REVIEWING THE NATURAL HISTORY OF HEPATITIS C INFECTION

1. INTRODUCTION

Hepatitis C virus (HCV) is a blood-borne virus that is an important cause of chronic liver disease and liver cancer in the UK. Data from the Health Protection Agency (HPA) estimate that 142 000 individuals aged 15-59 years are living with chronic hepatitis C infection in England and Wales.[1] Routes of transmission vary worldwide and include exposure to infected blood products, injecting drug use, vertical transmission and rarely through sexual transmission. In the UK, the introduction of blood donor screening for HCV antibodies in September 1991 has had a major impact on the acquisition of HCV, and injecting drug use is now the most common reported route of transmission.

Characterising the natural history of HCV infection is important to understand its impact on an individual, but also to determine the population burden for health service planning. However, the changing epidemiological pattern and a greater understanding of the impact of co-factors on disease progression have added to the complexity of developing a general model that describes the natural history of HCV.[2]

Infection with HCV causes acute and chronic liver disease with differing severity and outcomes, and is associated with extra-hepatic manifestations that are related to chronic stimulation of the immune system and to virus-induced autoimmunity.[2] This paper reviews published evidence on the different stages of HCV infection, rates of progression and impact of disease in each of these stages. The evidence was then reviewed by an expert working group set up by the Department of Health (see Appendix 1 for list of members).

2. NATURAL HISTORY

a. Clinical course of acute hepatitis C infection

Acute hepatitis C refers to the period immediately following incubation. Exposure to the virus is normally followed at around 6-8 weeks by a rise in alanine aminotransferase (ALT) with or without mildly raised bilirubin.[3] Infection may be asymptomatic, but can be accompanied by a short-lived acute hepatitis (including malaise, anorexia and jaundice). Acute HCV infection is asymptomatic or mild in 70-80% cases [4] and a fulminant course is extremely rare in the absence of co-infection

or other modifiable co-factors.[2] Therefore, acute infection is infrequently diagnosed and the majority of acutely infected individuals are unaware of their diagnosis.[5] In a prospective study of 117 patients with post-transfusion hepatitis, sustained clearance of serum HCV RNA was observed in 15%, 12% had normalised alanine transaminase or ALT (but remained viraemic) and 73% progressed to chronic hepatitis.[6] In a systematic review of 31 longitudinal studies (n=675), the proportion with viral clearance ranged from 0.0-0.8 with a weighted mean of 0.26 (95%CI: 0.22-0.29).[7] In addition, where acute infection is detected and treated promptly, high response rates to standard or abbreviated treatment courses (up to 98%) have been reported.[8,9] The impact of acute HCV infection on an individual therefore appears to be limited unless those individuals progress to chronic infection.

Chronic hepatitis C is marked by the persistence of HCV RNA in the blood for at least 6 months after the onset of acute infection. Approximately 75-85% of infected patients do not clear the virus by 6 months and chronic hepatitis C infection develops.[5,7] The proportion of patients who develop chronic HCV infection may be determined by many factors. These include age at time of infection, gender, ethnicity, presence of symptoms during the acute infection, genotype, immunosuppression and HIV infection.[5,10]

Chronic HCV infection may develop with or without ALT abnormalities and with persistent or intermittent viraemia.[2] Prospective studies suggest that around 60-90% of acutely infected individuals have ALT abnormalities and progress to chronic infection (see below) while the remaining 10-40% have persistently normal ALT levels and progress more slowly.[2]

b. Progression of chronic hepatitis C infection

Determining the natural history of HCV infection and rate of progression to cirrhosis is challenging. Estimates of progression have largely been derived from cross-sectional studies based in secondary or tertiary care. Long-term prospective follow-up of large cohorts are required to provide accurate estimates of progression to cirrhosis and hepatocellular carcinoma. Such cohorts are difficult to identify and data from one cohort may not be generalisable to another that differs with respect to their route of acquisition, their age and gender profile and the presence of other factors important to progression.

A number of studies have assessed the long-term clinical and histological outcomes of HCV in different cohorts of patients with a well-defined time point of contamination.[11,12,13,14] In one of the most extensive studies, Seeff *et al.* followed a large number of cases who acquired post-transfusion hepatitis between 1968-1980.[11] Assessment at twenty years after infection found 26% cases had cleared infection and 15% had developed cirrhosis.[12] Follow up of 376 (n= 390) Irish women infected with HCV during 1977-78 from contaminated anti-D immunoglobulin found that only 2% had cirrhosis 17 years after infection.[15] This low rate of significant fibrosis persisted at the 27 year follow-up study.[16] In a multi-centre cohort study of 847 haemophiliac patients with hepatitis C, the cumulative incidence of end stage liver disease was 11.5% in HIV-negative patients after 35 years.[17] Overall mortality was reported at 24% with 6% of patients dying of liver disease, although the proportion of deaths amongst co-infected individuals was not reported. Risk factors for rapid progression included alcohol abuse, HIV co-infection, older age at infection and presence of HCV genotype 1.

A number of other studies have attempted to measure the time interval from infection to cirrhosis and hepatocellular carcinoma in different population groups. Although the mean time to cirrhosis is estimated at 20 years, only 10-20% patients will actually develop cirrhosis within this time period.[18] In a European study by Castells *et al.* the mean time to development of cirrhosis and HCC was 24 years and 27 years, respectively.[19] The prognosis for patients infected for longer than three decades remains uncertain but there are increasing data suggesting that disease progression increases with age, probably leading to higher rates of cirrhosis in patients infected for more than 30 years.

In a systematic review of 111 published studies, the estimated prevalence of cirrhosis at 20 years was 16% (95%CI: 14-19%) for all studies, but only 7% (95% CI: 4-12%) for studies conducted in non-clinical settings.[20] Data on 987 HCV-infected patients from 3 UK observational cohorts from different referral sources demonstrated different progression rates.[21] The estimated 20 year probability of progression to cirrhosis was 12% (95% CI: 6-22) in a hospital based cohort, 6% (95%CI: 3-13) in a post-transfusion cohort and 23% (95%CI: 14-37) in a cohort recruited from a tertiary referral centre.[21] These studies suggest that observed progression rates appear to be higher in cohorts presenting for clinical care; in contrast, individuals recruited prior to the development of symptoms have a more favourable course. Despite this potential bias in many published studies, factors that have been associated with progression

include gender, age at acquisition, duration of infection, ALT levels, genotype, smoking, alcohol consumption and presence of co-morbidities (including co-infection with HIV or HBV).[22, 23] Observational prospective studies and modelling predictions suggest that the risk of progression to severe fibrosis/cirrhosis is minimal in those with persistently normal ALT levels.[24]

c. Mortality

In a UK study of HCV-infected transfusion recipients, all-cause mortality during the first decade of infection was 1.4 times greater than that observed in a similarly traced group of transfusion recipients negative for HCV, and after 16 years all-cause mortality was 1.2 times greater.[25,26] However, this did not reach statistical significance. During the first ten years, the risk of dying directly from liver disease was almost 6 times higher for people infected with HCV, but this difference was not significant.[25] Excess alcohol consumption was implicated in 40% of the deaths from liver disease among patients. Other studies have quoted mortality rates between 2.5-14%, which may be due to differences in follow-up and inclusion of patients at different stages of HCV-related disease.[11,24] In a multi-centre cohort study of 847 haemophiliac patients, overall mortality after 35 years was reported at 24% with 6% of patients dying of end stage liver disease.[Error! Bookmark not defined.]

3. SPECTRUM OF CLINICAL OUTCOMES IN HCV INFECTION

HCV infection can lead to a wide spectrum of clinical outcomes ranging from acute asymptomatic infection with spontaneous resolution to decompensated liver cirrhosis and hepatocellular carcinoma (Table 1). The severity and stage of compensated chronic HCV infection can be defined according to histological criteria on the basis of the extent of necroinflammation and fibrosis:[27]

a. Mild chronic hepatitis C

Many patients with chronic hepatitis C infection are found to have a mild form of liver disease. This includes individuals who are asymptomatic with persistently normal or nearly normal ALT levels or those with abnormal ALT who have minimal/mild liver histological lesions.[24]

Population-based studies have demonstrated that approximately 50% of chronically infected individuals have persistently normal ALT levels and around two thirds have mild histological liver lesions.[24] Studies on the natural history of mild disease indicate

that the short-term outcome is always benign. However, progression of liver fibrosis can be observed in the longer term, particularly in those with elevated and/or fluctuating ALT levels.[24] Patients with mild liver damage associated with hepatitis C may report symptoms such as fatigue, malaise, bodily pain and joint symptoms.[28] Reduced health-related quality of life (HRQoL) is commonly reported in these individuals.[29] In a trial of therapy, the mean baseline HRQoL score for patients with mild disease was reported as 0.77 (where HRQoL score of 0= death; score of 1 is perfect health)[28] (Table 2). This is slightly lower than a UK general l population where the mean score was 0.825, although HRQoL is associated with a range of demographic factors, including age, sex and social class.[30] Furthermore, reductions in HRQoL score may not simply be a function of health compromises from HCV infection, but due to the patient's awareness of having a serious disease.[31] A diagnosis of HCV infection alone can affect patient quality of life.[29] Studies have also investigated the impact of HCV infection amongst haemophiliac patients. In a Dutch cross sectional study of registered haemophiliac patients, patients with HCV infection demonstrated a decrease in HRQoL domains of general health and vitality compared with non-infected haemophiliacs.[32]

The impact of HCV infection on employment and absenteeism remains unclear. Although there are no published UK data, one large US study (n=339,456) which compared absenteeism between employees with HCV infection (but not stratified by stage of infection), reported that HCV-infected workers had 4.15 more days of absence per employee per year than those without HCV infection.[33] This suggests that some loss of productivity does occur with HCV infection but that it is not clear at what stage of disease this would become significant.

b. Moderate and severe chronic hepatitis C

Moderate chronic hepatitis C infection is characterised by portal and periportal fibrosis, while severe chronic HCV infection is a pre-cirrhotic stage with histological evidence of binding fibrosis and incomplete regenerative nodules.[24]

Studies have demonstrated an association between impairments in HRQoL in patients with HCV and severity of liver disease.[34] In one trial of combination therapy, over 60% of patients with moderate disease (prior to therapy) reported problems with either pain and discomfort or anxiety and depression, and the HRQoL associated with moderate disease was 0.66 (table 2).[28] In studies amongst haemophiliacs, patients with HCV infection demonstrated a decrease in HRQoL domains of general health and vitality compared with non-infected haemophiliacs.[Error! Bookmark not defined.]

Table 1: Hepatic manifestations of HCV infection

STAGES OF CHRONIC HEPATITIS C INFECTION	DESCRIPTION
Presence of HCV RNA persisting for more than 6 months.	
A. **Mild**[24]	A. **Mild**: asymptomatic HCV carriers with persistently normal or nearly normal ALT **OR** HCV carriers showing minimal/mild liver histological lesions (no/minimal fibrosis) independent of ALT profiles
B. **Moderate**[24]	B. **Moderate**: evidence of portal and peri-portal fibrosis
C. **Severe (pre-cirrhotic)**[24]	C. **Severe**: Pre-cirrhotic stage with binding fibrosis and incomplete regenerative nodules
Compensated cirrhosis	Defined histologically as a diffuse hepatic process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules. Modified HAI (Ishak) score $\geq$ 6
Decompensated cirrhosis	Functional deterioration of the liver. Evidence of cirrhosis with development of any of the following complications: • Variceal haemorrhage • Ascites **OR** • Encephalopathy
Malignancy associated with hepatitis C infection	Hepatocellular carcinoma
Liver transplant	Transplant as a result of decompensated cirrhosis / HCC from HCV

Table 2: Mean HRQoL for each disease stage

Mild disease 0.77	**Treatment for mild disease** 0.65	**SVR after mild disease** 0.82
Moderate disease 0.66	**Treatment for moderate disease** 0.55	**SVR after moderate disease** 0.72
Cirrhosis 0.55	**Decompensated cirrhosis** 0.45	
Hepatocellular carcinoma 0.45	**Post liver transplant** 0.67	

(Source: Wright *et al.* 2006[28])

c. Cirrhosis

The progression to cirrhosis is often clinically silent and some patients are not known to have hepatitis C until they present with the complications of end stage liver disease or hepatocellular carcinoma (HCC). Although studies have demonstrated reduced quality of life measures in patients with HCV infection (Table 2), the impact of cirrhosis on quality of life (QoL) is not straightforward. In a study to evaluate the quality of life in cirrhotic and non-cirrhotic patients (n=271), no significant association was found between mean utility and disease stage.[35] Changes in HCV disease stage appeared to explain only small changes in QoL and with factors such as underlying co-morbidities, income and marital status having a greater effect on QoL than disease stage.[35]

The morbidity and mortality associated with severe liver fibrosis can be severe. Of patients with cirrhosis, approximately 75% remain stable and do not develop decompensation during 5 years or longer.[36] Approximately 80% of patients with stable cirrhosis and no previous episodes of decompensation will survive the next 10 years.[37] Conversely after a patient with chronic HCV infection develops a major complication of cirrhosis, their survival significantly declines: 50% after 5 years and 30% during the next 10 years.[36] The rate at which patients with stable cirrhosis develop complications is approximately 3-5% per year.[37] In a UK study of 150 HCV-infected patients with severe liver fibrosis, 25% of the 131 patients with no prior history of decompensation died or were transplanted, when assessed after a median interval of 42 months.[38] The probability of survival without liver transplantation was 97%, 88% and 78% at 1, 3 and 5 years, respectively. In non-UK studies, mortality amongst individuals with compensated cirrhosis has been reported at 9% during a mean follow-up of 5 years (with HCC and liver failure being the main causes of death).[36] The probability of survival after diagnosis of compensated cirrhosis was 96%, 91% and 79% at 3, 5 and 10 years respectively.[36]

d. Decompensated cirrhosis

Studies have estimated that the annual incidence of developing decompensated cirrhosis is 3.9% during the first 5 years.[36] The features of decompensated cirrhosis include the development of ascites, upper gastrointestinal bleeding secondary to varices or portal hypertensive gastropathy, hepatorenal syndrome and hepatic encephalopathy.[5] In patients with HCV-induced cirrhosis, decompensation (functional deterioration of the liver) or liver cancer occurs at a rate of approximately 5-6% per

year. The 5 year mortality following decompensation has been reported at 13%.[36] HRQoL for decompensated cirrhosis is significant and has been reported at 0.45 (Table 2).[28]

e. Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is a major complication of chronic HCV infection. However, unlike individuals with chronic hepatitis B infection, HCC appears to almost always develop in HCV-infected patients with cirrhosis.[39] In a European study of 384 patients with compensated cirrhosis due to HCV (different routes of transmission), the 5 year risk of HCC was 7% and the annual incidence was 1.4%.[36] During a 5 year follow-up of HCV-infected cirrhotic patients, complications relating to HCC accounted for 33% of deaths.[36] Genetic factors, alcohol consumption and gender are known to influence the risk of developing HCC. The impact of HCC on quality of life is very significant with the mean HRQoL score estimated at 0.45 (Table 2).[28]

f. Liver transplant

Patients transplanted for HCV have survival rates of 80% and 70% at 1 and 5 years, respectively.[40] Re-infection in the graft occurs in nearly all patients.[41] Re-infection with HCV then leads to cirrhosis in 25-33% of patients in 5 years, and 1-5% develop rapidly progressive fibrosing cholestatic hepatitis leading to hepatic failure in 1-2 years.[42]

4. ANTI-VIRAL THERAPY FOR CHRONIC HEPATITIS C

Drug therapy for hepatitis C has been the subject of technology appraisals by NICE and involves a 6 or 12 month course of therapy with a combination of pegylated interferon and ribavirin.[28,43] Combination anti-viral therapy (pegylated interferon alpha and ribavirin) is now recommended for individuals with mild, moderate and severe chronic hepatitis C. A complete (sustained) virological response (SVR) is defined as the sustained loss of HCV RNA with normalisation of transaminase values, 6 months after discontinuing treatment.[44]

Therapy for chronic HCV infection eliminates the infection in the majority of individuals and viral elimination is associated with reduced disease progression and a marked reduction in the incidence of disease sequelae. For patients infected with either genotype 2 or 3, response rates after a 24 week course of therapy approach 80%, although there may be some differences.[45] For patients with genotype 1

infection sustained virological response occurs in up to 50% after a 48 week course of therapy. Sustained viral response rates are also affected by a range of factors including age, viral load, certain host genetic polymorphisms and co-infections. [40,46,47,48,49]

The APRICOT and RIBAVIC studies investigated the effects of interferon and ribavirin in HIV co-infected patients. In those studies the highest SVR rate was 62%, lower than published rates of SVR for monoinfected individuals.[50,51] The use of low doses of ribavirin has been identified as a contributing factor to lower rates of SVR, due to the susceptibility of patients with HIV to haemolytic anaemia, a side-effect associated with ribavirin use. However, rates of SVR published are generally lower in HIV co-infected patients treated for HCV even when full doses of ribavirin are used, rather than reduced doses.[52]

Response rates are higher in patients with mild and moderate disease than in those with cirrhosis. Patients with compensated cirrhosis have SVR rates of 41-43% for pegylated interferon-ribavirin compared to 51% for those without fibrosis.[53,54] There is also evidence that combination therapy significantly reduces the rate of fibrosis progression in patients with chronic hepatitis C and in some cases, reverses the degree of fibrosis.[41] There is evidence that interferon treatment reduces the incidence of HCC in treated patients, particularly those who showed an SVR.[41,55,56] Antiviral therapy can also be used to prevent re-infection in transplanted patients.[42]

Although therapy with interferon-alpha is generally well tolerated, studies report approximately 10% of patients fail to complete a therapy course.[57,58] Symptoms such as depression, myalgia, lethargy, influenza-type symptoms and biochemical and haematological abnormalities are common on treatment and account for much of the drop-out in the trials. Symptoms are more frequently reported in patients with cirrhosis, and very poorly tolerated in those with decompensated cirrhosis. Neutropaenia and thrombocytopaenia are more common than in non-cirrhotic patients, particularly with pegylated interferon regimes.[40]

Studies assessing the impact of treatment with interferon alpha on HRQoL show that following successful treatment patients have significant improvement in their total HRQoL score and in individual categories including work and sleep.[59,60] A fall in HRQoL while on treatment followed by return to baseline after cessation (and improvement in those who achieve an SVR) is well-documented,[60] although persistent impairments in QoL despite viral clearance have been reported.[61] In the 2006 Health Technology Assessment of combination therapy for mild chronic HCV

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infection, the HRQoL score during treatment for mild disease fell to 0.65 but increased to 0.82 in individuals who achieved an SVR following therapy for mild disease (Table 2). There did not appear to be any gains in HRQoL following treatment for those who did not have an SVR. A similar pattern was observed for those with moderate disease; reported HRQoL for patients with moderate disease on treatment is lower (0.55) than baseline values but increased above pre-treatment levels (0.72) in individuals with an SVR.[28] Studies have also shown that maintenance pegylated interferon therapy was associated with statistically and clinically significant declines in sexual health that did not rebound after cessation of treatment, despite minimal worsening of fatigue and well-being.[62]

Future therapies for HCV infection (e.g. telaprevir and boceprevir) appear to increase SVR rates and have potential to lower side-effect profiles and lower therapy induced HRQoL impairment.[63,64,65]

5. HIV AND HCV CO-INFECTION

Studies have found that, compared directly to HCV-monoinfected patients, HIV-HCV co-infected patients appear to develop cirrhosis 9-12 years earlier on average.[66,67] In addition, the incidence of cirrhosis in the first 10 years of HCV infection is greatly increased in HIV positive patients.[68] A study of men with haemophilia demonstrated a cumulative risk for liver-related mortality of 6.5% in HIV-HCV co-infection versus 1.4% in HCV monoinfection.[69] Extrapolating to the current rate of progression for co-infected patients needs to be done with some caution, as many of these individuals would not have been on optimal fully suppressive HAART for a considerable length of time.

The effect of antiretroviral therapy on the natural history of HCV infection has been investigated by a number of clinical groups. Some studies found no association between the use of antiretroviral therapy and the progression of liver fibrosis[70,71] with HAART not fully correcting the adverse effect of HIV infection on HCV prognosis.[72] In other studies, there is evidence that HAART slows the rate of fibrosis progression and reduces long-term liver-related mortality in those co-infected with HIV and HCV.[73,74,75] Brau *et al* additionally reported that the fibrosis progression rate in co-infected patients with undetectable HIV RNA through HAART was similar to HCV-monoinfected individuals.[75]

6. EXTRA-HEPATIC MANIFESTATIONS

It is increasingly clear that chronic HCV infection may have an impact on patients beyond liver damage. These extra-hepatic manifestations can involve multiple organ systems, including renal, dermatological, haematological and rheumatological systems. Approximately 1-2% of HCV-infected individuals will develop extra-hepatic manifestations.[5] Based on available data in 2007, one review determined that the only clearly linked extra-hepatic condition was mixed cryoglobulinaemia. The authors concluded that the link between the virus and many other extra-hepatic manifestations needed further confirmation (Table 3).

Cryoglobulins are found in 50% of patients with chronic HCV infection.[5] Only 25-30% of HCV patients with mixed cryoglobulinaemia develop clinical symptoms, ranging from fatigue, skin rashes, purpura, arthralgias, Raynaud's phenomenon, vasculitis, renal disease and peripheral neuropathy.[76] The clinical manifestations are thought to be caused by immune complex deposition in various organs. Severe symptoms from cryoglobulinaemia appear to respond to interferon treatment, but relapse can occur once treatment is discontinued.[77]

The existence of an association between HCV infection and B-cell non-Hodgkin's Lymphoma (NHL) has been a matter of debate.[78] A statistically significant association between NHL and HCV infection in Italian subjects was initially reported[79] and then subsequently confirmed by a number of national and international studies.[80,81] However this was not consistent with findings from Northern European and North American data which may reflect a geographic variation in prevalence. [82,83]

A strong association between the sporadic form of Porphyria cutanea tarda (PCT) and HCV was suggested by the high prevalence (>50%) of HCV markers in these patients, mainly in studies from Southern Europe.[84] However, in HCV-positive patients without PCT, no significant alteration in porphyrin metabolism was shown, suggesting an indirect role of infection, probably acting as a triggering factor in genetically predisposed individuals.[85]

In addition to these more specific clinical syndromes, chronic HCV infection has also been associated with more common conditions, where attribution of an individual's condition to the infection is more difficult. In several studies, a high prevalence of diabetes mellitus type 2 has been observed in patients with chronic HCV

infection.[86,87,88] Another commonly reported association was with impaired cognitive function; this latter association is supported by evidence of CNS involvement. [89,90,91,92]

Table 3: Classification of extra-hepatic manifestations of HCV infection

A. Association on the basis of high prevalence and pathogenesis
Mixed cryoglobulinaemia
B. Association defined on the basis of higher prevalence than controls
B-cell Non Hodgkins Lymphoma
Monoclonal gammopathies
Porphyria cutanea tarda
Lichen planus
C. Association to be confirmed/characterised
Autoimmune thyroiditis
Thyroid cancer
Sicca syndrome
Alveolitis – lung fibrosis
Diabetes mellitus type 2
Non-cryoglobulinaemic nephropathies
Aortic atherosclerosis

(Adapted from: Zignego et al. 2007[78])

7. SUMMARY AND RECOMMENDATIONS

Hepatitis C is an important cause of chronic liver disease in England. It is a disease characterised by onset that is largely silent due to the paucity of clinical symptoms during the acute infection. The majority of individuals who develop acute HCV infection will progress to chronic infection (detectable HCV RNA for more than 6 months). Given the lack of morbidity associated with acute infection, individuals who are acutely infected and clear infection within six months should not normally require hardship payments.

For those who progress to chronic infection, which is associated with demonstrable reductions in quality of life, a hardship payment is warranted. Mild, moderate and severe chronic HCV infection are all associated with a range of non-specific symptoms and some loss in quality of life, although the latter is not clearly linked to

stage of liver disease. In addition, chronic infection has been associated with a range of extra-hepatic symptoms including neurocognitive effects that impact on daily life. Prior to the development of cirrhosis, current therapy is able to achieve sustained virological response (effective viral clearance) in the majority of recipients, although therapy itself is associated with a range of side-effects. Following successful treatment, the prognosis for disease progression and quality of life largely improves. Although a range of extra-hepatic manifestations have been associated with chronic HCV, many of these are difficult to attribute to HCV infection in an individual patient, and many more specific syndromes should subside with effective treatment. Within the next few years more successful and better tolerated therapies are likely to become available. The hardship payment for individuals in this stage is designed to take account of the range of symptoms caused by HCV infection, or the treatment of HCV infection, including specific and non-specific symptoms (such as depression and fatigue), as well as the risk of extra-hepatic manifestations (such as diabetes).

The progression to cirrhosis, decompensated cirrhosis, or hepatocellular carcinoma will have a substantial impact on life expectancy. Quality of life is also substantially reduced and liable to deteriorate over time. Current anti-viral therapies are poorly tolerated and have a low chance of achieving viral response in this patient group. Even if an SVR can be achieved in cirrhotic patients, liver fibrosis is not completely reversed and the risk of decompensation or of developing liver cancer is retained. Some patients will be eligible for liver transplantation, but this in itself involves considerable morbidity and re-infection occurs in nearly all patients. These individuals therefore would warrant an ongoing payment to reflect the long term hardship encountered during these later stages of chronic HCV infection. Patients who develop life threatening hepatitis C-related tumours, specifically B-cell non-Hodgkin's lymphoma, will experience ongoing hardship of a similar level to those who develop cirrhosis and severe liver disease and should also be eligible for this on-going payment.

Individuals who acquired both HIV and HCV infection from blood or blood products will continue to be in receipt of separate hardship payments for their HIV infection. Co-infection with HIV can increase the rate of progression to chronic HCV infection and cirrhosis. The advent of more effective antiretroviral therapy has improved the quality of life of individuals with HIV, and is likely to markedly improve the prognosis for their HCV infection. It seems reasonable, therefore, that the criteria for and level

of HCV related-payment for these individuals should be the same as for HIV negative individuals and that the separate hardship payment for HIV should not be affected.

APPENDIX 1: MEMBERSHIP OF EXPERT WORKING GROUP

Advisory Group on Hepatitis
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Expert Advisory Group on AIDS
Professor Brian Gazzard – Chair
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