course of the guideline development process, and was supplemented by reference lists of relevant papers and group members' own files. The Medline version of the main strategies can be found on the SIGN website.

14.4 CONSULTATION AND PEER REVIEW

14.4.1 NATIONAL OPEN MEETING

A national open meeting is the main consultative phase of SIGN guideline development, at which the guideline development group presents its draft recommendations for the first time. The national open meeting for this guideline was held on 3 November 2005 and was attended by 215 representatives of all the key specialties relevant to the guideline. The draft guideline was also available on the SIGN website for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

14.4.2 SPECIALIST REVIEW

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. SIGN is very grateful to all of these experts for their contribution to the guideline.

Dr Idranil Banerjee	<i>Consultant Physician Genitourinary Medicine, Victoria Hospital, Kirkcaldy</i>
Dr James Beattie	<i>General Practitioner, Inverurie</i>
Dr Alan Begg	<i>General Practitioner, Montrose</i>
Ms Christine Beveridge	<i>Lay representative, Brighton</i>
Dr Doris Campbell	<i>Reader in Obstetrics, University of Aberdeen</i>
Dr Philip Dolan	<i>Chairman, Scottish Haemophilia Forum</i>
Dr Raymond Fox	<i>Consultant in Infectious Diseases, Gartnavel Hospital, Glasgow</i>
Dr Hugh Gilmour	<i>Senior Lecturer/Consultant Pathologist, Royal Infirmary of Edinburgh</i>
Mr Charles Gore	<i>Chief Executive, Hepatitis C Trust, London</i>
Professor Peter Hayes	<i>Professor of Hepatology, Royal Infirmary of Edinburgh</i>

Ms Paula Hynd	<i>Senior Specialist Dietitian (Gastroenterology), James Cook University Hospital, Middlesbrough</i>
Professor William Irving	<i>Professor and Honorary Consultant in Virology, Queen's Medical Centre, University of Nottingham</i>
Professor Deirdre Kelly	<i>Professor of Paediatric Hepatology, Birmingham Children's Hospital</i>
Mr David Liddell	<i>Director, Scottish Drugs Forum, Glasgow</i>
Dr Janice Main	<i>Reader and Consultant Physician in Infectious Diseases and General Medicine, Imperial College and St Mary's Hospital, London</i>
Dr Mike Makris	<i>Reader and Honorary Consultant in Haemostasis and Thrombosis, Sheffield Haemophilia and Thrombosis Centre</i>
Dr Claire McIntosh	<i>Consultant Psychiatrist, Community Alcohol and Drug Service, Stirling</i>
Dr Alan Merry	<i>General Practitioner, Ardrrossan</i>
Dr David Mutimer	<i>Consultant Hepatologist, Queen Elizabeth Hospital, Nottingham</i>
Dr Fortune Ncube	<i>Consultant Epidemiologist, Health Protection Agency, London</i>
Dr Peter Rice	<i>Consultant Psychiatrist, Tayside Alcohol Problems Service, Montrose</i>
Professor Philip Robinson	<i>Professor of Clinical Radiology, St James' University Hospital, Leeds</i>
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14.4.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows:

Dr David Alexander	<i>British Medical Association Scottish General Practice Committee</i>
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Abbreviations

ALT	Alanine aminotransferase
BCCA	Branched chain amino acids
BMI	Body mass index
BTR	Branch chain tyrosine ratio
CHC	Chronic hepatitis C
CI	Confidence interval
ELISA	Enzyme linked immunosorbent assay
EPP	Exposure prone procedures
EVR	Early viral response
G-CSF	Granulocyte-colony stimulating factor
GUM	Genitourinary medicine
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIC	Hepatic iron concentration
HIV	Human immunodeficiency virus
IDU	Injecting drug users
IFN	Interferon
LFT	Liver function tests
ME	Myalgic encephalomyelitis
NAT	Nucleic acid test
NICE	National Institute for Health and Clinical Excellence
OLT	Orthotopic liver transplantation
PNALT	Persistently normal serum ALT
RCT	Randomised controlled trial
RNA	Ribonucleic acid
RR	Relative risk
RT PCR	Reverse transcription polymerase chain reaction
RVR	Rapid viral response
SIGN	Scottish Intercollegiate Guidelines Network
SVR	Sustained viral response
UK	United Kingdom
UNOS	United Network for Organ Sharing

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MANAGEMENT OF HEPATITIS C

REQUIRED TESTING

- D** The following groups should be tested for HCV:
- blood/tissue donors
 - patients on haemodialysis
 - healthcare workers who intend to pursue a career in a specialty that requires them to perform exposure prone procedures
 - healthcare workers at six, 12 and 24 weeks following an isolated acute percutaneous exposure to blood infected, or strongly suspected of being infected, with HCV, and anti-HCV testing at 12 and 24 weeks.

- B** In children born to women infected with HCV, an HCV antibody test should be performed at 12 months of age or thereafter.

REFERRAL

- A** Patients with acute HCV infection should be referred to specialist care immediately.

- D** Individuals, including injecting drug users, diagnosed with chronic HCV should be offered integrated multidisciplinary care.

TREATMENT

Treatment of acute HCV

- D** Patients with acute HCV infection which does not resolve spontaneously should start treatment between three and six months after diagnosis and receive IFN therapy for 24 weeks irrespective of genotype.

Treatment of chronic HCV

- A** A combination of pegylated IFN and ribavirin is the treatment of choice for patients with hepatitis C.

- B** SVR should be used as a marker for viral clearance.

RECOMMENDED TESTING

- D** Anyone with one of the following criteria should be offered an HCV test:
- an otherwise unexplained persistently elevated alanine aminotransferase
 - a history of injecting drug use
 - a child with an HCV antibody positive mother
 - HIV positive
 - recipient of blood clotting factor concentrates prior to 1987
 - recipient of blood and blood components before September 1991 and organ/tissue transplants in the UK before 1992
 - a healthcare worker following percutaneous or mucous membrane exposure to blood suspected to be/infected with HCV
 - received medical/dental treatment in a country where HCV is common and infection control may be poor
 - have had a tattoo or body piercing in circumstances where infection control procedure is suboptimal
 - had a sexual partner/household contact who is HCV infected.

PREVENTION OF SECONDARY TRANSMISSION

- D**
- Advise individuals infected with HCV to avoid activities which could result in percutaneous or mucous membrane exposure to their infected blood, eg sharing razors or toothbrushes.
 - Advise injecting drug users infected with HCV on how to prevent transmission of infection to other injecting drug users.
 - Advise individuals co-infected with HIV/HCV to practise safe sex, using condoms.
 - Healthcare workers who know they are HCV RNA positive should not undertake exposure prone procedures.
- B**
- Knowledge of HCV RNA positive status should not influence obstetric management of pregnant women or standard advice regarding breast feeding.

MANAGEMENT OF CHRONIC HCV

Who to treat

- B** There should be early consideration of antiviral therapy for patients with HCV with HIV co-infection.

- A** Patients with CHC and HIV should receive treatment for 48 weeks irrespective of genotype.

- A** In patients with HCV genotype 1 infection and HIV, the lack of an EVR at week 12 predicts absence of an SVR, and treatment can be stopped.

The following patient groups should all be consider for treatment with pegylated IFN and ribavirin:

- B**
- patients with mild CHC
- A**
- patients with chronic hepatitis C and normal ALT
- C**
- patients with chronic hepatitis B and C co-infection
- C**
- patients with CHC who are on a drug treatment programme
- B**
- patients with stable mental health problems should not be excluded from treatment for CHC. Psychiatric symptoms should be monitored prior to and throughout IFN treatment
- D**
- children with evidence of moderate or severe liver disease.

Duration of treatment

- B** The duration of treatment should be:
- 12-24 weeks for patients with genotype 2 or 3
 - 48 weeks for patients with genotype 1 or 4.

- A**
- Patients with genotype 1 infection should be tested for EVR at 12 weeks.
 - Patients with genotype 1 infection who fail to achieve an EVR at 12 weeks should be considered for cessation of treatment.
 - Patients with genotype 1 infection with an EVR at 12 weeks should continue treatment for 48 weeks. Those who are still HCV RNA positive at 24 weeks should be considered for cessation of treatment.

- B**
- Patients with genotype 2 or 3 infection should have an HCV RNA test performed 4 weeks after starting antiviral therapy and, if this is negative, the duration of therapy may be reduced to 12 or 16 weeks.