Commonwealth Department of Health and Aged Care

Hepatitis C

Informing Australia's National Response

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Preface

The development of Australia's National Hepatitis C Strategy 1999–2000 to 2003–2004 (the Strategy) involved extensive public consultation. Interested parties from across the country with personal and professional expertise in the various aspects of Australia's hepatitis C epidemic made valuable submissions to the Commonwealth Government, including submissions about the significant impacts of hepatitis C for those affected by this serious population health issue. The Department of Health and Aged Care (the Department) would like to acknowledge these contributions and thank everyone who took the time and effort to draft submissions and attend the public consultation forums held across Australia during late 1999.

The public submissions were also supported by advice and contributions from experts in population health and hepatitis C. As part of the Strategy's information collection phase, the Department commissioned research papers on key issues to inform the development of the Strategy. The commissioned papers spanned the main branches of research that contribute to the population health effort, specifically:

- clinical research
- epidemiology
- social and behavioural research, and
- virology and basic scientific research.

This publication represents the technical core of the policy development process. Time constraints meant authors were commissioned to review the available literature on the identified issues, rather than conduct action-research projects. This collection of papers is the outcome of their fruitful research and analysis. The Department thanks the authors for their important contribution to the National Hepatitis C Strategy.

The high quality of the papers combined with the public interest they have generated warrants the publication of this collection. It is hoped they will contribute to an improved understanding of population health in the area of hepatitis C by providing a valuable resource for people working in the area as well as policy makers, researchers and practitioners in related areas of population health.

The views and recommendations expressed in this collection are those of the authors and do not necessarily reflect the views of the Commonwealth Department of Health and Aged Care.

Issues Related to the Treatment of Chronic Hepatitis C Infection

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Introduction

This paper provides a synopsis of issues relevant to antiviral therapy for people with chronic hepatitis C virus (HCV) infection. The issues designated for discussion in the original commission include:

- a statement on the role of interferon monotherapy;
- a summary of data on combined therapy with interferon and ribavirin including subgroup analysis;
- tailoring antiviral therapy to those people most likely to achieve a benefit from such treatment and a description of people who may not require antiviral treatment; and
- treatment of acute hepatitis C.

Background

Safe and effective antiviral therapy for chronic hepatitis C infection is an area of intense investigation internationally. Recent studies have shown that antiviral therapy for chronic hepatitis C can slow or reverse the progression of hepatic fibrosis and decrease the frequency of serious complications such as hepatocellular carcinoma in some HCV infected patients. However, some patients who are unlikely to develop progressive liver disease are exposed to potential adverse events and toxicity from antiviral therapy that may not be of long-term benefit. Thus, the current challenge is to provide the best treatment available, supported by patient education and counselling, to those who are most likely to develop progressive liver disease.

Definitions

The U.S. National Institutes of Health Consensus Development Conference suggested a standardised approach to defining a response to anti-viral therapy (National Institutes of Health 1997). This approach, which has been widely adopted (European Association for the Study of the Liver Consensus Panel 1999), has allowed a comparison of treatment outcomes from studies involving different investigators, patients, treatment regimens and countries.

A response at the cessation of a course of treatment is defined as an *end-of-treatment response* (ETR). A response at the end of a 6–12-month period following the end of treatment is defined as a *sustained response* (SR). An ETR and SR can be described *biochemically* by normalisation of the serum aminotransferase levels (specifically ALT). Similarly, an ETR and SR can be described *virologically* by the disappearance of the viral genetic material (HCV RNA) from serum. HCV RNA is best measured by a sensitive test such as the polymerase chain reaction (PCR). A sustained virological response (SVR) is the most reliable indicator of a beneficial treatment response.

Other patterns are observed during and after treatment. *Relapse* occurs in those patients who develop abnormal ALT values or detectable HCV RNA following a biochemical or virological ETR. In some patients the ALT may become normal (or serum HCV RNA may be undetectable) during the initial phase of treatment but later become abnormal (or 'breakthrough') while still on treatment. In others, the ALT may remain abnormal throughout treatment (with persistently detectable HCV RNA). Failure to achieve either an ETR or SR is ultimately a *non-response*. Some investigators have therefore confined the terminology to either SVR or 'non-SVR', which includes relapse, breakthrough and primary non-response.

Interferon monotherapy

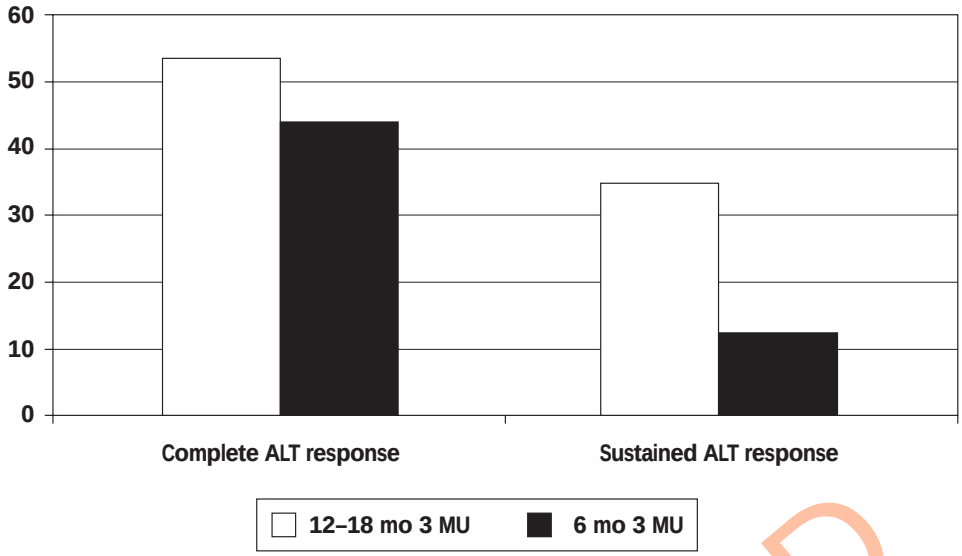
Interferons are naturally occurring anti-viral proteins that were first studied for their ability to inhibit viral replication and to stimulate a cellular immune response. The ability to produce pharmacological amounts of interferon through recombinant molecular biological techniques has led to world-wide clinical trials of recombinant interferon in thousands of people with chronic viral hepatitis, including an experience with over 200 000 treated patients in Japan. The first report of recombinant alpha interferon used for the treatment of non-A, non-B hepatitis was in 1986 (Hoofnagle et al. 1986).

Four interferons have been widely studied. The two alpha interferons, 2a and 2b, are derived from human leucocytes by recombinant techniques. Interferon alpha n-1 and other natural interferons are derived from a lymphoblastoid cell line. Consensus interferon has been derived by defining the most commonly encountered amino acid at each position and constructing a hybrid or 'consensus' molecule. These compounds have been studied in thousands of HCV-infected patients in controlled trials around the world and appear to be clinically equivalent in 12-month treatment regimens (Gish 1999).

A recent meta-analysis of over 2000 patients included in over 30 randomised controlled trials has established the most effective interferon regimen to be 3 MU given three times weekly over 12 months (Poynard et al. 1996). A sustained *biochemical* response occurs in approximately 35% of patients following this regimen, which has a lower relapse rate than that seen after six months of treatment (Figure 1). While data on sustained virological response were not available, almost certainly the sustained virological response is lower than the observed sustained biochemical response (as has been shown in the interferon control arms in the combination therapy trials discussed later).

The role of interferon monotherapy has changed significantly in light of new data regarding the combination of interferon and ribavirin (discussed below) and a better understanding of hepatitis C viral kinetics. Recent studies indicate that more frequent dosing intervals with standard interferon or the use of long acting (e.g. pegylated) interferons provide more rapid viral clearance in the early phase of treatment compared to standard thrice-weekly dosing. Those patients in whom HCV RNA is undetectable in blood early in a course of interferon treatment are more likely to achieve a sustained response compared to those who remain persistently viremic at that time. Two studies have shown that daily dosing results in rapid clearance of virus from blood, probably by first clearing circulating virions and then by eliminating cells that are actively producing virus (Lam et al. 1997, Neumann et al. 1998). The high viral replication rate (estimated at 10^{11} virions daily), the high viral mutation rate and the short half-life of current interferon formulations provide an explanation for the very low success rates with thrice-weekly interferon dosing.

Figure 1. Meta-analysis of sustained biochemical response rates following interferon monotherapy



Adapted from Poynard et al. 1996

The ability of the virus to replicate in large amounts and to form quasi-species may be potentially overcome by high dose, daily interferon given for the initial phase of therapy, a concept known as induction dosing. There are currently few data available regarding the sustained virological response to induction dosing regimens, either alone or in combination with ribavirin. A number of studies have employed high dose regimens, reporting either biochemical or virological response, but have not included a control arm using standard thrice weekly regimens. In most of the high dose monotherapy studies, a sustained virological response was not achieved in the majority of patients (reviewed in Shiffman 1999). The problem of relapse following high dose therapy may be improved by the addition of ribavirin, but there are no published data available. An ongoing Australian study (AusHep 06) comparing induction dosing with or without ribavirin in 218 patients with a primary non-response to interferon will address this important issue (Sievert et al. 1999).

The efficacy of interferon monotherapy may also be enhanced by the use of recently developed long-acting interferon preparations. Conjugation of a molecule of polyethylene glycol to a molecule of interferon forms pegylated interferon. Pegylated interferons are eliminated from the circulation over a much longer time than unmodified interferons and thus the potential exists for a single weekly dose to provide more constant exposure to the therapeutic effect of interferon. Both the major manufacturers of interferon have a pegylated interferon product and these are being studied both as monotherapy and in conjunction with ribavirin (data on file with Schering Plough Pty Ltd and Roche Products Pty Ltd). Results of early phase clinical trials of pegylated interferons will soon be available and are likely to alter clinical practice significantly.

Combined therapy with interferon and ribavirin

The combination of two antiviral drugs—interferon and ribavirin—has provided a significant step forward in hepatitis C therapy. Ribavirin is a guanosine analogue with a broad spectrum of activity but it is ineffective in treating hepatitis C when given alone. However, the combination of interferon and ribavirin has shown substantial activity in patients who have not been previously treated with interferon and in those who have relapsed following interferon. Those patients who fail to respond to an initial course of treatment (given for at least 12 weeks) remain an especially difficult treatment problem. Several ongoing international studies are addressing the efficacy of combination therapy for nonresponders, including the AusHep 06 study discussed earlier.

Two international placebo-controlled multi-centre studies randomised 1773 previously untreated patients to either interferon and ribavirin given for either 24 or 48 weeks or to interferon alone given for 48 weeks (Poynard et al. 1998, McHutchison et al. 1998). Interferon was administered at a dose of 3 MU thrice weekly and ribavirin was given twice daily (1000 or 1200 mg total dose). Patients were stratified for genotype (1 versus non-1), viral load (greater than or less than 2×10^6 copies/ml) and the presence or absence of cirrhosis. A treatment response was defined by absence of detectable HCV RNA at 24 weeks following the end of therapy (sustained virological response) and by improvement in histologically determined liver inflammation.

Of the 1744 patients who commenced treatment, 1407 (81%) completed the assigned treatment course. The composite results from the two studies showed a 41% SR for the 48-week combination therapy arm, which was significantly better than the 33% SR in the 24-week interferon and ribavirin arm. The sustained responses in both combination therapy arms were significantly better than those for thrice-weekly interferon monotherapy for 48 weeks (only 16%). Further analysis showed that the improvement in SR was the result of a higher ETR in the combination therapy arms plus a lower relapse rate compared to interferon alone. Treatment responders to either combination or monotherapy had a better histological outcome than non-responders. However, combination therapy for either 24 or 48 weeks significantly improved hepatic necroinflammation compared to interferon alone. There was no effect of combination therapy on hepatic fibrosis during short-term follow-up.

Pretreatment variables also had an effect on treatment outcomes. While the overall superiority of combination therapy was independent of any of the pretreatment variables, there were important effects of these variables on treatment in some patient groups. Thus a SVR occurred in 65% of patients with genotypes 2 or 3 after six months of treatment and there was no improvement in this response when treatment was extended to twelve months. In comparison, those patients with genotypes 1 or 4 required 12 months of treatment to achieve a 30% sustained response rate. Only 9% of patients with genotype 1

treated for 48 weeks with interferon alone achieved a sustained response (Table 1). This finding strongly suggests that interferon given at a dose of 3 MU tiw has such a low ratio of efficacy to adverse event or cost in this group of patients that such a dosing regimen is not justified. However, the possibility that high dose induction therapy or pegylated interferon might achieve a comparable response to combination therapy awaits further study. The availability of an effective interferon monotherapy regimen would be advantageous for patients unable to tolerate combination therapy.

Table 1. Comparison of sustained virological responses stratified by pretreatment variables

Baseline characteristic	*I + R 24 wk*	*I + R 48 wk*	*I + P 48 wk*
Fibrosis stage			
0–1	35.6% (129/363)	42.9% (158/368)	17.9% (63/351)
2–4	23.1% (27/117)	35.6% (36/101)	11.8% (14/119)
p value (2–4 vs 0–1)	0.01	0.2	0.1
Genotype			
1	17% (58/341)	29.5% (102/346)	9.1% (31/341)
2–3	65.9% (108/164)	65.3% (103/158)	31.5% (51/162)
p value (2–3 vs 1)	<0.00001	<0.00001	<0.00001
Viral Load			
≤ 2 X 10^6 copies/ml	43.5% (74/170)	45.5% (87/191)	29.7% (47/158)
≥ 2 X 10^6 copies/ml	27.5% (92/335)	37.6% (118/314)	10.1% (35/345)
p value (≤ 2 vs ≥ 2)	0.0003	0.08	<0.00001

Adapted from Poynard et al. 1998 and McHutchison et al. 1998

The other pretreatment variables studied were viral load and the degree of liver fibrosis. Combination therapy was equally effective if given to patients with a low viral load (< 2 x 10^6 copies/ml) for 24 or 48 weeks. Patients with a high viral load (≥ 2 X 10^6 copies/ml) had a greater response when treated for 48 weeks (Table 1). Patients with bridging fibrosis or cirrhosis required 48 weeks of combination therapy to achieve a response similar to patients with little or no fibrosis. It may therefore be possible to tailor therapy based on pretreatment variables. For example, patients with non-1 genotypes have a similar SR (≈ 60%) following either 24 or 48 weeks of combination therapy whether they have a high or a low viral load. However, genotype 1 patients with a high viral load require 48 weeks of treatment to achieve a response similar to those with a low viral load (≈ 30%) (Table 2).

A practical approach to monitoring a response to combination antiviral therapy has been suggested following a recent re-evaluation of the data from the two large multi-centre

trials described earlier (Poynard et al. 2000). In these studies, a sustained response to six months of therapy was most likely in patients with favourable pre-treatment predictors: female gender, genotype 2 or 3, a viral load less than 3.5 million copies/ml and a liver biopsy showing no or portal fibrosis only. The authors proposed that after six months of treatment, those patients with undetectable HCV RNA in serum and four or more favourable factors would be able to stop treatment; those with fewer than four factors, however, should continue for a full twelve months. A patient with detectable HCV RNA in serum following six months treatment has only a 2% chance of achieving a sustained virological response and treatment should stop at that time.

It should be noted that these predictive factors were identified retrospectively and will require confirmation in a prospective study. The ongoing AusHep 08 study in which 668 patients have been randomised by genotype to six or twelve months of combination therapy with or without induction dosing should provide further prospective data regarding the positive predictive ability of these host and viral factors.

Table 2. Sustained virological response as a function of genotype and viral load

GT	*RNA*	*I + P 24 wk*	*I + R 24 wk*	*I + P 48 wk*	*I + R 48 wk*
Non-1	$\leq 2 \times 10^6$	25%	61%	36%	64%
Non-1	$\geq 2 \times 10^6$	11%	62%	26%	60%
1	$\leq 2 \times 10^6$	4%	32%	25%	33%
1	$\geq 2 \times 10^6$	0.8%	10%	3%	27%

Adapted from Poynard et al. 1998 and McHutchison et al. 1998

Some patients will have an ETR following interferon alone but will subsequently relapse. Combination therapy with interferon and ribavirin for this group of patients has recently been approved for use in Australia for a total of six months treatment—based on studies similar in design to the two treatment naive trials. Two international multi-centre clinical trials of 345 relapsed patients examined the response to six months therapy with either interferon plus ribavirin or interferon alone (Davis et al. 1998). Combination therapy for six months resulted in viral clearance in 49%, compared to 5% in those receiving interferon alone. As was seen in the treatment naïve studies, combination therapy in those with genotype 1 resulted in a significantly lower virological SR (29%) compared to those with non-1 genotypes (74%). While not examined in the study by Davis et al., it would be logical to give patients who relapse after interferon monotherapy twelve months of combination therapy, rather than six months, if they have genotype 1, significant hepatic fibrosis or a high viral load.

Adverse events due to antiviral therapy

Adverse events are more common with combination therapy than with interferon monotherapy. For example, in the multi-centre trials (Poynard et al. 1998, McHutchison et al. 1998), patients receiving ribavirin and interferon more commonly reported anorexia, dyspnoea and rash than those receiving interferon alone. However, side effects such as depression, which is related to interferon, occurred in a similar proportion in those receiving combination therapy and those receiving monotherapy. Depression is a common condition in patients with hepatitis C that may have a considerable impact when planning and undertaking interferon-based antiviral therapy. Psychiatric monitoring and antidepressant therapy should be actively considered in patients with a history of depression before interferon is commenced (reviewed in Zdilar et al. 2000).

Ribavirin is concentrated in red blood cells and causes a dose-related haemolysis. Dose reduction for anaemia was required in approximately 8% of patients in the treatment naïve studies (Poynard et al. 1998, McHutchison et al. 1998) and this action resulted in an increase in haemoglobin levels. Discontinuation of therapy was most commonly required for emotional disturbances, of which depression was the most frequent cause. Overall rates of dose reduction and discontinuation from the studies are given in Table 3. It should be emphasised that ribavirin is a known teratogen in animals and because it remains in red cells following cessation of therapy, both patients and their sexual partners must use effective contraception during and following treatment for six months.

Table 3. Discontinuation and dose reduction rates for combination therapy compared to interferon monotherapy

	I + R 24 wk	*I + R 48 wk*	*I + P 24 wk*	*I + P 48 wk*
Discontinuation for any severe event	8%	21%	9%	14%
Dose reduction for anaemia	7%	9%	0%	0%
Dose reduction for other adverse event	13%	17%	12%	9%

Adapted from Poynard et al. 1998 and McHutchison et al. 1998

Absolute contraindications for interferon therapy include present or past psychosis or severe depression, pregnancy, and uncontrolled seizures. Similarly, renal failure, pregnancy, and the absence of a reliable contraceptive method are absolute contraindications for ribavirin. A history of depression, uncontrolled diabetes mellitus or hypertension—especially if complicated by retinopathy, psoriasis, symptomatic heart disease or active autoimmune disorders (especially autoimmune thyroiditis)—are relative contraindications for interferon or the combination of interferon and ribavirin.

Tailoring antiviral therapy to those most likely to benefit

The ability to target antiviral therapy to those patients most likely to achieve a benefit will eventually be derived from comprehensive studies of the natural history of hepatitis C infection and the long-term follow-up of patients who have received antiviral therapy. There is a complex interplay between viral factors such as genotype and viral load and host factors such as age at acquisition, gender and alcohol use that occurs over decades. It is likely that there are other significant viral, host and environmental determinants in the pathogenesis of HCV-related liver disease that have not yet been characterised. Current estimates are that 20–30% of patients will progress to cirrhosis over 30 years or more. A proportion of those who do not become cirrhotic will have chronic hepatitis with variable degrees of fibrosis. Thus, there is a substantial challenge in providing antiviral therapy to those with the greatest risk of developing advanced liver disease and avoiding therapy in those who are unlikely to benefit from it. While every patient with hepatitis C should be considered for antiviral therapy, it does not follow that all should be treated.

Given the current understanding of the natural history of chronic HCV infection, selection of patients for therapy has often been based on an arbitrary level of serum ALT elevation. Serum ALT levels are nonspecific and do not correlate well with histological liver injury. The goal of antiviral therapy is to prevent the onset of advanced fibrotic liver disease but predicting which patient will ultimately develop cirrhosis is difficult, if not impossible, in many instances. Consequently there is a need for an intermediate outcome that can be used as a surrogate for the eventual development of cirrhosis and thus provide clinically useful information on which to base a decision to treat or not to treat. In practice, this surrogate is the histological grade and stage of disease identified by liver biopsy, which provides substantially more information than the serum ALT level.

The NIH Consensus Development Conference and the EASL Consensus Conference have suggested that the extent of inflammation and fibrosis seen at liver biopsy be used to guide patient selection for therapy (National Institutes of Health 1997, Consensus Panel 1999). Using these guidelines, treatment would be strongly considered for patients who have active necroinflammatory changes on biopsy and/or any fibrosis. This is the group most likely to develop progressive liver disease and therefore most likely to benefit if a sustained response is achieved.

Antiviral therapy in patients with cirrhosis

An important treatment indication concerns those patients who have already developed advanced disease. Patients with compensated cirrhosis are at the highest risk for developing hepatic decompensation (i.e. ascites, variceal haemorrhage, encephalopathy) and liver cell cancer (Hu and Tong 1999). Indeed, with the exception of some patients with severe bridging fibrosis (cirrhosis in evolution), patients with established cirrhosis are the only HCV-infected persons who will develop these life-threatening complications. Sustained biochemical response rates following interferon monotherapy have generally been lower (by approximately 50%) in cirrhotics than in patients with less severe fibrosis (Valla et al. 1999). However, a correlation between biochemical and virological responses is not always evident (Pockros et al. 1998) and a recent randomised controlled study has shown that sustained virological response rates were similar between cirrhotics and noncirrhotics following consensus interferon treatment (Everson et al. 1999).

Combination therapy with ribavirin and interferon has been studied in only a small number of patients with advanced fibrotic liver disease. A recent analysis of individual patient data from six controlled studies showed a significantly enhanced efficacy of combination therapy compared to interferon monotherapy in HCV-infected cirrhotic patients (Schalm et al. 1999). For previously untreated cirrhotic patients, a SVR occurred in 7% of genotype 1 and 24% of genotype 2/3 treated with combination therapy, compared to 1% and 5% respectively treated with interferon alone. In the two previously discussed treatment naïve studies, the sustained virological response in patients with stage 3/4 fibrosis was 12% following interferon alone for 48 weeks compared to 23% and 36% for combination therapy for 24 and 48 weeks, respectively (Table 1). As already noted, there was no significant difference in sustained virological response at 48 weeks of combination therapy between patients with bridging fibrosis and cirrhosis compared to those with less fibrosis. Furthermore, recent data, described below, have indicated that interferon treatment, with or without a sustained virological response, may be associated with less progressive fibrosis and a lower risk of developing HCC.

The sustained virological response rates following combination therapy in patients with cirrhosis appear to be equivalent to the results of interferon monotherapy in non-cirrhotic patients. Therefore, it seems illogical and inconsistent to exclude cirrhotic patients specifically from receiving combination antiviral therapy since these patients may benefit significantly from a treatment response. Current data now provide compelling evidence to support antiviral therapy in patients with cirrhosis, especially for younger patients (under age 55) who are more likely to develop decompensation over the longer term.

Antiviral therapy in other patient groups

Consideration should be given to withholding or delaying treatment in patients with minimal inflammation and no fibrosis. The NIH Consensus Development Conference recommended 'observation, serial measurement of ALT and liver biopsy every 3 to 5 years' as an acceptable alternative to antiviral therapy in patients with no fibrosis on liver biopsy and minimal inflammatory changes (National Institutes of Health 1997). Another group in whom treatment may not be beneficial is patients with persistently normal ALT levels. In general, such patients exhibit a very slow progression to cirrhosis (Mathurin et al. 1998) and interferon monotherapy has not been shown to provide a consistent benefit (Serfaty 1996, Sangiovanni et al. 1998). Finally, patients with HCV related cirrhosis who have signs of decompensation (i.e. a low serum albumin, prolonged prothrombin time, raised serum bilirubin, ascites, jaundice, or variceal haemorrhage) should be considered for liver transplantation. Patients with decompensated cirrhosis should not be offered antiviral therapy since it has a higher rate of adverse events in this group.

Various host and viral factors have been examined for their ability to predict a treatment response; those most commonly cited are genotype (or clade), viral load and the degree of hepatic fibrosis. These retrospectively determined 'pretreatment response predictors' correlate with, but cannot absolutely predict, a sustained response to antiviral treatment. For example, as a group, patients with genotype 1 are less likely to respond to interferon therapy than are patients with genotypes 2 or 3. However, approximately 15% of genotype 1 patients will achieve a sustained response. Overall, the accuracy of each factor in predicting a response to interferon monotherapy is low, ranging from 40% to 70% (Davis and Lau 1997). Therefore, patients should not be denied therapy based on an unfavourable genotype, viral load or degree of fibrosis, including cirrhosis, determined prior to treatment. This concept has been strongly supported by the consensus conferences in Europe and the United States. In addition, retrospectively determined factors following interferon monotherapy are not applicable to patients receiving treatment with combinations of ribavirin and different interferon formulations or dosing regimens.

Studies of interferon monotherapy (administered thrice weekly) have shown that a biochemical and virological response at week 12 of treatment correlates with ultimately achieving a sustained virological response. Normalisation of serum ALT during the first 12 weeks of therapy in many studies has been a highly accurate predictor of an ETR. Patients who fail to normalise ALT or lose viremia at that time are unlikely to respond to further treatment and should generally discontinue therapy, although some exceptions, such as patients with cirrhosis, may exist. While normalisation of ALT and loss of viremia tend to mirror each other, it is possible to identify patients with low-level ALT elevation and no detectable viremia during treatment. This ALT elevation may be due to concurrent conditions, such as fatty infiltration or increased iron stores, and so ALT normalisation does not predictably correlate with loss of viremia (Pockros et al. 1998).

In treating a chronic viral infection, it is intuitive that the most appropriate predictor of ultimate response would be loss of detectable virus from serum during treatment. A recent study has suggested that the rate of decline in viral load during the first four weeks of treatment may be a more accurate predictor of a sustained response than either normalisation of ALT or genotype (Zeuzem et al. 1998). Interestingly, in the recent combination therapy studies of treatment naïve patients, different early response patterns were observed. In 59% of patients treated with combination therapy for 48 weeks who eventually attained a sustained response, HCV RNA was detectable in serum until week 12 or 24. This phenomenon of 'late' viral clearance was also seen in 50% of the sustained responders to 24 weeks of combination therapy, 23% of the sustained responders to 24 weeks of interferon, and 50% of the sustained responders to 48 weeks of interferon (McHutchison et al. 1998). From these data it appears that week 12 is not the correct time to make a decision regarding cessation of combination therapy. An additional 10–15% of patients treated for 24 or 48 weeks may ultimately attain a sustained virological response if the decision point for treatment cessation is week 24 rather than week 12 (personal communication, John McHutchison, March 1999). These data require confirmation in a prospective study and an analysis of cost implications.

Long-term benefits of antiviral therapy

Cost-benefit analyses have supported the use of interferon for treatment of hepatitis C despite its sub-optimal sustained response rates when used as monotherapy (Kim et al. 1997). A recent study has confirmed that patients who do achieve a sustained response to interferon appear to have a durable response with no detectable virus in either blood or liver (Marcellin et al. 1997). This important study from France found that the severity of histological inflammation decreased significantly in treated patients. Most patients (88%) had moderate or severe chronic hepatitis prior to treatment; following treatment the majority (85%) showed either no chronic hepatitis or only mild changes. However, no change in fibrosis was noted in treated patients. More recently, a large Japanese study has been reported that confirms regression of fibrosis in patients with a sustained virological response to antiviral therapy (Shiratori et al. 2000). In that study, 487 interferon-treated patients were compared to 106 patients with chronic HCV infection who were not treated; all patients underwent a repeat liver biopsy from 1 to 10 years after the initial, pretreatment biopsy. Fibrosis progression was demonstrated in 38% of the untreated patients; conversely regression of fibrosis occurred in 59% of patients with a sustained virological response to therapy. These findings suggest that the severity of liver inflammation is an important factor in the progression of liver fibrosis and that reduction of inflammation leads to regression of fibrosis. These findings also challenge the concept that hepatic cirrhosis is an irreversible condition.

Exciting data are now accumulating that suggest interferon treatment is associated with a lower incidence of hepatocellular carcinoma. An intriguing study from Japan in 1995 followed 90 patients with cirrhosis from chronic hepatitis C infection and found a lower incidence of hepatocellular carcinoma in interferon-treated patients compared to untreated patients (Nishiguchi et al.). In this and several uncontrolled studies, patients with a sustained response to interferon did not develop HCC. A study of 1022 patients with chronic hepatitis showed that a lack of response to interferon was associated with a higher risk of developing hepatocellular carcinoma (Kasahara et al. 1998). A recently published retrospective cohort study of 2890 HCV infected patients from Japan showed an HCC incidence of 3.7% in 2400 interferon-treated patients, compared to 11% in 490 untreated patients. The annual incidence of HCC was 0.5% in patients with minimal fibrosis compared to 7.9% in those with cirrhosis (Yoshida et al. 1999). Further studies are required to confirm these potentially very significant findings.

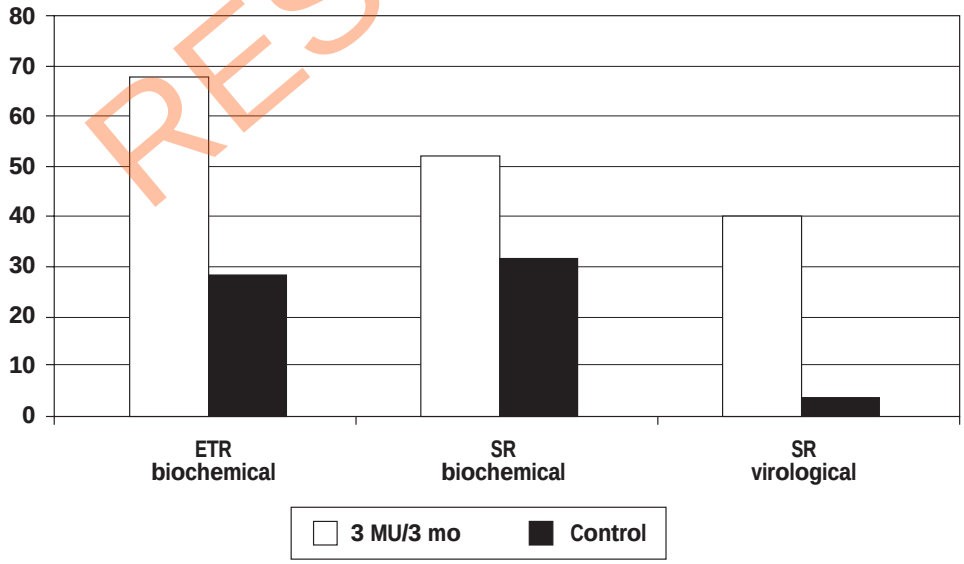
Complementary and alternative medicines for chronic HCV infection

The use of complementary and alternative medicines by patients with chronic liver disease, including chronic HCV infection, is widespread and based on traditional empirical practices involving a variety of herbal preparations. Herbal medicines are generally marketed as food supplements rather than therapeutic agents and thus are exempt from strict governmental controls. Various molecules have been identified as the biologically active substances in herbal medicines and these molecules have shown anti-oxidant, immunoregulatory and anti-fibrotic properties *in vitro*. Some of the more extensively studied molecules include glycyrrhizin, which is derived from licorice root; silymarin, derived from the milk thistle plant *Silybum marianum*; and compound 861, an extract of ten herbs used in traditional Chinese medicine. Specific recommendations for the use of these compounds in chronic HCV infection is not possible due to a lack of controlled studies of efficacy and safety (for review see Schuppan et al. 1999). The scientific community has recognised the need to encourage and support further basic and clinical investigation of herbal preparations with the expectation of expanding the treatment repertoire for chronic viral hepatitis (National Institutes of Health 1999).

Treatment of acute hepatitis C

Approximately 20% of patients who are exposed to hepatitis C resolve their infection, while 80% become chronically infected. For the small number of people who present with acute hepatitis C or for those with a recent known exposure to hepatitis C (e.g. following needlestick injury) the efficacy of immediate antiviral therapy is of paramount importance. Currently there are no data to support the use of prophylactic antiviral therapy following an acute occupational exposure. The lack of data is related to the low transmission risk (4–10%) and the infrequency with which patients with acute HCV are identified, so that large studies have not been performed to assess efficacy and adverse events. However, if acute hepatitis C develops (i.e. in a patient with a clinical syndrome of acute hepatitis in whom HCV RNA and subsequently HCV antibody become detectable) then antiviral treatment clearly has a role. Two recent meta-analyses have shown that interferon monotherapy is more effective in eliminating HCV RNA in acute than chronic infection. Poynard et al. analysed four randomised controlled trials and found that interferon given at 3 MU for 12 weeks resulted in a sustained virological response in 41% compared to 4% in untreated controls (Poynard et al. 1996) a better response than that seen in chronic infection (Figure 2). Quin analysed six controlled trials and found that HCV RNA was eliminated in 40% of treated patients (Quin 1997). Both meta-analyses emphasised the small number of patients included in the reported studies, which is to be expected given that most patients present with established HCV infection.

Figure 2. Meta analysis of interferon vs no treatment for acute HCV



Poynard et al. 1996

Two major considerations—interferon dose and timing of therapy—remain controversial. While most studies have used doses of between 3 and 6 MU tiw, one study, reviewed by Quin, utilised a daily dose of 10 MU for four to six weeks, with a 90% clearance of HCV RNA. High dose, daily therapy seems rational in light of what is known about HCV replication (Lam et al. 1997, Neumann et al. 1998) but there are no controlled trials on which to build a consensus in this regard. Side effects are likely to be dose limiting with such a high dose regimen. Similarly, there are no prospective data to establish the optimal timing for treatment of acute HCV. This implies that some patients, perhaps as many as 20% who might otherwise develop an effective immune response and clear HCV spontaneously, may receive unneeded therapy.

Recognition of acute HCV infection is an uncommon event and it seems unlikely that in future there will be data from randomised control trials to offer guidance. A reasonable recommendation for therapy in presumed acute HCV infection would be 3 MU tiw for at least 12 weeks, with some latitude for employing daily injections at higher doses. Currently there are no data on the use of combined therapy with ribavirin and interferon for acute HCV infection, although it is likely that the clinical benefit would be greater than with interferon monotherapy.

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Hepatitis C Infection in Non-Australian Born Populations in Australia

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Contents

The global epidemiology and impact of hepatitis C

The hepatitis C epidemic is no respecter of persons. The global epidemiology of the epidemic has been defined by rapid and widespread transmission. As with hepatitis A and B viral infection, the prevalence of hepatitis C virus (HCV) infection is greater in certain parts of the globe and Australia is less affected than a number of countries in our immediate vicinity (Heintges and Wands 1997, Batey and Bollipo 1996, Moyer and Mast 1994). Those living in Australia, America and England are fortunate in that the background rate of hepatitis C exposure in blood donors is of the order of 0.3–1.0% while that in the general population is of the order of 1.5%. This rate is lower than that in other parts of the world such as a number of Middle Eastern countries and in Asia, where population prevalence rates reach 2% (Heintgs and Wands 1997, Aymard et al. 1993, Murphy et al. 1996, Mutimer et al. 1995, Shakil et al. 1995, Kaba et al. 1998).

Higher prevalence rates are found in Thailand, Malaysia and India (Suwanagool et al. 1995, Irshad et al. 1993, Duraisamy et al.1993). In Northern Africa, Saudi Arabia, Ethiopia and Somalia reported prevalence rates are 1.4–2.1%. In other parts of Sub-Saharan Africa, rates range from 1.4% to 13.1% and in Egypt, up to 14.5% of the population have antibodies against HCV. Table 1 documents our current knowledge of the prevalence of HCV in those countries where data exist.

It is important to note that in a number of significant and potentially high-risk countries, information on HCV prevalence is not yet available. A determined effort is required to complete the picture of this major global infectious disease.

Table 1. Countries from which patients have come to receive treatment for HCV infection under S100 Scheme

List of Countries					
AFRICA	AFRICA	**EGYPT**	EGYPT	**SOUTH AMERICA**	ARGENTINA
	EAST AFRICA				BRAZIL
	ETHIOPIA	**EUROPE**	AUSTRIA		CHILE
	KENYA		BELGIUM		EL SALVADOR
	MAURITIUS		ENGLAND		JAMAICA
	SOMALIA		FRANCE		URAGUAY
	ZIMBABWE		GERMANY		
			HOLLAND	**SOUTH EASTERN**	CYPRUS
ASIA	ASIA		IRELAND	**EUROPE**	GREECE
	BALI		SCOTLAND		ITALY
	BURMA		SPAIN		MACEDONIA
	CAMBODIA		SWITZERLAND		MALTA
	EAST TIMOR		UK		SICILY
	INDONESIA				TURKEY
	KOREA	**INDIA**	AFGHANISTAN		
	LAOS		BANGLADESH	**VIETNAM**	VIETNAM
	MALAYSIA		INDIA		
	PHILIPPINES		PAKISTAN	**AUSTRALIA**	AUSTRALIA
	SINGAPORE		SRI LANKA		
	TAIWAN				
	THAILAND	**MIDDLE EAST**	IRAN		
	TIMOR		LEBANON		
CHINA	CHINA	**NEW ZEALAND**	NEW ZEALAND		
	HONG KONG				
	JAPAN	**NORTH AMERICA**	AMERICA		
			CANADA		
EASTERN EUROPE	BOSNIA		USA		
	CZECHOSLOVAKIA				
	HUNGARY	**PACIFIC REGION**	FIJI		
	POLAND		PNG		
	ROMANIA				
	RUSSIA	**SOUTH AFRICA**	SOUTH AFRICA		
	SLOVENIA				
	USSR				
	YUGOSLAVIA				

HCV genotypes

Current and future population studies have the capacity to identify the prevalent genotypes in each of the countries involved. Earlier studies did not provide this information as genotype testing was not readily available. This has had the potential effect of hindering the development of a full understanding of the natural history of the disease in different populations.

HCV infection results from one of six major genotypes of the virus and the genotype profile in different countries varies significantly (Simmonds et al. 1996, Crofts et al. 1999, Davidson et al. 1995, Simmonds 1996). In Australia, for example, the majority of infections are due to genotypes 1 (50%) and 3 (35–45%), whereas in the USA >90% of infections are due to genotype 1 and in Egypt, a vast majority of patients are infected with HCV genotype 4. In Vietnam, genotypes 9 and 10 have been recorded, although more recent virological work has reclassified these genotypes into the major six genotypes (and in particular genotype 6) originally described by Simmons et al. (Simmonds et al. 1996). The impact of the different genotypes on the natural history of the disease is still being evaluated. Some data suggest a genotype-specific influence on the natural history of HCV infection, but a majority of studies to date are unable to differentiate between a genotype effect and the effect of duration of infection on the severity of liver disease.

It is possible that other genotypes of this virus will be discovered as the worldwide epidemic is studied in more detail. Increased mobility will add to the complexity of the disease in ensuing years, globally, nationally and individually, as individuals travel and expose themselves to viral subtypes different from those in their home country. Australia is likely to witness an increase in infections from currently less common genotypes as immigration trends continue to widen the ethnic diversity of our population. The current ethnic mix of the Australian population makes it quite different from a number of other countries. The Australian HCV epidemic is affected by the complex population mix that characterises our population. Already in Australia, multiple genotype infections are being recorded and as the Australian-born population is exposed to genotypes from other countries, even more complex patterns of infection and of disease progression and treatment responsiveness will appear (Kaba et al. 1998). It is imperative that the impact of multiple genotype infections on the natural history of this infection in individuals and in the overall population in Australia be documented.

Current knowledge

A recent paper from Westmead Hospital has reported on the molecular epidemiology of hepatitis C in a population drawn from Western Sydney (Kaba et al. 1998). The data are most informative. In the study population of 425 HCV RNA positive patients, a single genotype infection was identified in 420. The patients' place of birth was Australia and New Zealand (62%), Asia (13%), Europe (12%), Mediterranean (6%), Middle East (6%) and other countries (<1%). Genotype 1 infection was found in 52% and genotype 3 in 32%. Genotypes 2, 4 and 6 accounted for 9.3%, 5.5% and 1.7% respectively. Farrell's group documented that patients infected with genotype 1b were more commonly born outside Australia, whereas non-1b subtypes were common in Australian born patients. Of 23 patients with type 4 infection, 21 were born in Egypt and six of seven patients with a genotype 6 infection were born in Vietnam. This paper has highlighted the importance of knowing the place of birth of patients with HCV in relation to the likely infecting genotype. Increasingly, treatment is being influenced by the genotype of the virus causing the infection and this trend will continue, allowing much more specific therapy to be delivered. An advantage of this will be a lower cost of therapy in the long term as some genotype infections (2, 3) respond to a shorter course of treatment. The Farrell study has also highlighted the frequency of non-Australian born patients in the HCV-infected Australian population. The experience recorded has allowed comparison with data from those countries represented in the Australian population and results are of interest and importance (Colley et al. 1996, Colley and Batey 1995, Mellor et al. 1995, Zein et al. 1995, Nousbaum et al. 1995, Yoshioka et al. 1992, Lin et al. 1996, Bruno et al. 1997, Silini et al. 1996, Martin 1995, McOmish et al. 1993, Qu et al. 1994, Driesel et al. 1994).

The individual impact of hepatitis C infection

Coping with hepatitis C infection is a major problem for all affected individuals. This is an infection that creates medical and social problems for the sufferer. Community attitudes to hepatitis are, in general, negative. The disease is regarded as highly infectious and as a serious health problem. Public awareness of the means by which different forms of hepatitis are transmitted is poor and this leads to a stereotyped response to all hepatitis sufferers, to everyone's disadvantage. It is hoped that strategies such as the recent NSW Government HCV awareness campaign will improve awareness by both the public and health care workers of the facts about this infection. In Australia, enormous time is spent with English speaking patients dealing with the questions, fears and anger with which they present. This reality highlights the important anxieties that are engendered by the diagnosis of HCV infection. It is evident that people born in non-English speaking countries experience the same problems. However, it is likely that they will have a much less meaningful encounter with the health system in Australia than their English speaking counterparts unless excellent access is provided to translation services. Often this is not the case and busy clinics force patients to move through the system quickly, in a way that, of necessity, leaves many of their questions unanswered. Significant effort is being directed towards ensuring equitable access for all to treatment facilities for HCV-infected individuals.

HCV infection in non-Australian born populations in Australia

Australia has a remarkable mix of people of many different ethnic backgrounds contributing to our total population. Of the total Australian population, 24% have been born out of Australia (Kaba et al. 1998). A significant number of these individuals have been born in other English speaking countries. This has to be accounted for in any analysis of the impact of the disease on non-Australian born members of our community, as English speaking patients will have less difficulty with the health system than those unable to speak English fluently. A number of groups have suggested that the access to treatment for non-Australian born patients is restricted. Often these claims have been made without recourse to what data do exist. A review of the ethnic background of the patients treated with S100 interferon between October 1994 and September 1996 and the data from Westmead Hospital (Kaba et al. 1998) suggests that individuals born outside Australia have had similar access to therapy as those who were born here (Batey et al. 1999).

This may not be reflected in certain geographical areas, but limited access is a problem for all residents of some areas in Australia that are significant distances from tertiary treatment facilities.

The Hepatitis C National Data Base

In October 1994, alpha interferon was made available under the highly specialised drugs scheme for a subset of patients with chronic hepatitis C. Patients who were eligible for this form of treatment agreed to have de-identified data relating to their disease and its response to therapy entered into a database. The Hepatitis C National Data Base was established to document the efficacy of this form of therapy for chronic HCV infection. The final report on the five-year experience has now been completed (Batey et al. 1999). A review of the treated population has provided valuable insights into the infection in Australian individuals born here or in another country.

Of the 2986 patients treated with S100 interferon from October 1994, 859 were born in countries other than Australia (Colley et al. 1996, Colley and Batey 1995). It is of interest that most of the 63 centres in all States of Australia that were providing interferon for patients with chronic HCV infection treated some patients who were non-Australian born. The data indicate that:

1. Nearly 30% of the total treated population were born outside Australia, a figure that equates closely to the 24% in the general population. This suggests that specific barriers to therapy may not be as significant as many argued.
2. Despite the fact that this treatment was quite demanding, that is, six and later 12 months of therapy involving the self-injection of the drug thrice weekly, these patients received adequate information to allow them to complete therapy safely.

The significant number of patients that have already been treated highlights the extent of the problem in this special group in our community and supports the need for widespread dissemination of information aimed at improving the understanding of health care workers about the specific needs of patients born outside Australia. The needs of all those with chronic HCV infection are many and complex.

Hepatitis C National Data Base analysis

The 859 patients born outside Australia and treated with S100 interferon provide considerable useful information about the epidemic in this country. It is important to note that many individuals born outside Australia contracted their HCV infection in Australia and in this respect would be expected to have a genotype infection reflecting the Australian epidemic rather than that of their country of birth. The demographic details of the groups of patients from the various countries are similar to those who were born in Australia in most regards. The countries represented in our Australian experience and the number of individuals from each country are shown in Table 2. In the Hepatitis C National Data Base population, 28.5% of the total non-Australian born group came from Vietnam (16% of the total treated population). This is in contrast to the general Australian population where persons born in Vietnam, Cambodia and Laos make up a little over 1% of the population. The high percentage coming from one country perhaps reflects the interest of a number of centres in Sydney treating patients with hepatitis C, but it is of importance that this large group has been identified. Certainly Baird and co-workers and Sievert et al. (Baird personal communication, Sievert personal communication) have also identified a significant population of Vietnamese HCV patients in South Western Sydney and Melbourne (Sievert personal communication, Baird and Vella 1999). The needs of this ethnic group are being studied in those cities.

General features of the group

The male-to-female ratio in patients from each of the other countries listed, approximates that seen in patients born in Australia, namely, 70% males/30% female. Heintges & Wands report no sex predilection in their paper (Heintges and Wands 1997). Our consistent finding of a higher male-to-female ratio in hospital treatment clinics suggests that females are less likely or less able to come forward for this form of therapy for HCV infection.

A high proportion of patients who have been born in other countries are unaware of when or how they may have contracted their hepatitis C. This accords with the report from Westmead (Kaba et al. 1998). Where a source of infection (and thus the likely time of infection) has been identified, a significant majority appear to have contracted HCV in the period from 1970 to 1989, as with the Australian born population.

Source of infection

The source of infection for hepatitis C in the treated group born outside Australia has been recorded as ‘country of birth’ in 320 of the 859. The category ‘country of birth’ assumes either vertical transmission from an infected mother or infection early in life

from HCV-contaminated household or medical utensils or equipment. Injecting drug use was the second most common source of HCV infection in the non-Australian born population, with 255 of the 859 cases (29.7% compared with 56% in the Australian born group) assumed to have been infected in this way. Receipt of a blood product is attributed as the cause in 134 of the patients (15.6% versus 15.7%). As indicated already, a proportion of people born outside Australia have contracted their infection in Australia. Injecting drug use is one source more likely to reflect infection here rather than in the patient's home community.

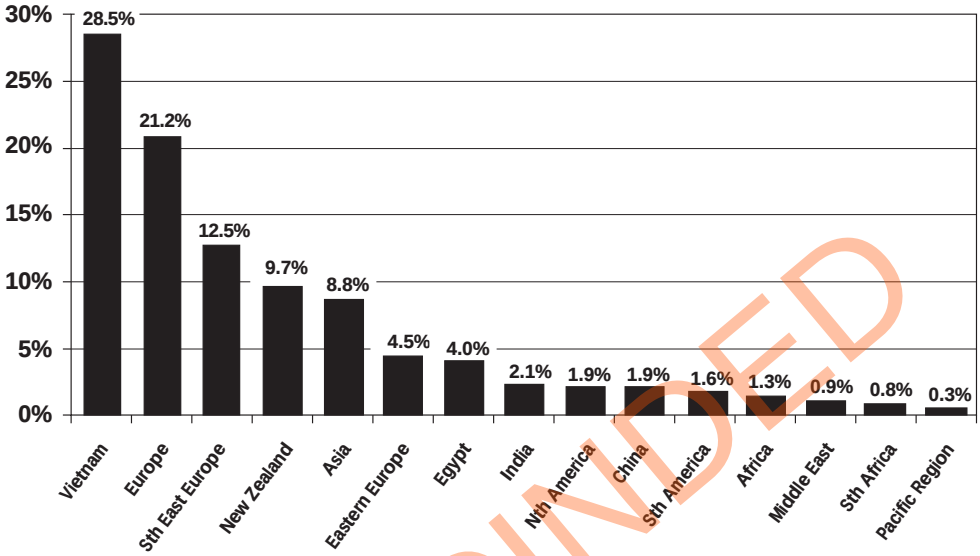
Table 2. Country of birth and source of infection

Country of Birth		*Blood Product*	
Vietnam	181	Vietnam	28
Europe	2	Europe	40
Sth East Europe	45	Sth East Europe	16
New Zealand	0	New Zealand	7
Asia	38	Asia	13
Eastern Europe	11	Eastern Europe	9
Egypt	20	Egypt	5
India	6	India	4
Nth America	0	Nth America	0
China	7	China	7
Sth America	2	Sth America	2
Africa	5	Africa	1
Middle East	1	Middle East	0
Sth Africa	2	Sth Africa	2
Pacific Region	0	Pacific Region	0
	320		**134**

Intravenous Drug User		*Unknown*	
Vietnam	13	Vietnam	15
Europe	104	Europe	19
Sth East Europe	28	Sth East Europe	16
New Zealand	56	New Zealand	7
Asia	9	Asia	8
Eastern Europe	10	Eastern Europe	3
Egypt	0	Egypt	5
India	1	India	5
Nth America	12	Nth America	1
China	0	China	1
Sth America	7	Sth America	1
Africa	4	Africa	0
Middle East	6	Middle East	1
Sth Africa	3	Sth Africa	0
Pacific Region	2	Pacific Region	0
	255		**82**

Injecting drug use is the most common source of infection for Europeans born outside Australia whereas in individuals born in Asia, South America and Africa, injecting drug use is a very infrequent source of HCV infection. Blood transfusion as a cause of hepatitis C in those born outside Australia is more common in European born (20%) than in Asian born individuals (11% in Vietnam born individuals). Figures 1–7 document these data more clearly.

Figure 1. Region of birth (n=859)



The region of birth for patients treated with S100 interferon. Figure 1 shows the percentage represents a percentage of the total population of 859.

Figure 2. Source of infection (n=859)

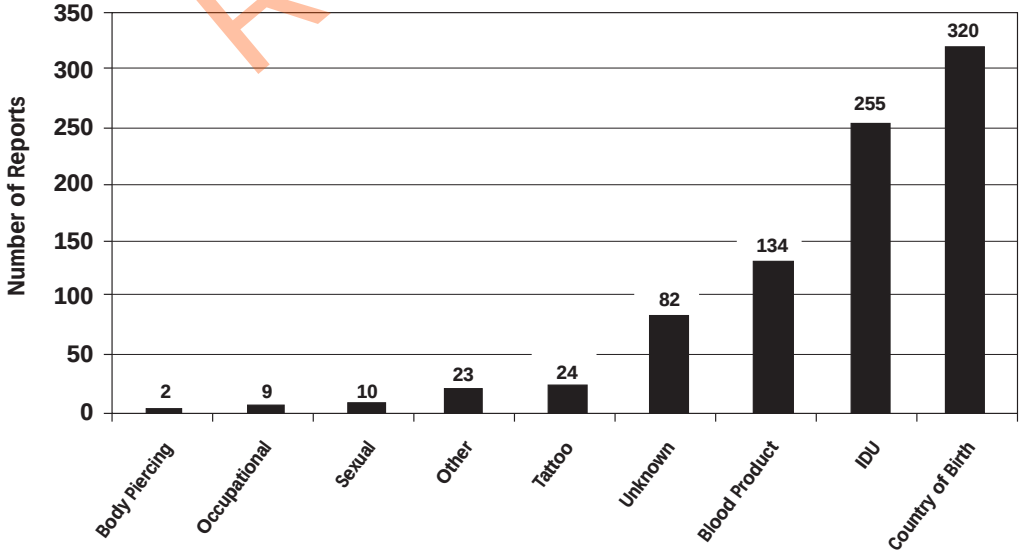
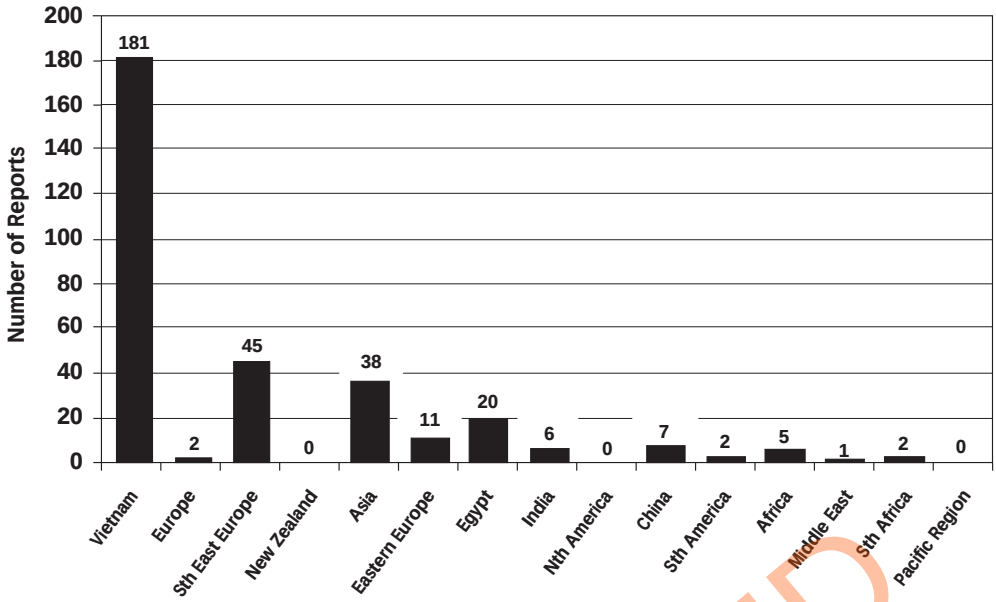


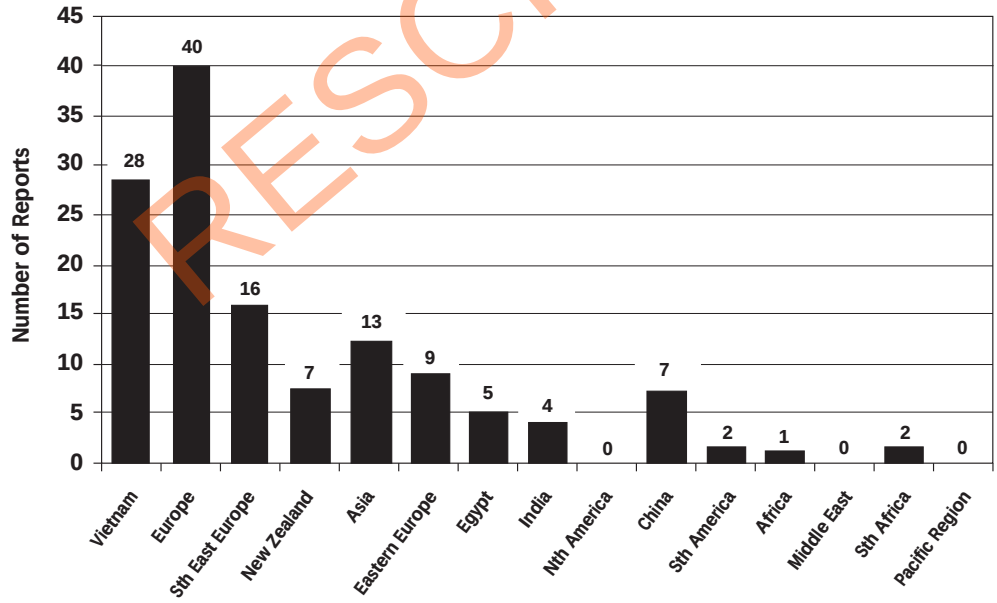
Figure 2 shows the likely source of infection and the absolute numbers of patients in each of the attributable groups.

Figure 3. Source of infection: country of birth (n=320)



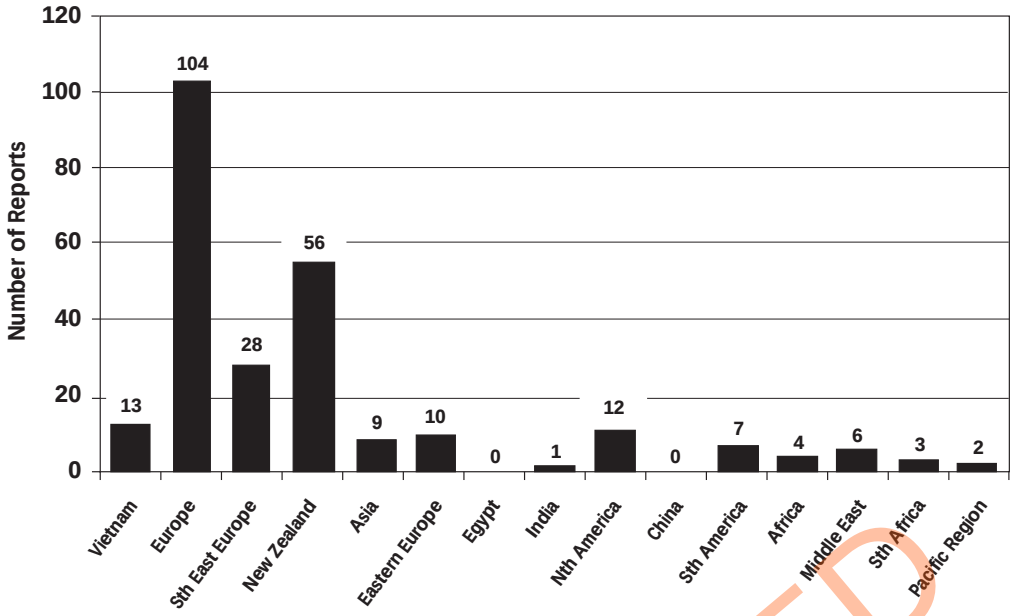
The country of birth of those patients for which country of birth was identified as the likely risk factor. Figure 3 shows the percentage figures represents the percentage of the total number of 320 that came from the country or region identified.

Figure 4. Source of infection: blood products (n=134)



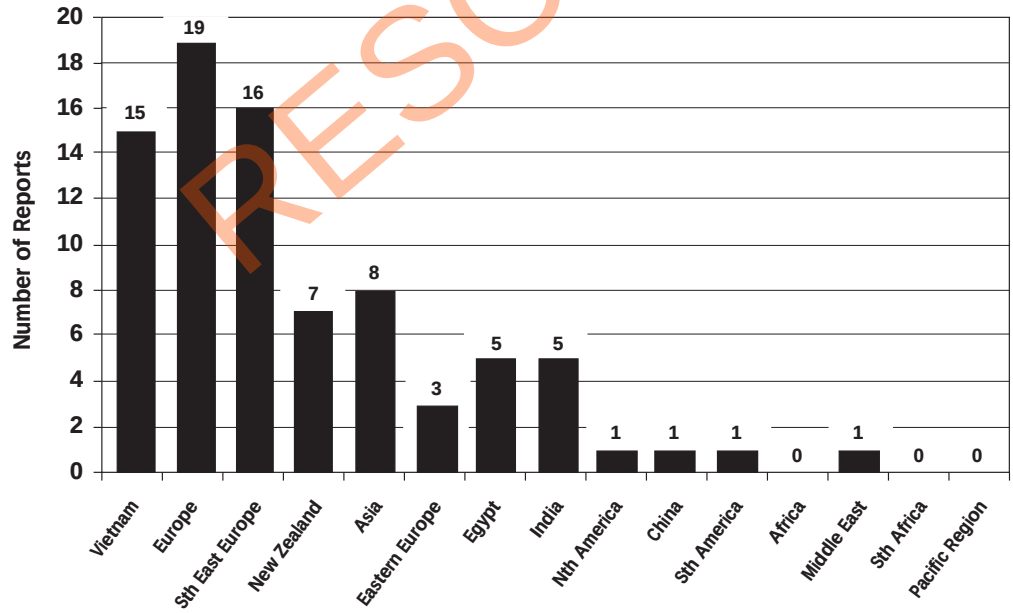
Receipt of infected blood product was identified as the possible source of infection in 134 patient born outside Australia. Figure 4 identifies a country of birth or region of birth of those patients. The percentage represents the percentage of the total number infected from blood products.

Figure 5. Source of infection: IDU (n=255)



Injecting drug use was identified as the source of infection in 255 patients born outside Australia. Figure 5 shows the country of origin for those patients. Percentage figures represent the percentage of the total 255 patients.

Figure 6. Source of infection: unknown (n=82)



Eighty two patients had no identifiable source of infection. Figure 6 shows the make up of this population with respect to country of birth.

Figure 7. Year of infection (n=859)

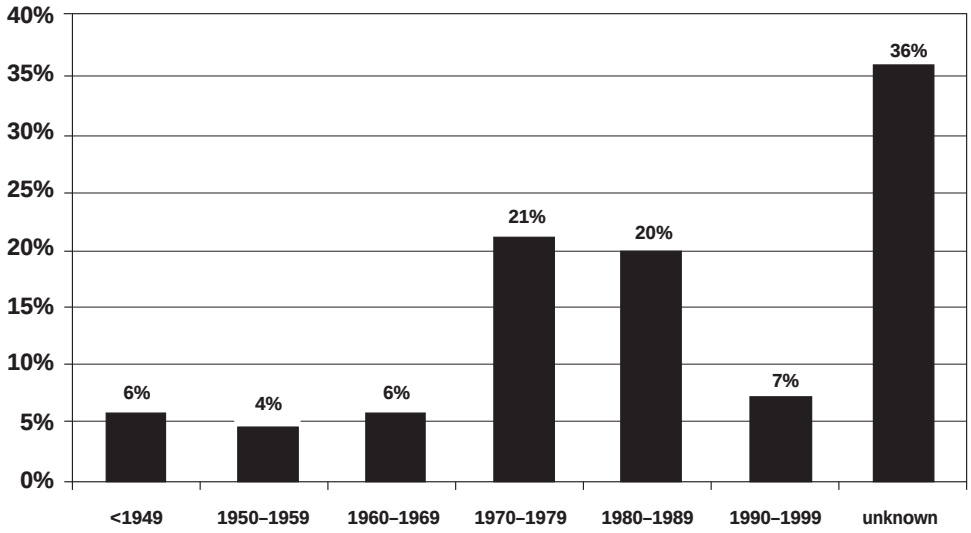


Figure 7 shows the likely year of infection with hepatitis C for all patients born outside Australia. It is of interest that where a likely date has been attributed, the pattern strongly reproduces that seen in Australian born patients. A high percentage, 36%, have no identifiable date suggesting that their infection may have been long standing from early childhood infection. This has not been proven.

The possible importance of country of birth in determining the expected natural history of the HCV infection has been highlighted by the data. Those born in Southern Europe or Egypt have been shown to have a higher fibrosis score than those born in Australia or in other countries. Of the total 859 born outside Australia, 9.2% had a fibrosis score of 3–4. The score reflects severity of fibrosis and a score of 4 reflects the presence of cirrhosis (Ishak et al. 1995) Of those born in Southern Europe, 50% had a score of 3–4 and of those born in Egypt, 50% had a score of 3–4. A higher percentage of patients in these populations were thought to have contracted their disease earlier in life than the average Australian born patient. The data do not allow any conclusion regarding the likely contribution of genotype as opposed to duration of infection to the higher fibrosis score. The number of patients from some countries is quite small but the percentage in these groups with a high fibrosis score is significantly raised in comparison with the Australian born population, suggesting that further data are needed to clarify the issue.

It is not appropriate to attempt an analysis of the impact of country of birth, genotype infection or duration of infection on the natural history of HCV infection in this document. Many other papers have wrestled with the complexity of this issue and many questions are yet to be answered regarding the most important factors influencing the natural history of this disease (Sharara et al. 1996, Seeff 1999, Dienstag 1983, Gilliam et al. 1984, Kiyosawa et al. 1984, Bruix et al. 1989, Colombo et al. 1989, Kiyosawa et al. 1990, Alter et al. 1997, Alter et al. 1992, Tong et al. 1995, Takahashi et al. 1993).

Summary

The impact of hepatitis C is felt by every ethnic group in the Australian community. Considerable work is needed to document the extent of the HCV problem in Australia, especially as it relates to those born outside Australia. Data that are available indicate that in certain racial groups the expected prevalence of HCV infection will be higher than that in the Australian born community. Our data show that patients with HCV are coming forward for treatment at similar rates for Australian born and non-Australian born populations.

A number of important issues are raised by this review:

1. Many HCV-infected individuals in Australia have come to Australia from another country. Of these, many were infected in their country of birth, while others have been infected after arrival here.
2. Non-Australian born individuals come with belief systems that differ from ours and often they have problems in conversing freely in English. Both of these factors can create difficulties for the individual seeking help with a complex and socially stigmatising condition.
3. Patients infected in certain countries other than Australia are more likely to be infected with genotypes of the HCV that are less responsive to therapy (genotypes 1b and 4).
4. Non-English speaking groups are likely to have problems in their contact with the health system. Translation services may not always be readily available. Explaining the relative resistance of the different genotypes to treatment is more difficult in this group than in an English speaking group. Attention needs to be given to this issue in developing HCV services across the country.
5. Patients from other countries often form subgroups within a suburban area and these groups may avoid contact with the routine health care systems in our cities. Whether this is due to fear or a lack of understanding of what may be offered by the health care workers, this avoidance of the system can favour spread of the infection in families and can deprive individuals of the opportunity of adequate therapy.
6. Treatment of HCV infection is demanding and complex. Obtaining informed consent and ensuring compliance with current treatment schedules can be difficult in this group of patients. Despite this, it is encouraging that 29% of the first 3000 patients treated with S100 interferon were patients born outside Australia.

It is suggested that more effort is needed to define the needs of this specific group of patients further so that they can receive the same level of treatment that is available to those born in Australia.

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Hepatitis C Infection in Indigenous Communities in Australia

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Introduction

This paper reviews the available information on the rates of injecting drug use among Indigenous Australians and the prevalence of hepatitis C infection among Indigenous injecting drug users (IDUs).

Central to this document is the inclusion of previously unpublished data analysed from the Australian Needle and Syringe Program (NSP) surveys conducted through the Collaboration of Australian Needle and Syringe Programs.

Surveys of IDUs attending selected NSP have been conducted annually over a one-week period at participating sites from 1995 to 1998. Overall, 7316 IDUs have participated in the NSP surveys. Sites were selected for their large attendances and represented all jurisdictions. In 1995, the survey sites were responsible for distributing approximately 40% of all syringes throughout the needle and syringe programs. Participants were invited to complete a self-administered questionnaire and provide a finger-prick blood specimen. Overall, response to the survey was around 50% per year of IDUs who attended the needle and syringe programs during the survey weeks. Information is collected on injecting behaviour, particularly in relation to sharing, frequency of injecting and type of drug injected. HIV and hepatitis C antibody prevalence is determined from dried blood-spot specimens. Self-identified Indigenous status has been reported in all four surveys, with 395 Indigenous participants between 1995 and 1998. The proportion of Indigenous participants has been relatively stable between 1995 and 1998, and only 3% of participants over this period have not reported Indigenous status (Table 1).

Further to this analysis, we reviewed published and unpublished literature on injecting drug use in Indigenous communities, prevalence of hepatitis C in Indigenous IDUs and comparisons of risk behaviours for hepatitis C infection among Indigenous and non-Indigenous IDUs. Implications for health services for Indigenous IDUs with hepatitis C infection are also discussed.

Table 1. Australian NSP survey participants 1995–1998 by Indigenous status

Indigenous status	*1995*	*1996*	*1997*	*1998*	*Total*
Yes	52 (5%)	66 (4%)	101 (5 %)	176 (6%)	395 (5%)
No	987 (92%)	1333 (90%)	1844 (93%)	2534 (92%)	6696 (92%)
Not reported	33 (3%)	98 (6%)	33 (2%)	59 (2%)	223 (3%)
Total	1072	1497	1978	2769	7316

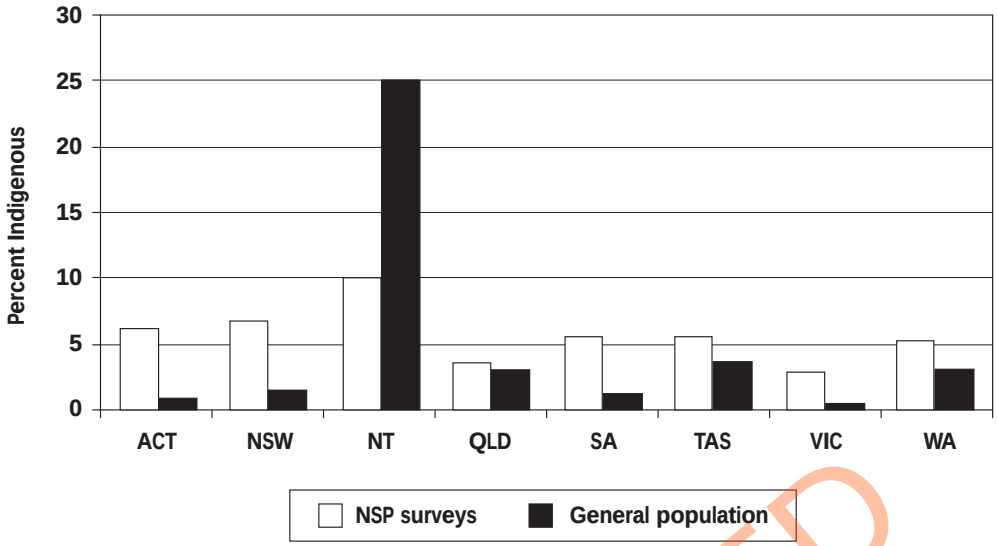
Injecting drug use in Indigenous communities

Among IDUs in the NSP surveys, 5.4% of participants self identified as Indigenous, a proportion more than double the 2.1% of the Australian population who self identify as Indigenous (Australian Bureau of Statistics 1998). The proportion of NSP survey participants who were Indigenous, compared to the proportion in the general population, is illustrated by State and Territory in Figure 1. As 96% of NSP survey participants were aged between 15 and 49 years, the comparison is confined to this age group. With the exception of the Northern Territory, the number of Indigenous people appears disproportionately greater in the injecting drug user population than in the general population. The major limitation of this comparison is that it relies on data from injecting drug users who both access needle and syringe programs and participated in the NSP surveys. If Indigenous IDUs are less likely to attend needle and syringe programs, or less likely to participate in the NSP surveys, then the rate of injecting among Indigenous people could be even higher relative to non-Indigenous people. In the Northern Territory, the NSP survey was based in Darwin only, where the proportion of the population that is Indigenous is lower than in the Northern Territory overall. Alternative access points for injecting equipment could also explain the apparently lower rate among Indigenous people in the Northern Territory.

Prison populations may also be an indicator of the prevalence of injecting drug use in Indigenous communities relative to non-Indigenous communities. Although Indigenous people make up around 2% of the general population, more than 10% of the prison population is Indigenous (Dolan, personal communication). A study in correctional services in New South Wales (Butler et al. 1999) found that the proportion of Indigenous prisoners who reported a history of injecting drug use was similar to non-Indigenous (40.9% and 41.9% respectively). Therefore the proportion of individuals who are both in prison and inject appears to be higher in the Indigenous population. Indigenous prisoners make up more than 25% of IDUs in NSW prisons (Dolan, personal communication).

Incarceration is known to be a predisposing factor for injecting drug use. The Victorian Aboriginal Health Service Co-operative Ltd investigated the qualitative issues surrounding injecting drug use for Indigenous people through interviews of community members. Their report identified that many began injecting in prison (Edwards et al. 1999). The larger proportion of Indigenous people who experience incarceration may account, in part, for an apparently higher prevalence of injecting drug use in Indigenous communities.

Figure 1. Proportion of Indigenous participants in the Australian NSP surveys 1995–8 aged 15–49 and proportion of Indigenous people in the Australian population aged 15–49 by State or Territory



The National Drug Strategy *Urban Aboriginal and Torres Strait Islander Peoples Supplement 1994* reported on 2943 interviews with urban Indigenous respondents. These results were compared to the 1993 National Household Survey in the general population. In this report, 3% of Indigenous respondents indicated they had ever injected illegal drugs, compared to 2% in the general population. A further 2% of Indigenous respondents indicated they currently injected, compared to 0.5% in the general population. It is possible, for both the Indigenous and national estimates, that these figures are underestimates due to either under-reporting by participants or poor coverage of groups such as people who are homeless, who may be more likely to inject drugs.

In another survey of 531 participants examining all drug use (injecting or otherwise) in Indigenous communities, 6% indicated they had ever used heroin and 5% indicated ever using cocaine (Perkins et al. 1994). The survey did not state whether these drugs were injected or administered via other routes. The survey's authors compared their results with surveys of non-Indigenous participants and suggested that the proportion of heroin use among Indigenous participants was higher.

Perceptions of drug use and health risks within Indigenous communities in the Australian Capital Territory were investigated by the National Centre for Epidemiology and Population Health at the time a heroin trial for injecting drug users was being considered (Humes et al. 1993). In this study, Indigenous leaders indicated they believed that heroin use was a substantial but covert problem in the Indigenous community. Limited available evidence suggests, therefore, that the prevalence of injecting drug use among Indigenous people is higher than among non-Indigenous people in Australia.

Injecting risk behaviours in Indigenous communities

Among IDUs in the NSP surveys between 1995 and 1998, significantly more Indigenous participants reported sharing injecting equipment in the last month than non-Indigenous participants (27% and 20% respectively, p=0.003). However, among both Indigenous and non-Indigenous IDUs, the proportion who reported sharing injecting equipment steadily declined between 1995 and 1998 (Figure 2).

Figure 2. Proportion of IDUs in the Australian NSP survey who re-used someone else's used syringe in the last month by Indigenous status

The overall pattern of injecting drug use differed significantly between Indigenous and non-Indigenous IDUs in the NSP surveys, both in type of drug injected and frequency of injection. The most common drug last injected was heroin, which was reported by 43% of Indigenous and 53% of non-Indigenous respondents. Fifteen per cent of Indigenous IDUs reported last injecting speed, compared to 20% of non-Indigenous IDUs. Indigenous participants were more likely to report injecting more than one drug (polydrug use) than non-Indigenous participants (18% compared to 8% respectively). Indigenous participants were also more likely to report an injecting frequency of at least daily (Table 2). In a survey of 77 Indigenous injecting drug users in Queensland, Larson et al. (1999) found that 39% of participants indicated they had shared injecting equipment in the past month. This proportion increased to 63% among injectors who were aged less than 20 years. In a rural NSW study of 89 injecting drug users, 21%

reported sharing a needle and syringe when they last injected and Indigenous status was an independent predictor of sharing injecting equipment (Yu et al. 1999). Indigenous participants were three times more likely to report sharing injecting equipment than non-Indigenous participants in this study.

Table 2. Injecting behaviour in the Australian NSP survey

	Indigenous (n=355)	*non-Indigenous (n=6169)*	*p value*
Last drug injected (%)			<0.001
Heroin	43	53	
Speed	15	20	
Cocaine	3	2	
Methadone	12	11	
Polydrug	18	8	
Frequency of IDU (%)			0.009
Daily + (%)	57	49	
< Daily (%)	38	44	
Not last month	4	7	

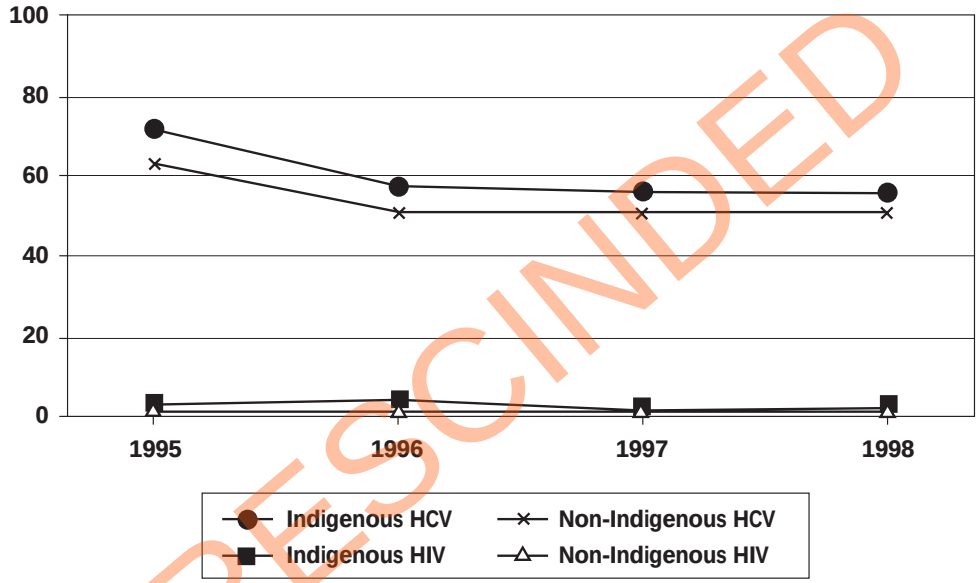
In examining the issues that lie behind risk behaviours among Indigenous IDUs, a small, qualitative study by Shoobridge (1997) suggested there may be cultural factors that influence the adoption of safer injecting behaviours by Indigenous people. Shoobridge found that among 25 Indigenous IDUs, injecting frequently occurred in the company of close friends and relatives with whom they were accustomed to sharing possessions. Shoobridge suggested that such a social setting for injecting in Indigenous communities might encourage the sharing of injecting equipment in Indigenous cultures.

Similarly, in the survey of Indigenous IDUs by Larson et al. (1999), most (65/77) participants indicated that they first injected with a close friend, relative or sexual partner. The authors suggested that sharing needles with close friends and relatives might be considered as 'not really sharing' by Indigenous IDUs 'because the person is "known" to be disease-free or because one probably already has the same diseases' (Larson et al. 1999 p56–7). These observations may indicate the presence of a cultural basis for increased risk behaviours among Indigenous injecting drug users that need to be considered in the design of harm reduction strategies.

Prevalence of hepatitis C among Indigenous injecting drug users

Hepatitis C antibodies were tested in 90% (355/395) of Indigenous IDUs participating in the NSP surveys. The prevalence of hepatitis C was 56% (200/355), which was not significantly higher than among non-Indigenous injectors who were tested (51%, p=0.7). Among both Indigenous and non-Indigenous IDUs, the prevalence of hepatitis C infection has steadily declined between 1995 and 1998 (Figure 3).

Figure 3. HCV and HIV prevalence 1995–1998 in the Australian NSP surveys by Indigenous status

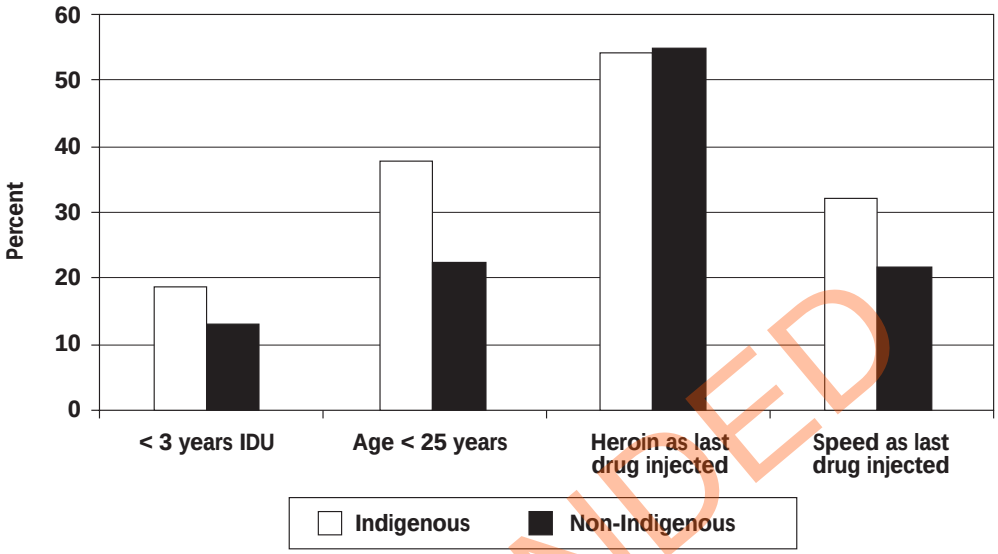


Among IDUs who were aged less than 25 years, hepatitis C prevalence among Indigenous participants was significantly higher than among non-Indigenous participants (38% and 23% respectively, p<0.001). The prevalence of hepatitis C among Indigenous participants who had been injecting for less than three years was also higher (19% versus 15%), although this difference was not significant (p=0.4, see Figure 4).

The survey undertaken in correctional centres in New South Wales assessed the prevalence of markers for hepatitis C infection in prisoners by Indigenous status (Butler et al. 1999). There were 235 Indigenous participants in this study. Of these, 228 were tested for hepatitis C antibodies, and 35.5% were positive. This proportion was slightly lower than that in 510 non-Indigenous participants (40.6%). Among Indigenous participants who were injecting drug users (n=96) the prevalence of hepatitis C

antibodies was 65.6%, which was again slightly lower than that in non-Aboriginal injecting drug users (75.4%). Multivariate analysis including all study subjects demonstrated a higher risk of hepatitis C infection among non-Aboriginal compared to Aboriginal prisoners (p=0.01).

Figure 4. HCV prevalence and injecting patterns in the Australian NSP surveys 1995–8 by Indigenous status



Health services for Indigenous injecting drug users

A collaborative study conducted by the National Centre for Epidemiology and Population Health examined health issues and services for the Indigenous community in the Australian Capital Territory (Moloney et al. 1993). This study analysed interviews with Indigenous community leaders and service providers to determine perceptions of health needs and to assess the quality and appropriateness of services provided. Among the Indigenous community leaders, hepatitis was considered a serious health issue with the potential to be a major cause of disease. Young people were identified as most at risk. Several strategies were suggested to address the potential risks, including focus by Indigenous health organisations on communities and families at risk, and the development of education programs about hepatitis. Service providers strongly recommended an increase in the number of Indigenous workers and Indigenous-specific services. However, they also related that there was insufficient funding to implement these services (Moloney et al. 1993).

Health services for Indigenous injecting drug users were also reviewed by the National Drug and Alcohol Research Centre in a scoping document for research into illicit drug use (Hando et al. 1998). The authors observed that while there were a number of drug treatment programs targeted at Indigenous people, d there has been little evaluation on the effectiveness of programs adapted for use in an Indigenous context. Further evaluation of the effectiveness and appropriateness of programs such as new pharmacotherapies and strategies such as harm reduction and home detoxification for Indigenous drug users was raised as an important emerging issue.

Conclusions

While data from the Australian NSP and prison surveys indicated that the prevalence of hepatitis C among Indigenous IDUs is similar to non-Indigenous IDUs, the prevalence of risk-taking behaviour such as sharing needles appears to be higher, particularly among younger Indigenous IDUs. This, coupled with the likelihood that injecting drug use is more prevalent in Indigenous communities, suggests that hepatitis C has the potential to have a substantial impact in Indigenous communities. Higher rates of chronic hepatitis B infection and other co-factors among Indigenous communities could also contribute to a greater impact of hepatitis C through more rapid progression to advanced liver disease.

The evidence presented suggests that younger Indigenous IDUs may be at the highest risk of hepatitis C infection. In the NSP surveys, hepatitis C prevalence was significantly higher in Indigenous participants aged less than 25 years compared to non-Indigenous participants in the same age group. Interviews of Indigenous IDUs by Larson et al. found that reports of sharing injecting equipment were nearly double among participants aged less than 20 years than reported by the whole sample.

The disproportionately high rate of incarceration of Indigenous people relative to the general population may also contribute to increasing the risk of hepatitis C infection through higher rates of injecting drug use and the sharing of injecting equipment in prison.

Injecting drug use in Indigenous communities may occur in settings involving close friends and relatives, where sharing possessions is considered acceptable and desirable. For this reason, harm reduction strategies that are culturally appropriate are essential. These strategies need to be sensitive to the specific circumstances of Indigenous IDUs.

To date, the information available in this area remains limited. We can therefore only broadly describe the extent of the effect of the hepatitis C epidemic on Indigenous Australians and postulate on the impact it may have on Indigenous communities.

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The Epidemiology of Hepatitis C Infection in Prison Populations

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Executive summary

Prisons are probably one of the most difficult settings for the study of risk behaviour, transmission and the prevention of blood-borne viral infections, such as hepatitis C. The difficulties lie in gaining access to inmates, obtaining representative samples and reliable reports of risk behaviours, and collecting conclusive evidence of transmission in prison. Nevertheless the study of hepatitis C infection in prison is crucial. Hepatitis C prevalence is high, risk behaviour is common and prevention programs are rare. In addition, the high level of inmate turnover means that transmission in prison threatens the ability to control transmission in the community when inmates are released. Despite circumstances that are conducive to widespread transmission of hepatitis C in prison populations, only a handful of cases have been documented in the world.

The implementation and evaluation of prevention efforts for hepatitis C infection in prisons have lagged behind efforts in the community. Research is urgently required to evaluate the effectiveness of hepatitis C prevention measures in prison settings, as virtually no such evidence exists in the world.

For all these reasons, the prison environment presents additional challenges to the surveillance and reduction of hepatitis C infection. Unless concerted efforts are directed towards the control of hepatitis C transmission among prisoners, it is unlikely that the hepatitis C epidemic in the broader community will be brought under control.

This paper addresses the following issues:

- the epidemiology of hepatitis C infection within Australian prisons
- risk behaviours for hepatitis C within Australian prisons, and
- the hepatitis C prevention measures presently implemented by jurisdictions

and examines them in an international context, where information is available. It begins by describing the characteristics of prisoners and Australian prison systems.

Background

Prisoners are failed risk takers. They are predominantly males aged between 20 and 40 years and as a group are usually considered very active sexually. Most come from disadvantaged backgrounds and have a low level of education. Aborigines make up 2% of the general population in Australia but represent at least 10% of prison populations. In one study in NSW prisons, Aboriginals accounted for 25% of injecting drug users (IDUs) (Dolan et al. 1999).

The prevalence of infections such as hepatitis B and hepatitis C (Crofts et al. 1995), sexually transmissible diseases (Cohen et al. 1992) and psychiatric conditions (Harding & Zimmermann 1989) are several times higher among prison entrants than general populations. Prisons can be stressful, crowded and violent places (Thompson 1993). Drug withdrawal is common (Jeanmonod et al. 1991, Turnbull & Stimson 1994). Imprisonment has been shown to reduce drug use (Shewan et al. 1994a), but some inmates have commenced drug injection (Taylor et al. 1995) or homosexual sexual activity (Dolan 1994) while incarcerated. These initiations into risk behaviour in prison have been attributed to boredom (P. Brown, personal communication 1994) and the single-sex nature of prisons. Alcohol and drug problems affect more than half of those in many prison systems (Wright 1993).

Each of the six Australian States and two Territories has its own prison system. There are no federal prisons and no national policy (nor mandate) for prisons in Australia. According to the 1996 National Prison Census, there were 18,193 prisoners, representing an imprisonment rate of 130 per 100,000 adult population. For indigenous Australians, however, this rate climbs to 3054 per 100 000. The overall prison population in Australia has increased by 58% over the past decade (Australian Bureau of Statistics 1997).

Hepatitis C infection in Australian prisons

In three Australian studies, approximately one third of male inmates in NSW (Butler 1997, Butler et al. 1997) and in Victoria (Crofts et al. 1995) were infected with hepatitis C. The prevalence of HCV among female inmates was double that for males, with two thirds of female inmates infected.

Table 1. Prevalence of HCV in general and non-IDU prisoners in NSW and Victoria

Location/ year	*Sample size and type*	*% HCV*	*Reference*
NSW 1994	408 Males on entry to prison	37	Butler et al. 1997
NSW 1996	653 Males during prison 119 Females during prison	33 66	Butler 1997
Victoria 1991	1749 Male non-IDU prisoners on entry 54 Female non-IDU prisoners on entry	16 26	Crofts 1995

The prevalence of hepatitis C infection among IDU inmates was even higher, at approximately 80% among male and female samples in NSW and Victoria. A recent study of IDUs on the methadone waiting list in NSW prisons found that 74% were positive for hepatitis C (Dolan et al. 1999a).

Table 2. Prevalence of HCV among IDUs prisoners in NSW and Victoria

Location/ year	*Sample size*	*% HCV*	*Reference*
NSW 1994	67 Male IDUs on entry	77	Butler 1997 et al.
NSW 1996	264 Male IDUs during prison 85 Female IDUs during prison	79 80	Butler 1997
NSW 1997–98	384 Male IDUs on methadone waiting list	74	Dolan et al. 1999a
Victoria 1992	1436 Male IDUs on entry 125 Female IDUs on entry	64 85	Crofts et al. 1995

Predictors of HCV infection in prisoners are injecting drug use and past exposure to hepatitis B virus (Butler et al. 1997).

Incidence of HCV in Australian prison populations

Ascertaining whether transmission occurred in prison or in the community prior to entry is complicated when infections such as HIV and hepatitis C have long incubation periods. Determination of hepatitis C transmission is further complicated by the fact that infection does not usually result in an acute illness. Past imprisonment has been associated with hepatitis C infection (van Beek et al. 1998).

IDU inmates with multiple admissions to all Victorian prisons in a one-year period had an incidence of 38% (Crofts et al. 1995), which is double the rate for IDUs in the community. However, the proportion of infections that occurred in prison could not be determined.

Four cases of hepatitis C transmission in NSW prisons were recently reported (Haber et al. 1999). HCV transmission was thought to result from the shared use of injecting equipment in two cases. The remaining two cases may have been infected from barber shears, a fight, or other blood-to-blood exposure.

Risk behaviour in Australia prisons

Hepatitis C infection is transmitted via blood contact, hence risk behaviours such as the shared use of injecting equipment and tattoo needles and sexual activity are of interest.

History of imprisonment among IDUs

While there are indications that the size of the population that injects drugs is increasing, there are signs that the proportion of IDUs being imprisoned is also increasing. In NSW, a reported history of imprisonment among IDUs increased from one third in 1987 to one half in 1994 (Crofts et al. 1996). Two thirds of respondents in a study of NSW prison entrants thought that there was a relationship between their drug use and subsequent imprisonment and one third (32%) expected to experience drug withdrawal after prison entry (Kevin 1992).

The Australian Study of HIV and Injecting Drug Use (ASHIDU) was carried out in 1994 (Loxley et al. 1995). The proportion of respondents in each city who had been in prison ranged from 23% in Melbourne to 54% in Sydney (see Table 3).

Table 3. Prison histories of ASHIDU sample

Imprisoned	*Sydney % (n=219)*	*Perth % (n=228)*	*Melbourne % (n=216)*	*Adelaide % (n=208)*
Youth detention	37	19	15	19
Ever in prison	54	33	23	39

Annual rate of imprisonment among IDUs

In the Annual Survey of Needle and Syringe Programs (NSPs), clients are asked about their experience with prison in the preceding year (MacDonald et al. 1997). The highest rate of imprisonments were in NSW, Victoria and the ACT, where approximately one in five male IDUs reported being in prison in the previous year. Male IDUs in every jurisdiction were more likely to report being imprisoned than female IDUs.

Table 4. NSP clients who were in prison and injected in prison in 1996

Location	*N*	*% Imprisoned*	*% Injected (of those in prison)*
NSW	M=335	25	35
NSW	F= 216	14	55
QLD	M=356	7	64
QLD	F=160	6	78
Vic	M=307	18	30
Vic	F=147	7	40
ACT	M=59	22	46
ACT	F=27	7	0
NT	M=76	12	33
NT	F=24	4	0

In eight studies, reports of a history of injecting drug use before incarceration ranged from 26% in South Australia to 64% in two NSW studies.

Table 5. Inmates with a history of injection before prison

Location	*N*	*% of inmates who were IDUs*	*Reference*
NSW	158	46	Potter & Conolly 1990
NSW	408	51	Butler et al. 1997
NSW	102	64	Dolan et al. 1999
NSW	181	64	Dolan et al. 1998a
Victoria	3627	46	Crofts et al. 1995
Sth Australia	373	36	Gaughwin 1991
Sth Australia	86	26	Seamark no date
West Australia	201	28	Close 1990

Injection and syringe sharing in prison

In contrast to significant risk reduction by IDUs in the community, risk behaviour in prison has remained unchanged over the past decade. Furthermore, prison appears to be a place where people start injecting—10% of IDUs in NSW prisons reported that they commenced injecting in prison (Dolan et al. 1999a).

In a Victorian study, six of the 36 who reported injecting and sharing when last in prison also reported that was the first time they had ever shared syringes (Crofts et al. 1995).

Table 6. Percent of IDUs who injected and shared in prison*

Location	*N*	*% injected*	*% shared (of those injecting)*	*Reference*
National	2482	36	60	Wodak 1991
NSW	73	68	94	Potter & Conolly 1990
NSW	209	74 ever	75	Wodak 1991
NSW	185	44 last time	70	Dolan et al. 1996a
NSW	113	68 ever	77	Dolan et al. 1998a
NSW	65	66 last time	91	Dolan et al. 1999b
NSW	26	31 last time	88	MacDonald et al. 1997
NSW	384	62 last time	89	Dolan et al. 1999a
SA	50	52	60	Gaughwin et al. 1991

* Updated from Crofts et al. 1996.

Tattooing in prison

Prisoners in a NSW study estimated that 40% of fellow inmates had used tattoo needles and that 68% of these had shared the tattooing equipment (Taylor 1994). Another study found 38% of prisoners reported receiving a tattoo in prison (Dolan et al. 1998a). A third study found that IDUs (48%) were significantly more likely to report receiving a tattoo in prison than non-IDUs (22%) (Dolan et al. 1998a).

Table 7. Percentage of inmates who received a prison tattoo

Location	*N*	*% tattooed*	*Reference*
NSW	102 m & f	38	Dolan et al. 1998a
NSW	?	40	Taylor 1994
NSW	384 males	11	Dolan et al. 1999a
NSW	648 males	35	Butler 1997
NSW	128 females	15	Butler 1997
WA	201	58	Close 1990

Sexual activity in prison

Sexual activity is thought to play a minor role in the transmission of hepatitis C infection. However, sexual assault occurs in prison and can involve blood-to-blood contact and therefore is of interest. Approximately 2% of males and females reported engaging in non-consensual sex in prison. In NSW, almost one quarter of male prisoners aged less than 26 years reported being sexually assaulted (Heilpern 1994). In another study of male IDUs released from prison in NSW, 5% reported being raped while in prison (Wodak et al. 1991).

Table 8. Sexual activity in prison

Location	*N*	*% Sexually active*	*Reference*
NSW	648 males	5	Butler 1997
NSW	128 females	15	Butler 1997
NSW	65 male IDU	5	Dolan 1997
NSW	37 non IDU	0	Dolan 1997

Injury and self harm

Injury includes fights, assaults and accidents in prison. The risks of transmission from these behaviours are yet to be investigated in any detail. There are also considerable occupational hazards for prison personnel when cleaning up after incidents of self-harm. One study indicated that about 10% of females and 5% of males engage in self harm in prison where blood is drawn (Butler 1997).

Rate of partner change and mixing in prison

Rate of partner change refers to the turnover of new injecting partners. The only study to investigate rates of partner change found that the mean number of partners with whom IDUs shared syringes in prison (five) was much higher than that for IDUs in the community (one) (Dolan 1997). Mixing refers to the bringing together of disparate individuals. One study found that among IDUs who shared syringes in prison, 71% reported that their sharing partners were either from a different suburb, city or from unknown location (prior to prison entry) compared with 31% of IDUs who reported sharing syringes in the community (Dolan et al. 1998a).

Multiple episodes of imprisonment are more common for IDU inmates than for other inmates. IDU inmates reported being imprisoned on a mean of approximately four occasions and non-IDU inmates reported being imprisoned on a mean of two occasions (Dolan 1997).

Estimates of the number of IDUs among prison inmates

The number of IDUs in prison can be estimated by using the prevalence of HIV and hepatitis among prisoners and among IDUs in the community. The proportion of prisoners with HIV, HBV or HCV infection ranges from 50% to 62%. With a census of approximately 6411 inmates in 1997 (Corben 1998), there will be between 3205 and 3975 IDU inmates in NSW prisons. While these figures will need adjusting, they do give an indication that over half of all prisoners in NSW have histories of injecting drug use. This figure is consistent with studies in which a history of injecting has been asked.

Hepatitis C prevention measures in prison

Options to reduce the transmission of HCV in prison include: methadone maintenance programs, needle and syringe cleaning programs, tattooing and piercing programs, condoms, education, and prison-based syringe exchange programs.

Prison methadone maintenance programs

Over a decade ago, Australia's National Methadone Guidelines listed conditions for which methadone treatment might be appropriate for prisoners (Drug Offensive 1988). These were: (1) withdrawal, (2) continuation of treatment for those on methadone prior to imprisonment, (3) commencement of treatment for those who are heroin dependent on prison entry or who have used heroin in prison in a harmful way, including those who are HIV positive, and (4) the reduction of intravenous opioid use upon release. In addition, the Guidelines stipulate that medical staff prescribing methadone in prison should be independent of the Department of Corrective Services to minimise potential conflicts of interest.

The NSW prison methadone program began in 1986. Currently there are almost 1000 inmate clients. There is some evidence that MMT reduces the frequency of injecting among inmates in NSW. In one study, IDUs in MMT in prison reported significantly fewer injections per week than IDUs not in MMT, but only when methadone doses exceeded 60 mgs and treatment was provided for the entire duration of imprisonment (Dolan et al. 1996b). A randomised-controlled trial of the New South Wales prison methadone program has just been completed. In that study, preliminary analysis indicated that methadone treatment significantly reduced the incidence of HCV (Dolan et al. 1999a).

Prisoners in South Australia and Tasmania are allowed to continue methadone treatment when they enter prison. In Queensland, only some prisons offer continuation of methadone treatment for inmates who enter on methadone. A small numbers of prisoners in Victoria receive methadone treatment if they are serving short sentences.

Bleach programs

Two studies of the bleach program in NSW found that most inmates could obtain bleach and most were using it to clean injecting equipment (Dolan et al. 1998a, Dolan et al. 1999b). However, there exists some uncertainty about the effectiveness of bleach to decontaminate hepatitis C infection from injecting equipment.

Table 9. IDU inmates always cleaning syringes with bleach

Location	*Year*	*N*	*%*	*Reference*
NSW	1988	47	30	Potter & Conolly 1990
NSW	1989	116	25	Wodak 1991
NSW	1993	35	85*	Dolan et al. 1999b
NSW	1994	31	85*	Dolan 1998
NSW	1994	66	48	Loxley et al. 1995
Queensland	1993	27	35	Spooner et al.1993
Perth	1994	75	11	Loxley et al. 1995
Melbourne	1994	49	4	Loxley et al. 1995
Adelaide	1994	82	33	Loxley et al. 1995

* Prisoners were asked about the last syringe they shared.

Programs for prisoners who tattoo

The NSW Department of Corrective Services developed a project, *Think before you ink*, directed at prisoners who tattoo themselves while in prison. The project offered a professional tattoo as a prize, but to win, the successful candidate was to have abstained from prison tattooing during the project.

Condoms and dental dams

State wide distribution of condoms has been evaluated in NSW (Lowe 1998). According to the evaluation, inmates thought the vending machines were accessible, there was a low level of harassment of inmates using the machines, incidents of improper disposal were rare, the level of safe sex was high, and there was no evidence of any unintended consequences as a result of condoms or dental dams being available.

Table 10. Percent of inmates who agree condoms should be available in prison

Location	*N*	*% agree condoms be available in prison*	*Reference*
NSW	37 non IDU males	65	Dolan 1997
NSW	65 IDU males	79	Dolan 1997
NSW	20 HIV+ males	90	Dolan 1997
NSW	135 HIV- males	80	Dolan 1997
NSW	605 males	33	Butler 1997
NSW	69	84	Lowe 1998

Education

One study found that inmates' knowledge about risk behaviours for hepatitis C was poor. Only 20% named injecting drug use as a risk, but recidivists were better informed than those new to prison (Butler et al. 1997).

NSW Department of Corrective Services has developed a comic book, *Skin Deep*, to address hepatitis C in prison. Issues include non-injecting routes of administration (NIROA), tattooing, self-harm, and the importance of not becoming infected with another strain of hepatitis C virus. The comic has an evaluation component that will be undertaken in 2000.

Needle and syringe exchange programs

No jurisdiction operates a prison-based needle and syringe exchange program in Australia. A feasibility study of syringe exchange in New South Wales prisons was conducted in 1995 (Dolan et al. 1996c). The study concluded that negotiations would need to be held with prison officers before a pilot scheme could commence (Rutter et al. 1995).

The following table summarises hepatitis C prevention measures presently implemented by jurisdiction.

Table 11. Implementation of prevention measures in Australian prisons

Location	*Bleach*	*Condoms*	*Methadone*
NSW	**YES**	**YES**	**YES** Maintenance program for 800. Inmates can start MMT in prison
Victoria	**YES** Available for general purposes. No formal distribution process	**YES** Via machine or health service	**NO** Remandees and sentenced prisoners (<6 months) and those pregnant are maintained.
Queensland	**YES** Available for general cleaning. Proposal to provide via health centres was rejected	**YES** Trial in 3 prisons	**YES** Townsville prison entrants on methadone may continue for 12 months. Program for female prisoners to start in August 1999
Western Australia	**NO**	**YES** Free via vending machine or store	**NO** Maintenance for HIV positive, pregnant or very short term inmates
South Australia	**NO** Under consideration	**YES** Condoms and dental dams are available	**YES** Maintenance available for those entering prison on methadone, nearing release or test positive for opiates
Tasmania	**YES** Available for general purpose cleaning and laundry	**NO**	**YES** Methadone treatment for those who enter prison on methadone
Northern Territory	**NO**	**NO**	**NO**
ACT	**YES**	**YES**	**YES** Detainees have priority access to the public methadone program

International situation with regard to hepatitis C in prisons

This section presents information on the prevalence and incidence of hepatitis C infection in prisons overseas. Studies of risk behaviour among prisoners and efforts to prevent hepatitis C infection are summarised.

Prevalence of hepatitis C infection in prisons

Numerous studies have measured the prevalence of hepatitis C among inmates. Most find that about 30–40% of prisoners are positive. (See Table 12, next page.)

Incidence of HCV in prison populations

The only cohort study of hepatitis C incidence among prisoners in the world was conducted in Maryland, USA between 1985 and 1987. The prevalence of hepatitis C among prisoners at entry was 38% (n=265) and incidence was 1.1 per 100 person years. This rate of transmission is very low and requires some examination (see Dolan 1997). Briefly, cohort studies are likely to underestimate incidence because they sample long-term prisoners who are usually held in maximum security prisons where there is less access to drugs, other prisoners who leave the system temporarily, and visitors. Therefore they have little chance to engage in risk behaviour and become infected. Indeed, Australian studies have found that prisoners in low security prisons are at a higher risk of infection as they are significantly more likely to inject drugs (48%) than those in medium (27%) or maximum security prisons (18%) (Dolan 1997).

Calculations from the UK indicated that a definitive study of 3000 prisoners for 10 weeks would expect to detect about six HCV seroconversions (Gore & Bird 1998).

Table 12. Prevalence of HCV, HBV and proportion of IDUs in prison populations

Location	*Sample size and type*	*% HCV*	*% HBV*	*% IDU*	*Reference*
America					
Canada	Females	40	–	–	Ford 1995a
Canada	113 females	40	–	–	Ford 1995b
Canada	Males	28	–	–	Pearson et al. 1995
Canada	Males	26	–	–	Prefontaine 1990
USA	3926 males	39	2.2	–	Ruiz et al. 1999
USA	587 females	54	1.2	–	Ruiz et al. 1999
USA	Males	39	–	–	Spaulding et al. 1999
USA	265 males	38	–	–	Vlahov et al. 1993
Brazil	HIV males	–	13	–	Osti et al. 1998
Asia					
Japan	504 females	–	–	63	Nara et al. 1997
Europe					
Berlin	519 males	37	50	–	Neifer et al. 1997
Berlin	Males	9.7	3.9	–	Stark et al. 1997
France	806 males	30	–	54	Gaube et al. 1993
Greece	106 males	32	–	100	Anastassopoulou 1998
Greece	544 males	58	58	69	Malliori et al. 1998
Italy	756 M & F	16	–	0	De Mercato et al. 1995
Norway	70 males	46	–	–	Holsen et al. 1993
Russia	750 males	45	–	86	Savin 1998
Spain	352 males	34	32	52	Anon et al. 1995
Spain	Males	48	–	–	Anonymous 1998
UK	409 males	–	43	74	Barry et al. 1990
UK	Females	32	–	76	Fennie et al. 1996
UK	1824 males	20	–	49	Hutchinson et al. 1998
UK	250 males	17	1	–	Mohanty and Biswas 1996

Imprisonment rates among IDUs

Imprisonment is a common event for many IDUs. In a national study in the United States of America, approximately 80% of 25,000 IDUs reported having been imprisoned at some stage (Normand et al. 1995). In a 12-city WHO study of HIV risk behaviour among IDUs (Ball et al. 1995), between 60% and 90% of respondents reported a history of imprisonment since commencing drug injection and most had been imprisoned on multiple occasions.

Also, multiple episodes of imprisonment were reported to be more common for IDU inmates than for other inmates in Scotland (Gore et al. 1995). IDU prisoners in Gore's study were significantly more likely to have been in prison on six or more occasions than non-IDU prisoners.

Drug injection before prison

Among general prisoners, reports of injection before prison ranged from 11% in England (Maden et al. 1992) to over 50% in Spain (Martin et al. 1990). The percentage of inmates with a history of injection in the United States of America, Great Britain and Europe appear in Table 13.

Table 13. Overseas inmates with a history of injection before prison

Location	*N*	*% of inmates who were IDUs*	*Reference*
USA			
Tennessee	759	47	Decker et al. 1984
Wisconsin	619	27	Anda et al. 1985
New Mexico	455	41	Hull et al. 1985
Iowa	818	28	Glass et al. 1988
Oregon	977	53	Andrus et al. 1989
Massachusetts	406	33	Barry et al. 1990
Michigan	802	20	Vlahov et al. 1993
Maryland	1932	34	Patel et al. 1990
New York	480	29	Smith et al. 1991
Great Britain			
Edinburgh	378	18	Bird et al. 1992
England	755	11	Maden et al. 1992
Scotland	404	16	Bird et al. 1993
Aberdeen	146	37	Bird et al. 1997
Lowmoss	298	53	Bird et al. 1997
Perth	284	41	Gore et al. 1995
Cornton Vale	278	29	Gore et al. 1997
Scotland	132	46	Gore et al. 1997
	559	28	Power et al. 1992
	234	32	Shewan et al. 1994a
	234	49	Shewan et al. 1994b
Europe			
Germany	539	?	Gaube et al. 1993
Spain	624	57	Martin et al. 1990
Asia			
Japan	504	63	Nara et al. 1997

The only factors identified that predict syringe sharing in prison have come from a study conducted in Scotland (Shewan et al. 1994). Factors identified include the injection of a wide range of drugs in prison, the use of buprenorphine (which is obtained on the black market) and the discontinuation of methadone treatment upon prison entry. Studies showing reports of injecting in prison appear in Table 14.

Table 14. Overseas inmates who injected in prison

Location	*N*	*% injecting*	*Reference*
Scotland	421	25	Bird et al. 1993
– Perth	80	85	Gore et al. 1997
– Cornton Vale	56	57	Gore et al. 1997
– Glasgow	64	60	Gore et al. 1997
– Ed, Dun, Fife	26	21	Gore et al. 1997
– Elsewhere	45	34	Gore et al. 1997
Scotland	1864	53	Gore et al. 1999
Scotland	234	11	Shewan et al. 1994a
Scotland	234	29	Shewan et al. 1994b

Tattooing

Tattooing has been associated with hepatitis C infection among prisoners in Norway (Holsen et al. 1993). Three studies estimating the prevalence of tattooing among inmates are presented in Table 15.

Table 15. Percentage of inmates who received a prison tattoo

Location	*N*	*% tattooed*	*Reference*
New Mexico	455 males	82	Hull et al. 1985
Spain	631 males	75	Martin et al. 1990
Spain	360 IDUs	91	Martin et al. 1990
Spain	271 non-IDUs	53	Martin et al. 1990
New York	480 females	24	Smith et al. 1991

Spanish prisoners were far more likely to report tattooing if they were injecting drug users. Even so, over half of non-IDU prisoners reported being tattooed in prison. Approximately one quarter of female prisoners in New York reported receiving a tattoo.

Sexual activity in prison

A review of studies of sexual activity of inmates found that approximately 5% of males reported being homosexually active while in prison (Gaughwin et al. 1991).

Table 16. Percentage of male homosexual activity during prison

Location	*N*	*% homosexually active*	*Reference*
USA	409	5	Barry et al. 1990
USA	369	4	Glass et al. 1988
New Mexico	455	3.6	Hull et al. 1985
Scotland	480	0.4	Power et al. 1992

Almost half of male inmates who were sexually active in England (Turnbull et al. 1992) reported engaging in anal sexual intercourse. One report indicated that approximately 20% of female prisoners engaged in homosexual activity while in prison (Turnbull et al. 1991). There have also been reports of prisoners engaging in heterosexual sex while in single-sex prison (Turnbull et al. 1991). Their partners have included prison officers, non-custodial staff and visitors.

Between 3% and 10% of male IDUs reported being sexually active while in prison (Table 17). Compared with reports of sexual activity by male prisoners in general, it would appear that slightly more male IDUs are sexually active in prison. This probably reflects the over representation of homosexuals among IDU populations compared with general populations (Ross et al. 1994).

Table 17. Percentage of male IDUs reporting sex in prison

Location	*N*	*% homosexually active*	*Reference*
England	139	6	Dolan et al. 1990
London	50	10	Carvell et al. 1990
England	474	3	Donoghoe 1992
London	207	6	Dolan et al. 1990

Injury and self harm

There has been one report of a prison officer acquiring hepatitis C from a blood splash resulting from two prisoners fighting (Rosen 1997).

Hepatitis C prevention measures in prison

Condoms, bleach and methadone maintenance are provided to inmates in 18, 13 and seven countries, respectively. Syringe exchange schemes for prisoners exist only in Switzerland and Germany (Nelles and Harding 1995, H. Stover, personal communication 1996). Although countries are listed as having implemented a prevention program in prison, the extent of implementation may be anything from minimal to universal.

Table 18. Hepatitis C prevention measures in prisons

Condoms	*Bleach*	*Methadone maintenance*	*Syringe exchange*
Australia	Australia	Australia	Switzerland
Austria	Belgium	Denmark	Germany
Belgium	Denmark	The Netherlands	
Brazil	Finland	Germany	
Canada	France	Spain	
Costa Rica	Germany	Switzerland	
Denmark	Luxembourg	USA	
Finland	Mauritius		
France	Netherlands		
Switzerland	Norway		
Germany	Scotland		
Iceland	Spain		
Luxembourg	Switzerland		
Netherlands			
Norway			
Spain			
Sweden			
USA			

* Based on Harding and Schaller 1992, updated in Dolan et al. 1995.

Prison methadone maintenance programs

The only overseas prison methadone program documented in the literature operates at Rikers Island Jail, New York City (Magura et al. 1993). Methadone provision began in Rikers Island Jail in 1986. There is no evidence whether this methadone program has had any impact on injecting in prison. However, injecting drug use is reported to be rare in Rikers Island Jail (S. Magura, personal communication 31 Jan 1995).

Bleach programs

No studies were identified where bleach programs had been evaluated in prisons overseas.

Condoms and dental dams

No studies were identified where condom or dental dam programs had been evaluated in prisons overseas.

Education

No studies were identified where educational programs on hepatitis C for inmates had been evaluated.

Prison-based syringe exchange programs

A Swiss evaluation of prison-based syringe exchange found that the frequency of drug use and injection had remained stable while sharing of injecting equipment virtually ceased. There were no seroconversions to HIV, hepatitis B or hepatitis C during the study period (Nelles et al. 1997). A trial syringe exchange program commenced in two German prisons in 1996 (H. Stover, personal communication 1996).

Prison-based heroin trial

A pilot program of heroin distribution operates in a Swiss prison for a small number of inmates (Nelles et al. 1997).

Mandatory drug tests in prison

The cost implications of random mandatory drug tests in prisons in England and Wales were assessed in 1995. Gore and colleagues estimated that the cost of random drug tests was equivalent to twice the cost of running a credible drugs reduction and rehabilitation program and around half the total healthcare expenditure for a prison with 500 inmates, which averaged $A105 000 per 28 days (Gore and Bird 1996).

Mandatory drug testing in the UK has been blamed for encouraging prisoners to switch from cannabis to heroin. Because cannabis remains longer in the system, prisoners changed to heroin, which is detectable for a much shorter time (Campbell 1996).

Conclusion

Hepatitis C infection is the most prevalent infection among Australian prisoners. While there is no doubt that hepatitis C transmission occurs in prison, the extent of the transmission is still to be determined. The substantial reductions in risk behaviour by IDUs in the community have not been replicated in prison.

Bleach and condom programs have been safely implemented in prisons in NSW without adverse consequences for prison staff or inmates. Preliminary analysis of data from the evaluation of the NSW prison methadone program is very encouraging. It would appear that methadone can significantly reduce hepatitis C incidence among prisoners.

The international situation with regard to hepatitis C infection in prison is similar to that of Australia. One major difference is that two countries have implemented and evaluated prison-based needle and syringe exchange programs. Results from both Switzerland and Germany are favourable.

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Natural History of Hepatitis C Virus Infection

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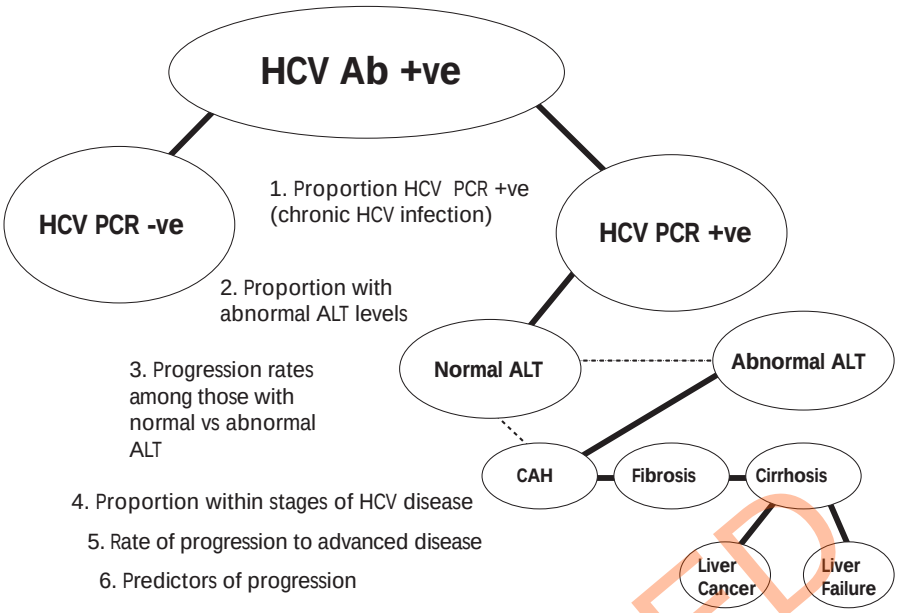
Introduction

Only a decade after the discovery of hepatitis C virus (HCV), a vast amount of literature exists on the epidemiology, virology, and clinical aspects of this blood-borne virus. There are, however, gaps in our knowledge, including many aspects of the natural history of HCV infection. Figure 1 below outlines some of the areas that need to be clarified before we can make more reliable predictions about the course of disease for people living with HCV infection.

A proportion of people who have acquired HCV infection will resolve their infection, generally within the first six months, and unless they are re-exposed they are not at risk of the complications of chronic HCV infection. The extent of HCV infection resolution is not clear, as estimates ranging from 10% to 50% have been reported for that proportion of people who do not develop chronic HCV infection. In general, they will test HCV antibody positive, but are non-viraemic as defined by negative HCV RNA on polymerase chain reaction (PCR) analysis. Furthermore, the host and viral factors that influence clearance of HCV infection have not been well defined.

Once chronic HCV infection has been established, as defined by persisting viraemia (HCV RNA positive on PCR analysis) six months post-exposure, the course of disease appears to vary enormously. Although there is a clear relationship between chronic HCV infection and cirrhosis, liver failure and hepatocellular carcinoma (HCC), the rate of progression to these advanced liver disease endpoints, the overall proportion of people who will develop these complications, and predictors of progression, are not clear. Among those people with chronic HCV infection, a proportion will have persisting normal liver function tests (LFTs), with no significant biochemical evidence of hepatitic inflammation. Whether these people are chronic ‘carriers’ of HCV infection with minimal risk of progression to advanced liver disease also needs to be examined.

Figure 1. Natural history of hepatitis C infection



Limitations in previous natural history studies

Although many studies have been published in the broad area of 'natural history' of HCV infection, some of the following factors have limited their ability to clearly define outcomes for people with HCV infection:

- lack of an acute clinical illness in the vast majority of people with newly acquired HCV infection;
- small number of cases and limited follow-up in studies of acute HCV infection;
- sub-optimal sensitivity and specificity of HCV diagnostic testing in earlier studies;
- longitudinal studies of HCV infection primarily among people with post-transfusion hepatitis, a group with high non-HCV-related mortality;
- cross-sectional analyses of HCV-related liver disease among highly selected (e.g. liver clinic), rather than population-based study populations;
- long interval between HCV infection and development of advanced liver disease (more than 20 years for most people).

The ideal natural history study would prospectively follow people with newly acquired HCV infection, with long-term assessment of HCV-related morbidity and mortality, including the contribution of host and viral co-factors to morbidity and mortality.

Proportion of people developing chronic HCV infection

Following initial HCV infection, a proportion of people appear to resolve infection, generally in the first six months, and therefore do not develop chronic HCV infection and are not at risk of HCV-related chronic liver disease. To assess the proportion of people who resolve HCV infection (and thus the proportion developing chronic HCV infection), two broad methodologies can be utilised, although both have limitations. They are as follows.

Method 1: Prospective follow-up of people with newly acquired HCV infection

Limitation: Small numbers of cases and limited follow-up in series of acute HCV infection.

Method 2: Cross-sectional analysis of presence of viraemia (as determined by PCR for HCV RNA) among people with positive HCV antibody

Limitation: Specificity of HCV antibody testing will influence estimates of the proportion with 'resolved' HCV infection, as people with a positive HCV antibody and negative HCV PCR test will include people who have truly resolved HCV infection and people with false positive HCV antibody tests. Factors that would increase the proportion of false positive HCV antibody results include use of earlier generation HCV antibody tests with lower specificity, and testing among low HCV prevalence populations (e.g. antenatal clinic, blood donor populations). Furthermore, lower sensitivity of HCV PCR testing in earlier studies could also artificially increase the 'resolved' proportion due to false negative results.

Prospective follow-up of people with newly acquired HCV infection

Table 1 below outlines studies of acute or newly acquired HCV infection in which chronic HCV infection status has been determined by PCR analysis for HCV RNA. The rate of chronic HCV infection as defined by persisting viraemia (HCV RNA positivity) beyond six months varies from 40% to 100% in these studies, most of which have small numbers of acute or newly acquired HCV cases. A pooled estimate of the rate of chronic HCV infection from these studies is 67% (204/306) (that is, 33% clearance of HCV infection). However, several of these studies are among people with acute clinical HCV infection, which has been demonstrated to have a higher rate of clearance than asymptomatic newly acquired HCV infection (Villano 1999, Sachithanandan 1997). The rate of chronic HCV infection appears to be higher among the four studies that included incident HCV cases among prospectively followed cohorts (Villano 1999, Prati 1997,

Oliva 1995, Okayama 1997), with a pooled estimate of 84% (56/67) among these cases. In contrast, the pooled estimate of chronic HCV infection among the studies based on acute clinical HCV infection is 62% (148/239).

Table 1. Studies of acute or newly acquired HCV infection

Study	*Population*	*Chronic HCV infection*[1]	
Villano 1999 USA	Incident HCV cases in IDU prospective cohort study	37/43	(86%)
Ishii 1998 Italy	Acute clinical HCV cases	22/34	(65%)
Rodger 1999 Australia	Acute clinical hepatitis (1971–1975)	51/99	(52%)
Prati 1997 Italy	Incident HCV cases among repeat blood donors	4/5	(80%)
Oliva 1995 USA	Incident HCV cases in haemodialysis unit	5/5	(100%)
Barrera 1995 Spain	Post-transfusion HCV	36/41	(88%)
Okayama 1997 Japan	Incident HCV cases in community cohort	10/14	(71%)
Missale 1996 Italy	Acute clinical HCV cases	11/21	(52%)
Diepolder 1995 Germany	Acute clinical HCV cases	6/14	(43%)
Hino 1994 Japan	Acute clinical HCV cases (PTH and sporadic)	22/30	(73%)
Total		**204/306**	**(67%)**

1. Chronic HCV infection as defined by persistence of HCV RNA for greater than six months

Cross-sectional analysis of presence of viraemia among people with positive HCV antibody

In general, the proportion of false positive HCV antibody tests will be higher when low prevalence population groups are tested. In a review of HCV transmission, which included 21 mother-to-child transmission studies, the proportion of HCV antibody positive pregnant mothers who were HCV RNA positive on PCR testing was 54% (Dore 1997). However, many of these studies used early generation HCV antibody testing methods with sub-optimal specificity. A recent population-based study of HCV prevalence in the United States, which utilised third generation HCV antibody testing, demonstrated a HCV RNA positive rate of 75% among those testing HCV antibody positive (Alter 1999).

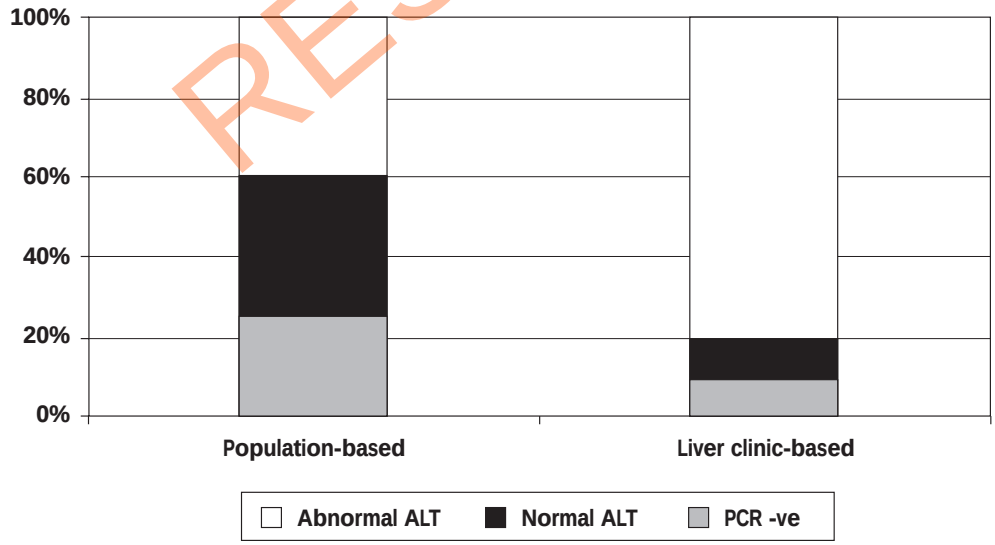
Among population groups at higher risk, such as people who inject drugs, recipients of blood products before the introduction of HCV screening, and people with acute hepatitis, false positive results on HCV antibody testing should be less common than among general population groups. Thus estimates of chronic HCV infection based on HCV RNA detection within these groups may provide a more valid assessment. In a study of HCV antibody positive Italian injecting drug users, at baseline 56% (106/189) were HCV RNA positive on PCR testing (Pirisi 1998). However, during follow-up a significant number of those initially HCV RNA negative became HCV RNA positive on re-testing (Pirisi 1998). Explanations for this phenomenon could include low sensitivity PCR testing, possibly related to low-level HCV viraemia, or re-infection with HCV related to the high risk of re-exposure among people who inject drugs.

People with normal liver function tests

Some important natural history aspects of HCV are the proportion of people with chronic HCV infection who have normal LFTs, the extent of fluctuation in LFTs among those with initially normal levels, and the risk of progression to advanced liver disease for this group.

The proportion of people with chronic HCV infection who have normal LFTs depends on the selection of the study population. Those studies based on liver clinic populations have relatively low proportions of people with normal LFTs, as an abnormal LFT is often the predominant reason for referral. In contrast, population-based studies provide a more valid assessment of this proportion as they lack the referral or selection bias of liver clinic-based studies (Figure 2). In a large cohort of women infected with HCV through contaminated anti-D immune globulin injections, 45% of those with chronic HCV infection had normal alanine aminotransferase (ALT) levels approximately 18 years after infection (Kenny-Walsh 1999). Among the Melbourne cohort of people hospitalised for acute hepatitis during 1971 to 1975, 31% (16/51) of those with chronic HCV infection had normal ALT levels when assessed at least 24 years after infection (Rodger, personal communication). However, another population-based study among people who inject drugs in the Unites States found a considerable proportion of those with initially normal ALT levels had intermittently abnormal ALT levels during a two-year follow-up period (Inglesby 1999).

Figure 2. Selection bias among liver clinic populations



Although people with chronic HCV infection and initially normal ALT levels can develop abnormal LFTs, these fluctuations are often transient and relatively low-level abnormalities (Pritchard-Jones 1999). Furthermore, despite reports of advanced liver disease in people with chronic HCV infection and normal LFTs (Puoti 1999, Healey 1995), most studies show mild–moderate changes (Mathurin 1998, Coltori 1995, Naito 1994, Montalto 1997, Shindo 1995), and the overall progression rate among this group appears to be considerably lower (Mathurin 1998). The vast majority of people with normal LFTs, in particular those with persisting normal LFTs, would appear to be at low risk of long-term complications of chronic HCV infection.

Progression to cirrhosis among people with chronic HCV infection

Although studies have demonstrated significant reduction in quality of life for people with chronic HCV infection before development of advanced liver disease, the major morbidity associated with HCV infection is acquired through progression to cirrhosis and subsequent liver failure and/or hepatocellular cancer (HCC). However, the rate of progression to cirrhosis, the proportion of people with chronic HCV infection who will eventually develop cirrhosis, and the factors that predict progression need further analysis.

Cross-sectional liver clinic based studies

The extent of advanced liver disease among people with chronic HCV infection varies widely, even in studies based in liver clinics. In Australia, three studies among people with chronic HCV infection undergoing liver biopsy demonstrated a prevalence of cirrhosis above 30% in two (Strasser 1995, Li 1997), and less than 10% in one (Roberts 1993). A French study involving more than 2000 people with chronic HCV infection who had undergone liver biopsy in a network of liver clinics estimated (based on estimations of duration of HCV infection) a median duration of HCV infection for progression to cirrhosis of 30 years (Poynard 1997). Other estimates included progression to cirrhosis of 33%, 50% and 60% by 20, 30 and 40 years of infection, respectively. Based on these analyses, one might expect the majority of people with chronic HCV infection to develop advanced liver disease. Although factors such as age distribution (and therefore duration of HCV infection) may have varied between these studies based in liver clinics, the most likely explanation for the contrasting findings is the referral patterns for the liver clinics. Studies based in liver clinics that report a high prevalence of cirrhosis are likely to have significant selection bias, given that clinics are referred patients with both more advanced liver disease and more rapidly progressive liver disease. These studies are therefore unlikely to represent the natural history of chronic hepatitis C at a population level.

Population-based studies

There have been relatively few population-based studies of the natural history of chronic HCV infection, however, the picture emerging from these studies is a considerable contrast to that of liver clinic series. Progression to advanced liver disease has been assessed in two cohorts of women HCV-infected through contaminated anti-D immune globulin during 1977 to 1978 in Germany and Ireland (Muller 1996, Kenny-Walsh 1999). The Irish cohort, in which more than 90% of women found to have chronic HCV

infection underwent liver biopsy, demonstrated a cirrhosis prevalence of only 2% after 18 years of HCV infection (Kenny-Walsh 1999). Furthermore, more than 80% of women had relatively mild disease on liver biopsy, with no or minimal fibrosis.

Explanations for this apparently more benign course of chronic HCV infection could include: (i) infection with a strain of HCV of low virulence (as all women were infected with a single strain); (ii) gender (as some studies have demonstrated slower progression rates among women); or (iii) a low level of other cofactors for progression, such as alcohol. However, all women were infected with HCV genotype 1b, which in some studies has been linked with more rapid progression to advanced liver disease than other genotypes, and there was no evidence of lower alcohol intake than in the general population. In fact, heavy alcohol intake was present as a probable cofactor in five of the seven women with biopsy proven cirrhosis (Kenny-Walsh 1999). Another explanation for the natural history within this cohort is that other studies such as liver clinic-based series, through considerable referral bias (Figure 2), concentrate on the more progressive and/or advanced end of the HCV-related disease spectrum, and that the true natural history of chronic HCV infection is very slowly progressive with the majority of people, possibly the vast majority, not progressing to advanced liver disease.

Support for a more slowly progressive disease course in chronic HCV infection comes from other population-based studies. Among the Melbourne cohort hospitalised with acute hepatitis in 1971–1975, the prevalence of clinical cirrhosis among those with chronic HCV infection was only 6% after 24 years of infection (Rodger 1999). Although more complete liver biopsy-based assessment may have revealed a higher prevalence of cirrhosis in this study, several studies among blood donors found to be HCV antibody positive also provide an estimate of progression to cirrhosis of 5–10% at approximately 20 years infection (Alberti 1991, Esteban 1991, Irving 1994, Alter 1997). One study in which the estimated median duration of HCV infection was 18 years, the same as the Irish anti-D immune globulin infected cohort, demonstrated a spectrum of liver disease almost identical to that of the Irish cohort, with approximately 80% having no or minimal fibrosis (Figure 3, next page).

Modelling progression to cirrhosis

Based on an analysis of these and other chronic HCV infection natural history studies, an estimate of 7–8% cirrhosis at 20 years of infection would appear reasonable. If further assumptions are made—that there is effectively no development of cirrhosis within five years of infection, and progression to cirrhosis thereafter is linear—then an estimate of approximately 20% cirrhosis prevalence is reached by 40 years of infection (Figure 4, next page). As virtually no longitudinal studies have been conducted with follow-up beyond 25 years, the estimates of progression to cirrhosis during the third and fourth decade of chronic HCV infection are far less reliable than that for 20 years. Rather than a linear rate of progression, an accelerated progression rate may be experienced beyond 20 years, while the alternative of a slowing of progression is also feasible (Figure 4). The

one study of long-term assessment of chronic HCV infection, demonstrated a cirrhosis prevalence of 12% at least 40 years following initial infection (Seeff 2000). However, this figure from a study of United States army recruits found to be HCV-infected on retrospective testing of stored serum from the 1950s is based on liver biopsy assessment of only 17 people.

Figure 3. Stage of liver disease in population-based cohort

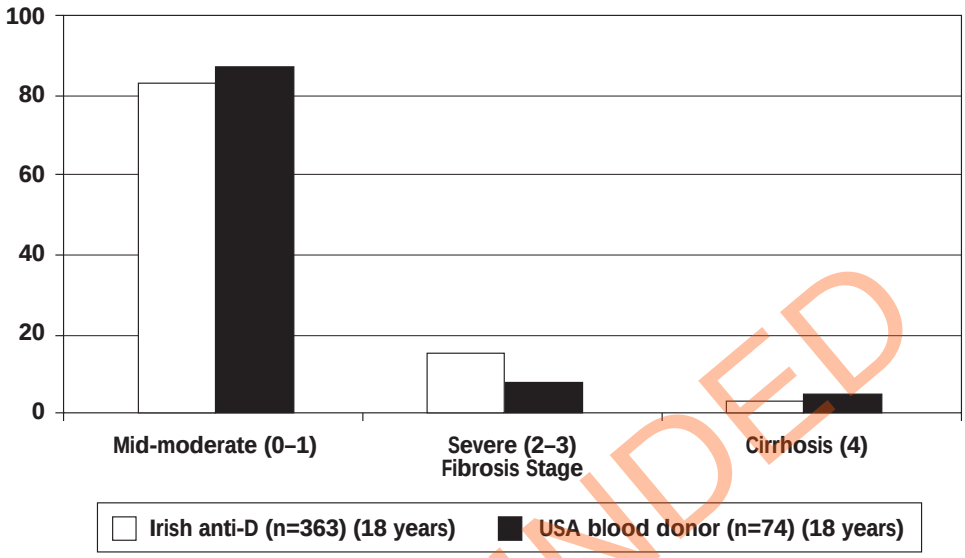
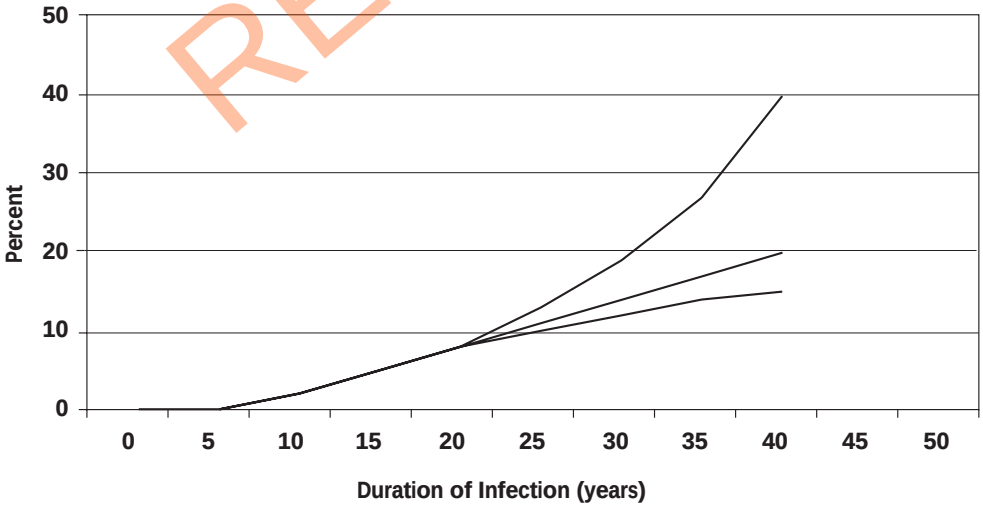


Figure 4. Estimates of progression to cirrhosis



Predictors of progression to cirrhosis

The course of liver disease in people with chronic hepatitis C is highly variable. While the majority of people will have either non-progressive or slowly progressive liver disease, a proportion of people (possibly 10%) will have relatively rapid liver disease progression with the development of cirrhosis in the first or second decade of infection. The elucidation of factors that predict more rapid liver disease progression could assist in targeting people for therapeutic intervention.

Possible factors that may influence progression to advanced liver disease include virus related (dose of initial inoculum, viral load, genotype and degree of viral diversity (quasi-species)), host related (age, race, sex), and other (alcohol, viral co-infection, environmental) (Seeff 1997).

There is conflicting evidence regarding the relationship between progression risk and mode of acquisition and/or dose of initial HCV inoculum. Some studies demonstrate more rapid progression among people with HCV infection acquired through transfusion of contaminated blood products (Roudot-Thoravat 1997). One possible explanation is the higher initial HCV inoculum relative to other modes of transmission. However, alternative explanations for variable progression rates include different age distribution and other host-related factors.

There is a clear relationship between HIV-1 viral load and rate of progression to advanced HIV-1 disease. In contrast, although some studies have demonstrated higher HCV viral load at more advanced HCV disease stages (Hagiwara 1993, Romeo 1996, Tassopoulos 1998), others have shown no correlation between HCV viral load and disease stage (Serfaty 1997, Wiley 1998, Bellentani 1999). Furthermore, no longitudinal studies have examined the relationship between baseline HCV viral load and subsequent risk of progression. Although HCV viral load does not currently appear to have a prognostic role in disease progression, in combination with HCV genotype it provides valuable information on likely response to antiviral therapy (Poynard 1998, McHutchison 1998).

The role of HCV genotype in predicting risk of progression is also unclear. Some studies have demonstrated a higher risk of advanced disease complications, in particular HCC, among people with genotype 1b (Silini 1996, Kobayashi 1996). However, this relationship may be confounded by duration of HCV infection, as in several settings people with genotype 1 have a longer estimated duration of infection (Simmonds 1999), and other studies have shown no relationship between HCV genotype and progression to advanced liver disease (Romeo 1996, Benvegnu 1997). Although genotype 1 may not be more pathogenic than other genotypes, people infected with this genotype (and genotype 4) clearly have a poorer response to antiviral therapy, including combination interferon and ribavirin therapy (Poynard 1998, McHutchison 1998).

Two factors that do appear to have a clear relationship with risk of progression are age at infection and alcohol intake. Although cross-sectional, a study by Poynard et al.

demonstrated a relatively linear relationship between age at infection and rate of progression to advanced liver disease, with those infected at an age older than 40 years having a rate more than double that of the group infected before 20 years (Poynard 1997). An Australian study has also demonstrated an independent relationship between higher risk of cirrhosis and older age of infection (Ostapowicz 1998).

Several studies have demonstrated an increased risk of advanced liver disease with heavy alcohol intake (Poynard 1997, Roudot-Thoravat 1997, Serfaty 1997, Wiley 1998, Bellentani 1999), including recent studies from Sydney (Khan 1998) and Melbourne (Ostapowicz 1998). Although an alcohol level of more than 10 grams/day is associated with increased HCV RNA load and ALT levels (Schiff 1997), most studies only demonstrate increased risk of progression to advanced liver disease associated with levels above 40 to 50 grams/day. Further research is required to determine the level of risk associated with lower levels of alcohol intake, and patterns of drinking (e.g. regular moderate versus sporadic high intake).

A large French study has demonstrated an apparently lower risk of cirrhosis among women, following adjustment for other factors such as alcohol intake, mode of transmission, and duration of HCV infection (Poynard 1997).

Chronic HCV infection, even when it does progress to advanced liver disease, does so slowly, with passage through stages of fibrosis severity prior to cirrhosis. These stages of fibrosis development are peri-portal fibrosis (stage 1), and linkage or bridging fibrosis (stages 2–3), with cirrhosis generally classified as stage 4 fibrosis (Desmet 1994). Based on studies in liver clinics, the estimated median rate of progression among people with chronic HCV infection and evidence of fibrosis is 0.13 units/year (Poynard 1997). Thus, on average it takes 7–8 years to progress from one stage of fibrosis to the next. Obviously, there is variability within this median progression rate, related to viral and host cofactors. However, the risk of progression to cirrhosis is clearly higher among people who have already progressed to stage 2–3 fibrosis (Poynard 1997, Yano 1996, Roudot-Thoravat 1997, Niederau 1998). A recent prospective Sydney study has also demonstrated a marked contrast in progression to advanced liver disease based on baseline liver biopsy fibrosis stage (Khan 2000).

There is clear evidence that co-infection with either HIV (Sanchez-Quijano 1995, Soto 1997, Telfer 1994, Eyster 1993), or chronic HBV infection (Alberti 1995) increases the progression rate to advanced liver disease. Co-infection with chronic HBV also considerably increases the risk of developing HCC (Benvegnu 1994, Chiba 1996, Tsai 1994). Fortunately in Australia, largely due to the low prevalence of HIV among people who have injected drugs, only an estimated 1% of people with chronic HCV infection are co-infected with HIV (Dore 1998). The co-infection rate with chronic HBV infection is also likely to be low due to the relatively small proportion of people infected with HBV who progress to chronic HBV infection (approximately 5%).

Possible cofactors for progression to advanced liver disease, and the strength of evidence for these cofactors are summarised in Table 2.

Table 2. Predictors of progression to advanced liver disease among people with chronic HCV infection

Strong evidence	*Some evidence*	*Not fully assessed*
Alcohol	Genotype	HCV viral load
Stage of fibrosis	Mode of acquisition	
Age at infection	Gender	
Duration of infection		
Co-infection with HIV		
Co-infection with chronic HBV		

Liver failure and hepatocellular carcinoma among people with HCV-related cirrhosis

Progression to cirrhosis, as an advanced disease complication of chronic HCV infection, generally occurs over decades in those people who have progressive disease. Neither is progression to liver failure and/or HCC among people with HCV-related cirrhosis generally rapid in the majority of cases. Table 3 outlines progression rates in cohorts of people with HCV-related cirrhosis from Europe and the United States. Based on these studies, more than 80% of people with HCV-related cirrhosis will survive for longer than five years, and HCC risk appears to be 1–3%/year (Fattovich 1997, Bruno 1997, Gordon 1998, Hu 1999, Serfaty 1998). The rate of progression to HCC in Japanese studies appears to be considerably higher (Takahashi 1993, Yousuf 1992), although the reasons for this disparity are unclear.

Table 3. Mortality and hepatocellular carcinoma incidence among people with HCV-related cirrhosis

Study	*5 year survival*	*10 year survival*	*HCC incidence/year*
Fattovich 1997 Europe (n=384)	91%	79%	1.4%
Bruno 1997 Italy (n=163)			2.2%
Gordon 1998 USA (n=173)			1.2%
Hu 1999 USA (n=112)	83%		2.0%
Serfaty 1998 France (n=103)	84% (4 year)		3.3%

A significant proportion, possibly 30% (Fattovich 1997), of people with HCV-related cirrhosis will die from non-HCV related causes. This is due to a combination of the advanced age of many people who have progressed to cirrhosis, and the presence of other underlying medical conditions (in particular for those with post-transfusion chronic HCV infection).

Although interferon monotherapy had extremely poor efficacy among people with compensated cirrhosis, and was contraindicated in decompensated cirrhosis, recent trials of combination interferon and ribavirin suggest that the response rate may be considerably improved (Poynard 1998, McHutchison 1998). Even with a response rate lower than for people with earlier stage disease, people who have progressed to cirrhosis are obviously at the highest risk of progression to liver failure and/or HCC and therefore have the most to gain from a favourable response to therapy.

Summary

Based on this analysis of the current literature on the natural history of HCV infection, the following estimates can be made:

- 65–85% of people with HCV infection will progress to chronic HCV infection;
- among people with chronic HCV infection, 5–10% will progress to cirrhosis by 20 years of infection, and possibly 20% by 40 years of infection;
- progression to cirrhosis is more likely in people with heavy alcohol intake, co-infection with HIV and chronic HBV infection, and those who already have moderate–severe fibrosis on liver biopsy;
- progression to cirrhosis would appear to be unlikely in those with repeatedly normal LFTs;
- 80–90% of people with HCV-related cirrhosis will survive more than five years;
- risk of HCC is 1–3%/year among people with HCV-related cirrhosis.

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Occupational Exposure to Hepatitis C in Health Care Settings

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Contents

Introduction

National monitoring of occupational exposure to hepatitis C virus (HCV), hepatitis B virus (HBV) and HIV infection among health care workers commenced in Australia in 1995. Specifically, the project aims to:

1. measure the extent of percutaneous and non-percutaneous occupational exposure to blood and body fluids among health care workers;
2. monitor the circumstances of occupational exposures to blood and body fluids among health care workers in Australia;
3. monitor occupational exposure to HIV, HBV and HCV infection;
4. describe the use of post-exposure prophylaxis for HIV infection; and
5. measure the risk of transmission following exposure to HIV, HBV and HCV.

This report summarises the information recorded by participating sites from July 1995 to December 1998 about transmission of HCV infection.

Methodological comment

A network of hospitals has provided State, Territory and national coordinators with biannual reports from July 1995 to December 1997, and annual reports in 1998, about routinely collected information on cases of occupational exposure to blood or body fluids.

Exposures included percutaneous injuries with a device previously in contact with another person's blood or other body fluids, or blood or body fluid contact with the eyes, mouth or skin.

Information was collected on the type and circumstances of exposures and the HIV, HBV and HCV infection status of the source patient and the health care worker at the time of the exposure. Infection status of the health care worker in regard to the three viruses at three months after exposure is also reported. In addition, information is collected on the number of hospital beds occupied during the study period and the average number of full-time equivalent staff employed at participating sites.

Exposure rates were calculated by dividing the number of exposures reported during the twelve-month period by the number of hospital beds occupied per day and also by the number of full-time equivalent staff employed.

Results

The number of sites providing information on the characteristics of occupational exposures to blood or body fluids increased from 13 sites in 1995 to 56 sites in 1997, then declined to 29 sites in 1998. The average daily bed occupancy for reporting sites declined from 303 in 1995 to 235 in 1998 (Table 1).

Table 1. Site characteristics

	Number of participating hospitals			
Type of hospital	**1995***	**1996**	**1997**	**1998**
Teaching	6	6	17	11
Referral	3	7	9	7
District / Community	2	6	17	3
Private	2	8	13	8
Total	13	27	56	29
Average daily bed occupancy (all sites)	303	237	253	235

* Information was only recorded for six months from July to December in 1995

Rate of exposure

There were 532 exposures reported in 1995 (82% percutaneous), 1572 in 1996 (82% percutaneous), 3092 in 1997 (83% percutaneous) and 1717 in 1998 (88% percutaneous). The rate of health care worker exposures per 100 daily occupied beds gradually declined from 29 in 1995 to 22 in 1997 (Table 2). In 1998, the rate increased to 25 per 100 daily occupied beds, however, when analysis was restricted to the 25 sites that participated in both 1997 and 1998, there was no difference between 1997 (25.4) and 1998 (25.6).

Table 2. Rate of occupational exposure to blood or body fluids among health care workers per 100 daily occupied beds by year and type of exposure

Type of exposure	*1995* Exposures/100 daily occupied beds*	*1996 Exposures/100 daily occupied beds*	*1997 Exposures/100 daily occupied beds*	*1998 Exposures/100 daily occupied beds*
Percutaneous	23.8	20.8	18.1	22.2
Hollow bore needles	14.2	12.9	10.6	13.0
Other percutaneous	9.6	7.9	7.5	9.1
Non-percutaneous	5.4	4.7	3.7	3.1
Total	29.2	25.5	21.8	25.2

* Rate of exposure per 100 daily occupied beds over 12 months.

Circumstances of exposures

Most exposures were reported by nursing staff (Figure 1). In 1998, the most frequently reported exposures were hollow bore needle exposures to blood (41%) or other body fluids (31%) and splash exposures to the eye (9%) (Figure 2).

Figure 1. Staff reporting occupational exposures

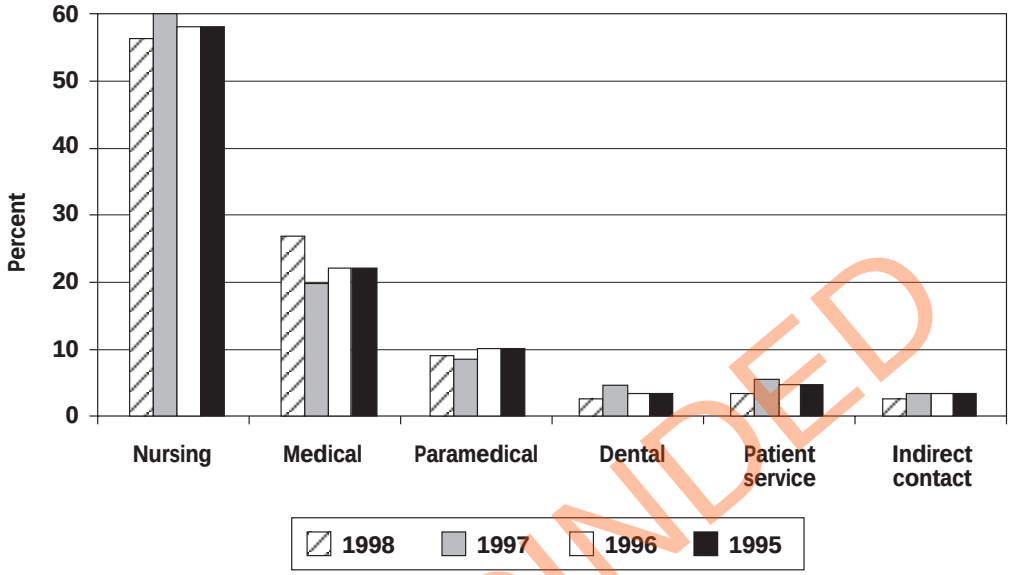
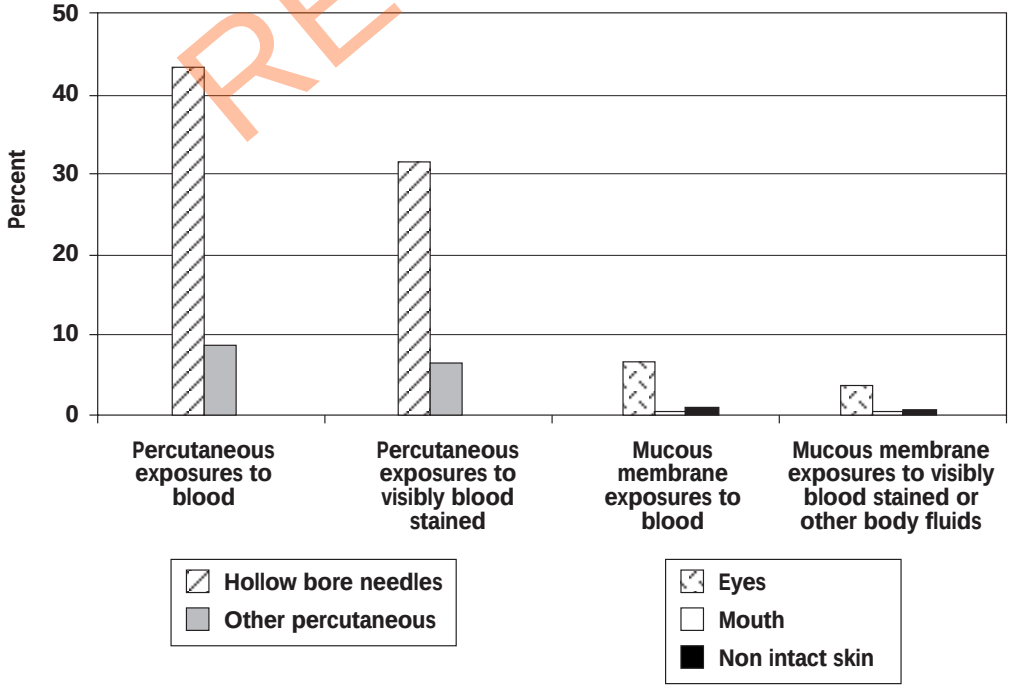


Figure 2. Occupational exposures reported in 1998 among health care workers by type of exposure and body fluid



Over the period 1995–1998, syringe needles (40%–46%) and suture needles (12%–17%) were the most frequently reported devices causing percutaneous exposures. Intravenous and intra-arterial access (21%–25%), intramuscular and subcutaneous injection (20%–23%) and suturing (11%–18%) were the most frequently reported purposes for devices attributed to percutaneous exposure.

HCV infection among exposed health care workers

The proportion of health care workers reported as tested for HCV antibody following occupational exposure to blood and body fluids declined from 1997 (70%) to 1998 (56%). HCV antibody prevalence among tested health care workers remained around 1% in all years (Table 3).

Table 3. Prevalence (%) of HCV antibody among health care workers (HCWs) tested within seven days of exposure

Year	*Number of HCWs tested (%)*	*% HCWs with anti-HCV*
1995*	394 (74%)	1.5
1996	1097 (70%)	0.8
1997	2165 (70%)	0.9
1998	962 (56%)	0.8

* Information was only recorded for six months from July to December in 1995

Exposures to source with HCV infection

The proportion of source patients tested for HCV antibody steadily increased from approximately one third in 1995 to three quarters in 1998. Prevalence of HCV antibody among source patients tested following percutaneous exposure to health care workers remained stable at around 5% from 1995 to 1998 (Table 4). In all years, HCV prevalence was significantly higher among source patients tested following non-percutaneous exposures to health care workers than among those tested following hollow bore needle or other percutaneous exposures ($p<0.001$).

Table 4. Prevalence (%) of HCV antibody among source patients tested following HCW exposure by year and type of exposure

Year	*Percutaneous*		*Non-percutaneous*	
	Number of source patients tested (%)	*% source patients with anti-HCV*	*Number of source patients tested (%)*	*% source patients with anti-HCV*
1995*	149 (34%)	6.0	44 (45%)	32
1996	646 (50%)	4.3	127 (44%)	11
1997	1520 (59%)	4.1	351 (67%)	11
1998	1158 (77%)	5.2	175 (84%)	22

* Information was only recorded for six months from July to December in 1995

Follow-up for seroconversion to HCV infection among health care workers

No health care workers were reported as seroconverting to HCV infection at three months post-exposure, however, in general, testing rates were low. Testing rates ranged from 17% to 68% per year among health care workers eligible for follow-up after exposure to a source patient with HCV antibody and from 13% to 51% among health care workers eligible for follow-up after exposure to a source patient whose HCV antibody status was not known. In each year, reported testing rates varied inconsistently according to the type of exposure and the serological status of the source patient (Table 5).

Table 5. Number of health care workers (%) tested for HCV antibody three months following exposure to blood or body fluids by year, source serostatus and type of exposure

Source serostatus/ Type of exposure	*1995 **	*1996*	*1997*	*1998*
HCV antibody positive				
Percutaneous	3 (38%)	3 (13%)	40 (77%)	24 (56%)
Non-percutaneous	6 (60%)	2 (23%)	16 (53%)	8 (35%)
Unknown HCV status				
Percutaneous	33 (16%)	82 (14%)	343 (42%)	162 (52%)
Non-percutaneous	8 (21%)	11 (7%)	55 (40%)	16 (43%)

* Information was only recorded for six months from July to December in 1995

Discussion

This project documents ongoing exposure to HCV infection among health care workers in Australia. No health care workers were reported as acquiring HCV infection in the workplace since monitoring began in 1995, however, reported testing rates at three months post-exposure were low. The annual rate of exposure to hollow bore needles and other percutaneous devices declined from July 1995 to December 1997 and remained stable from 1997 to 1998.

The annual rate of non-percutaneous exposures has gradually declined since monitoring commenced. Blood contact to the eye was the most frequently reported non-percutaneous exposure. Globally, there have been three case reports of HCV infection acquired following conjunctival blood splash: two in health care workers (Sartori et al. 1993, Ippolito et al. 1998), the other in a prison worker (Rosen 1997).

Prevalence of HCV infection in all reporting periods was much higher among source patients tested following non-percutaneous exposures to health care workers than among source patients tested following percutaneous exposure. HCV prevalence among source patients tested following percutaneous exposures was also higher than prevalence reported among antenatal patients in Australia (0.4%, 3% and 1.1% in 1989 (Fairley et al. 1990), 1990 (Williamson et al. 1990), and 1995 (Garner et al. 1997) respectively) but not higher than prevalence reported among renal transplants, dialysis patients or people with haemophilia (6%, 7% and 76% in 1989, 1989 and 1987 to 1989 respectively (Williamson et al. 1990). It is likely, therefore, that health care workers were more likely to report exposures, in particular non-percutaneous exposures, if the source was known to have HCV infection or if the source reported known risk factors for HCV infection

The estimated risk of HCV transmission is substantially higher than the risk of HIV transmission following percutaneous exposure to infected blood (Table 6). In cases where the source patient had detectable hepatitis C viraemia, the risk of transmission was estimated to be 6.1% (95% confidence interval 2.2%, 10.0%) (Dore et al. 1997). However, among ten studies of HCV transmission to health care workers following needle stick injury from a source with HCV antibody, the estimated risk of transmission was lower at 1.9% (range, 0–9%)(Crofts et al. 1999).

Table 6. Hepatitis C virus transmission to health care workers following percutaneous injury from a source with HCV RNA

Country	*Source with HCV RNA*	*Nº sero-conversions (%)*	*95% CI*	*Source without HCV RNA*	*Nº sero-conversions (%)*	*95% CI*	*Reference*
Japan	80	2 (2.5)	0.3, 9	10	0	0, 31	Sodeyama et al. 1993
Japan	68	7 (10.3)	4.3, 21	8	0	0, 37	Mitsui et al. 1992
Spain	29*	1 (3.4)	0.1, 18	13*	0	0, 25	Perez Trallero et al. 1994

*All source with HIV antibody

There is limited information on occupationally acquired HCV infection among health care workers in Australia. Two national surveillance systems collect information on the occurrence of newly acquired and prevalent HCV infection. The National Notifiable Diseases Surveillance System (NNDSS) receives case reports according to age, sex, and postcode from State and Territory health departments. Incident cases are not systematically identified and no exposure information is collected in this system. Consequently, the relative contributions of risk factors in the transmission of HCV in Australia cannot be ascertained from NNDSS data at this stage.

There is also the Communicable Diseases Intelligence Laboratory Reporting Scheme, which receives reports of laboratory diagnoses from sentinel laboratories according to age, sex, postcode, outcome and method of diagnosis. In 1995, enhanced surveillance for incident HCV cases was undertaken through NNDSS. There were 138 incident HCV cases identified through enhanced surveillance, of which two (1.4%) were attributed to needlestick injury among cases without a history of injecting drug use (Andrews and Curran 1996). In Brisbane, seven of 33 health care workers referred to a HCV clinic between 1990 and 1994 were thought to have occupationally acquired infection (Cooksley et al. 1996).

No cases of occupationally acquired infection were documented in our study. The rate of seroconversion in our study, however, is limited by the low rate of serological test results reported at three months post-exposure. It might be that health care workers who sustain a significant exposure seek care outside the reporting institution to maintain confidentiality. It is also likely that testing is carried out at three months post-exposure but is not reported to the project. In addition, estimates of the extent of infection in our study are limited by under-reporting of exposures by hospital staff. Obtaining an estimate of the rate of under-reporting is logistically difficult. Infection control and occupational health and safety practitioners surveyed in 1992 estimated that from 5% to 70% of exposures (median 25%) were not reported (MacDonald et al 1995).

Table 7. Expected cases of HCV among health care workers in Australia according to HCV RNA and HCV antibody prevalence among source patients

HCV prevalence among source patients	*Expected cases of HCV among health care workers in Australia (1998)*	
	*Assuming 6% risk of HCV transmission from source with HCV RNA**	*Assuming 2% risk of HCV transmission risk from source with HCV antibody**
1%	6–7	2–3
2.5%	15–18	6–8
5%	30–35	12–16

* Range from 20 exposures/100 DOB to 25 exposures/100 DOB

Note: Based on a total of 22 565 356 patient days per year (AIHW 1999).

Table 7 provides a range of estimated cases of HCV transmission following percutaneous exposure to health care workers that could have been expected in 1998. Based on HCV prevalence of 5% among source patients tested following percutaneous exposure, 6% transmission risk of HCV and assuming 75% would have HCV RNA, up to 35 cases of HCV transmission could have been expected in 1998. Health care workers may be more likely to report exposures if the source patient is known to have HCV infection or has risk factors for blood-borne viral infection. Calculations based on a prevalence of 1% among the patient population, consistent with the estimated adult HCV prevalence in Australia (Australian National Council on AIDS and Related Diseases Hepatitis C Sub-Committee 1998) should provide a reasonable lower bound to these estimates. The true HCV prevalence of the Australian patient population is likely to be somewhere between these two figures. A patient population HCV prevalence of 2.5% would have be expected to produce 6–18 cases of HCV transmission to health care workers in 1998, based on a level of transmission of between 2% (from HCV antibody positive patients) and 6% (from HCV RNA positive patients).

In France, over five years from 1993 to 1997, there were 33 cases of documented occupationally acquired HCV infection identified among health care workers. Most infections followed percutaneous exposures (29 cases), in particular exposure to a hollow bore needle used for venipuncture (17 cases). Other exposures included hypodermic needle (two cases), suture needle (one case), sharp items (two cases), cutaneous exposure to non-intact skin (one case) and for ten cases the information was not known (Domart et al. 1999).

Prevalence of HCV among health care workers tested following occupational exposure to blood and body fluid in our study was consistent with estimates of population prevalence in Australia (Australian National Council on AIDS and Related Diseases Hepatitis C Sub-Committee 1998). Globally there have been two reports of HCV infection transmitted from health care worker to patients, both involving surgeons. The first was reported from England (Anonymous 1995). The second involved a cardiac surgeon in Spain who infected five patients between 1994 and 1998. The surgeon reported an overall incidence of 20 percutaneous injuries per 100 procedures, but the commonest injury, and

the one thought to have been involved in HCV transmission, occurred during the procedure of tying the wires during closure of the sternum (Esteban et al. 1996).

Transmission of HCV infection in the health care setting can occur from patient to patient, from health care workers to patient and from patient to health care worker. Transmission of HCV infection to patients in a surgical setting has been reported from an Australian hospital (Chant et al. 1994). Following routine notification of two patients who presented with acute hepatitis C infection after undergoing minor surgical procedures in the same operating session, antibody screening and genotyping showed that five patients who had undergone surgery during the session were infected with the same genotype (genotype 1). The actual path of transmission was not determined.

Transmission to patients has also been reported from haemodialysis units. Cross-sectional surveys of haemodialysis patients without history of blood transfusion have found HCV prevalence of 7% (Yamaguchi et al. 1994) and 18% (Dussol et al. 1995). Isolation of patients with HCV antibody into a separate area reduced the incidence of HCV infection in one unit (Calabrese 1995).

The risk of transmission depends on the likelihood of transmission per blood contact, the prevalence of infection in the patient population and the frequency of blood contact. Reducing the frequency of blood contact will prevent transmission of HCV infection. Identifying risk factors for exposure provides policy makers with information to effect change in preventable workplace practices that predispose health care workers and patients to the risk of exposure.

There have been five reported cases in Australia of health care workers who acquired HIV infection in the workplace (NCHECR 1999), however, there is little information about health care workers who have acquired HCV infection in Australian workplaces. Over the past twelve months the database used for collecting information on national monitoring of occupational exposure to blood and body fluids has been revised. When completed, it is expected that data collection on serological results at three months post-exposure will improve and the number of reporting sites will also increase. Improved reporting of occupational exposures by health care workers and of serological results at three months post-exposure will markedly improve monitoring of occupational exposures to blood-borne viruses and occupationally acquired HIV, HBV or HCV infection in Australian hospitals.

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Hepatitis C and Discrimination

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Contents

Acknowledgment

This paper has drawn from the paper: ‘A literature review investigating discrimination based on injecting drug use and/or perceived or real HIV/HCV’ by Tenille Fort of the HIV/AIDS & Hepatitis C Section, Population Health Division, Commonwealth Department of Health and Aged Care, 1998.

I stress the responsibility of people in the health care system itself to take a lead in the elimination of discrimination against people with hepatitis C. It is a sad fact that many people do not present for treatment, or receive inadequate treatment because they are intimidated by the attitude of the medical profession towards them. It is not the role of that or any other profession to be judgmental, but rather to act in accordance with the best standards and principles of their profession, treating people as human beings with the need for medical attention and rendering it accordingly (Puplick 1998:228).

Introduction

The aims of this paper are to describe what constitutes hepatitis C-related discrimination, and to map the extent to which it occurs, who is affected by it, remedies that currently exist to address it, and their effectiveness.

The extent of hepatitis C-related discrimination is not comprehensively researched or documented in Australia. Anecdotal evidence suggests that individual discrimination occurs in a variety of forms, and including the avoidance of people with hepatitis C, calls for universal testing of the population and the isolation of people with hepatitis C, and stigmatisation of those infected. Many examples of individual discrimination have been lodged with the NSW Anti-Discrimination Board. Institutional and societal discrimination primarily manifest in two areas:

- policies and practices related to contagion fears and the possibility of transmission (for example, recruitment procedures and occupational health and safety policies and practices); and
- policies and practices related to fears about perceived deviant behaviour and their impact on the broader community (for example, injecting equipment in prisons and bans by education authorities on publications related to communicable diseases and injecting drug use).

Three recent studies highlight the existence of such discrimination:

- *Meeting the needs of people in Australia living with hepatitis C.* (1996) Dave Burrows and Bronwyn Bassett, National Hepatitis C Councils Education Reference Group.
- *Hepatitis C: The Neglected Epidemic—Inquiry into Hepatitis C in New South Wales.* (1998) Parliament of New South Wales Legislative Council Standing Committee on Social Issues.
- *Barriers to access and effective use of anti-discrimination remedies for people living with HIV and HCV.* (1999) Julia Cabassi, AIDS Council of New South Wales (unpublished).

These studies demonstrate that for people with hepatitis C, their carers and friends, discrimination is commonplace, occurring in a variety of settings, including the provision of goods and services, health care services, accommodation, employment, and education. However, discrimination is one of the least understood outcomes of hepatitis C infection. The lack of effective mechanisms to redress discrimination across all jurisdictions in Australia, and barriers to gaining access to these remedies, mean existing mechanisms are not well utilised.

Hepatitis C prevalence in the Australian population is estimated to be slightly more than one per cent, or 150 000 to 200 000 Australians, with 91 per cent of all new infections occurring among people who inject drugs (Cregan 1998). The estimated proportion of the population infected with hepatitis C depends on the sampling method used. Duration of injecting drug use is a primary factor for infection. Injecting for more than a couple of years increased the prevalence of hepatitis C to more than 80 per cent in one study (Wodak 1996). This is supported by empirical data that reports that the majority of the 11 000 Australians who become infected each year are people who inject drugs (ANCARD Hep C 1998).

As investigations into both the incidence and prevalence of hepatitis C infection in Australia become comprehensive, we can assume that more people will be affected by discrimination, particularly people who inject drugs. Therefore, the discrimination experienced by people affected by hepatitis C warrants serious consideration by governments and then in legislative and educative outcomes that provide legal remedies to address it.

Definitions

Discrimination

Discrimination is broadly defined as:

> *treating one person less favourably than another in similar circumstances. Discrimination does not have to be intentional or conscious. It often results from unconsciously held beliefs and attitudes. Nor does discrimination have to be direct and obvious but may be indirect and quite subtle. Indirect discrimination is when someone imposes a condition which on the face of it is harmless, but which has the effect of adversely affecting a particular person or group (Macquarie Easy Guide to Australian Law).*

Discrimination may be direct, indirect, reactive, proactive, or passive. Elaboration of these terms and examples from the literature reviewed for this paper follow.

Direct discrimination

Direct discrimination means treating a person who is, or is perceived to be, hepatitis C positive, less favourably than a person who does not have hepatitis C, in the same or similar circumstances.

> *All the dentist had to do was pull my tooth, but she refused and sent me to hospital where they wore space suits and treated me like a second class citizen (Burrows and Bassett 1996).*

Indirect discrimination

Indirect discrimination occurs when an unreasonable requirement, condition or practice, which appears to be neutral, has a disproportionately negative impact on people who are living with hepatitis C (Victorian EOC 1996).

Reactive discrimination

Reactive discrimination encompasses most discrimination. It occurs when a person is confronted with someone who is or who is perceived to be a member of a group against which the person holds strong prejudices. Reactive discrimination is not intentional or planned. It is a reaction to a person, situation or to information, which provokes an emotional and irrational response (NSW Anti-Discrimination Board 1992).

> *Discrimination! The anaesthetist when I was having an operation said: 'You've got to pay for your sins'. This was very offensive to me. I told him off. When I was on Interferon the doctor taking the tests said: 'You people' in a terrible way. I walked out. I work with doctors and I hear them saying: 'druggies', 'Don't touch him, he's hep C', 'Don't worry about them, they're just druggies'…(Burrows and Bassett 1996).*

I told a super fund representative in my office that I am planning to retire as soon as possible because I can't be sure of my health. Her reaction was as though I was transferring germs just by talking to her (Burrows and Bassett 1996).

Proactive discrimination

Proactive discrimination, however, is intentional and planned. It is often embodied in policies, procedures and rules that have purposely precluded particular categories of people. Such discrimination is therefore systemic.

I couldn't get my remote area (radiography) licence renewed. The casualty matron said: 'That woman will not lay a hand on a patient in this hospital'. I wanted to keep the permanent part-time job I had, but now I have no work, they refuse to call me (Burrows and Bassett 1996).

Passive discrimination

Passive discrimination is usually assumed to be active as it involves either reacting on the basis of personal characteristics or developing policies or procedures to discriminate against certain people. However, passive discrimination can also occur when the particular needs of particular groups are not met, by the failure to act on their behalf. This is often justified in terms of providing equal treatment for all, but it fails to meet the specific needs of some people (NSW Anti-Discrimination Board 1992).

I was told it was not necessary for me to disclose about my hepatitis C to health services because they should all be taking universal precautions. I did disclose my status to a doctor where I was going for minor surgery, to my detriment. They rang back to say they didn't have the facilities and cancelled the surgery. Then they thanked me for being 'responsible' (Burrows and Bassett 1996).

Related definitions

The HIV/AIDS Anti-Discrimination Campaign defined discrimination as any unfavourable treatment, action or inaction resulting in people being denied full or partial access to services or opportunities because of their known or imputed status (NSW Anti-Discrimination Board 1992). This definition illustrates that discrimination can take many different forms, from easily identifiable overt actions, through less recognisable and covert actions. Individuals may overtly perpetrate these actions, but discrimination may also be expressed in the manner in which services are delivered or denied.

Rotem, et al. (1994) defines discrimination in relation to hepatitis C as:

Any unfavourable treatment on the basis of known or imputed (sero)status; action or inaction that results in persons being denied full or partial access to otherwise generally available services or opportunities, because of known or imputed status (1994:3).

Fear of discrimination

There is another dimension to discrimination that the definitions detailed above fail to address: the fear of discrimination. Fear of discrimination is often an everyday reality for people living with hepatitis C. A major outcome of this fear is social isolation, generally exhibited as separation from family, information, skill-development and support mechanisms.

> *If people found out, it would be very hard to get a job (Burrows and Bassett 1996).*

> *Put it this way: when I go to the dentist, I never put down I've got hepatitis C (Burrows and Bassett 1996).*

> *…it is fear of discrimination, stigma and judgment that stops us going to the local needle exchange program, for fear of recognition. It stops us getting support and assistance from our families and friends because we do not want them to hate us or, worse still, for them to suffer hatred because of our behaviour. It stops us from seeking medical assistance for all sorts of health problems because we fear being labelled as drug seekers (NSW Drug Summit 1999).*

Stigma

Stigma is defined as a mark of shame and discredit, while discrimination is the action or treatment based on stigma. Stigma is a social construction. It has a dramatic impact on the lives of people with hepatitis C, their partners, family and friends. Stigma devalues people and impacts on their quality of life by reducing free and unimpeded social interaction (Alonzo and Reyonds 1995).

Stigma and social construction of illness

Green and Platt (1997) state that stigma is a key variable in the social construction of illness. It functions independently of the physical reality of the condition and is an important aspect of the social experience of the condition.

Stigma and social isolation

Stigma leads to social isolation.

> *You feel really alone. 'It's a very bad thing, but don't worry', they say. You feel alone and like a leper (Burrows and Bassett 1996).*

Stigma and disclosure

To avoid personal liabilities related to stigma, people may conceal their health status. However to maintain a positive sense of self, to preserve their social standing, and to live a full and meaningful life, they may need to challenge societal reactions to their health status. As Goffman (1986:42 in Siegel, Kune and

Meyer 1998) states, 'if a stigmatising condition is not immediately apparent—as is the case with HIV/HCV infection—managing information about it becomes a focal point. To tell or not to tell...to lie or not to lie; and in each case, to whom, how, when and where.' Using proactive strategies, stigmatised people may be exposed to greater risks of experiencing discrimination and social rejection, but this confrontation may ultimately assist in modifying norms and beliefs that may, over time, improve social standing (Siegel, Kune and Meyer 1998).

> *When I finally told my flatmates, I found out they told all their friends and all my friends, who then treated me as if I had the Ebola virus (Hepatitis C Council of Queensland 1998).*

> *There has been a huge breach of confidentiality at work about my condition. The area director said to my manager: 'I hear you have someone with hepatitis C working in your unit'. To this day I don't know how they found out (Burrows and Bassett 1996).*

> *When I first started with (employer) I ended up with a really bad knee bleed that saw me laid up for a week. Nobody said anything, but I felt that there was an undercurrent of hostility. I had to work pretty hard to build up my reputation as an able member of the team. After that disaster I certainly wasn't going to turn around and tell them I had Hepatitis C, I just hope I don't ever need any time off or get really sick (Burrows and Bassett 1996).*

Stigma and health care

Hepatitis C-related stigma is present and must be negotiated in all the social relationships, including those with health professionals, in which people living with hepatitis C are involved. Stigma may have a negative effect on the relationship between people with hepatitis C and caregivers in health care settings, and deter people from seeking health care (Alonzo and Reyonds 1995).

> *As a drug user for 13 years I can tell you that it is stigma and discrimination that has most prevented me and other drug users from making healthy choices (NSW Drug Summit 1999).*

Stigma and injecting drug use

The high degree of stigma attached to hepatitis C can be attributed to the fact that it is predominantly transmitted through injecting drug use. While peer-based user groups and other service providers advocate on behalf of people who inject drugs, the difficulties of challenging societal attitudes are compounded by the lack of support by public health practitioners (Wodak 1996). Obtaining support for some controversial measures necessary to reduce new HIV and AIDS infections was easier (according to Wodak 1996) because the community feared an epidemic stemming from the primary risk behaviours that would reach the general population via sexual transmission. No equivalent fear exists amongst the broader community about the transmission risks of hepatitis C.

Of course people with hepatitis C don't like being treated like junkies. Hell, drug users don't like being treated like junkies (Burrows and Bassett 1996).

It makes you feel like, you know, the leper's bell. Because hepatitis C is not understood by the average person, and those who do know, know just a little bit. Like: 'It's a junkies disease. Who cares? They should shoot the bastards anyway' (Burrows and Bassett 1996).

One major barrier is the tremendous stigma attached to being a drug user or, worse, an addict…the more common view is that drug addicts are weak or bad people, unwilling to lead moral lives and to control their behaviour and gratifications…This stigma, and the underlying moralistic tone, is a significant overlay on all decisions that relate to drug use and drug users (NSW Drug Summit 1999).

Stigma and stress

Whether experienced or fearfully anticipated, stigma appears to be a major source of hepatitis C-related stress. Demas et al. (1995) found that what was especially striking amongst a sample of people who inject drugs was the reported pervasiveness of stigma and the degree to which it was perceived to invade family life and intimate social relationships. People with hepatitis C who inject drugs may be more likely to experience emotional distress because of hepatitis C-related stigma.

Stigma and self-esteem

Stigma leads to decreased self-esteem, where people are held responsible for the stigmatising condition if it is acquired as an adult or able to be concealed (Crocker and Major 1990). These factors are also applicable to people with hepatitis C who inject drugs. When compared with other stigmatising conditions (e.g. HIV/AIDS and mental illness), people are also likely to be held personally responsible for their situation because drug addiction is seen as causing the onset of the condition (Weiner, Perry and Magnusson 1988 in Demas et al. 1995).

When someone gets cancer from smoking, they're treated respectfully in hospital. Whereas with hepatitis C 'you knew that it (injecting drug use) could be dangerous. You deserve what you get'. They want to get you out as quickly as possible (Burrows and Bassett 1996).

The extent of discrimination and stigmatisation

Burrows and Bassett—1996

In March 1996, the Hepatitis C Councils Reference Group (comprising members of Hepatitis C Councils nationally) invited tenders for a National Hepatitis C Education Needs Assessment. In April to June 1996, Dave Burrows and Bronwyn Bassett, the successful tenderers, interviewed 104 people living with hepatitis C either individually or in focus groups, as well as 102 people working with people with hepatitis C. The consultants also collected 73 strategies, plans, reports, articles, educational and information resources related to hepatitis C, which informed their report.

Participants (people with hepatitis C) interviewed believed it was most likely that they were infected through sharing injecting equipment. Fewer participants identified medically acquired routes of transmission such as blood products, blood transfusion or needlestick injuries. A small percentage of respondents believed they were infected through sexual activity or unsterile tattooing procedures. Participants were aged between 18 and 55, and were drawn from all Australian capital cities, and non-metropolitan areas of NSW, Queensland and Tasmania.

The majority of the 104 participants interviewed reported experiencing serious discrimination and stigmatisation. They reported receiving unfair or unequal treatment by employers, health care providers, family, friends, and the general community. They believed the discrimination occurred mainly due to irrational fear of transmission or because they were perceived to be current or past injecting drug users.

Coupled with a diagnosis of hepatitis C, discrimination significantly affected the ability of many participants to work or to continue their careers. For many, this led to major changes and difficulties in their family and social networks, including break-up of relationships.

Participants identified the following measures as necessary to addressing their needs in relation to discrimination:

- legal protection against discrimination;
- access to legal services;
- access to appropriate Social Security benefits;
- access by people with hepatitis C who inject drugs (or are on methadone) to treatments and procedures such as interferon (for current injectors), and liver transplants.

Since Burrows and Bassett produced their report, PBS100 criteria have been extended, but discrimination in accessing treatments is still reported by people who inject drugs.

The report made a number of priority recommendations, including:

1. *Based on the identified education and other needs of people affected by hepatitis C that, as a matter of urgency:*
   - *Appropriate, accurate and non-discriminatory pre- and post-test counselling, and referral to other appropriate counsellors;*
   - *Appropriate, accurate and non-discriminatory information and counselling about a range of treatments including Interferon and complementary therapies (including follow-up of patients who 'fail' Interferon therapy);*
   - *Non-discriminatory medical treatment for ongoing health issues of all people with hepatitis C, including injecting drug users.*

4. *That the Commonwealth Department of Health and Family Services fund Hepatitis C Councils to carry out the following national education programmes (in priority order):*
   - *Carry out a national discrimination project to provide:*
   - *Education about discrimination and an understanding of the needs of people with hepatitis C aimed at social and welfare workers, Department of Social Security and Housing staff, and families and friends of people with hepatitis C;*
   - *Education for doctors and other health care workers to address the issues of discrimination against people with hepatitis C, with particular reference to the links between hepatitis C and injecting drug use: IDU groups should be fully involved in this component of the project;*
   - *Education for people with hepatitis C about the ways that discrimination can be addressed in existing structures, and for Hepatitis C Councils and IDU groups on assisting people with hepatitis C to seek redress for discrimination.*

8. *That the Commonwealth Attorney General's Department:*
   - *Immediately fund the Human Rights and Equal Opportunity Commission to carry out an education programme on the Commonwealth Disability Discrimination Act and its use to redress discrimination;*
   - *Instigate an immediate review of national laws affecting drug use with regard to their effects on enhancing or retarding prevention of infection and re-infection with hepatitis C, as well as on ameliorating the symptoms of people living with hepatitis C.*

The recommendations are reproduced in this report to reinforce the importance of providing legal mechanisms to address discrimination against people with hepatitis C. These must be accompanied by education measures directed at health service providers to assist in providing better service delivery and in reducing stigma against people with hepatitis C in the broader community.

NSW Legislative Council 1998

During its inquiry into hepatitis C in 1998, the NSW Legislative Council's Standing Committee on Social Issues heard considerable evidence on the extent of hepatitis C-related discrimination, particularly in relation to the health care profession (NSW Legislative Council 1998):

> *Incidents reported included discrimination by health care workers (including nurses, general practitioners, medical specialists and dentists), friends of the infected person, and the general community. These distressing circumstances often result in the infected person opting for anonymity in all aspects of life (NSW Legislative Council 1998).*

Crofts, in his evidence to the inquiry, summarised the view that such attitudes, values (and hence practices) about injecting drug users in health care settings were the real underlying cause of discrimination:

> *For many people with hepatitis C, discrimination relating to hepatitis C is actually the least of their problems. Because of the discrimination relating to their injecting drug use status, hepatitis C is just the icing on the cake—double stigmatisation (NSW Legislative Council 1998 116:4).*

As a result of the evidence presented about the extent of discrimination against people with hepatitis C, the inquiry made a number of specific recommendations. The most relevant for the purposes of this paper are as follows:

> ***Recommendation 19**: That NSW Health design and implement an awareness campaign for all those working in the health care system addressing practices, values and attitudes that discriminate against those with Hepatitis C accessing the health care system.*

> ***Recommendation 20**: That the Minister for Health meet with representatives of the various professional colleges (including the Royal College of Surgeons, Royal College of General Practitioners, and Royal College of Nursing) and unions and urge them to support the awareness campaign addressing Hepatitis C related discrimination in the health care system proposed in Recommendation 19.*

> ***Recommendation 21**: That the Attorney-General instruct the Anti-Discrimination Board to conduct an inquiry into discrimination and Hepatitis C in New South Wales. The Committee further recommends that the resultant report of this inquiry be distributed widely to relevant employer and employee organisations, trade unions, education institutions, hospitals and relevant community organisations (such as the Hepatitis C Council of NSW) across the state.*

We endorse these recommendations. It is imperative to raise awareness of the discrimination experienced by people with hepatitis C in both occupational and health settings.

Discrimination and injecting drug use

McConachy and Booker (1994) suggest that some institutions may play an important role in contributing *passively or actively* to hepatitis C-related discrimination, such as health care services, the media and education authorities. It is apparent from our contact in providing services to people with hepatitis C that other government agencies such as departments of social security should be included. As well as contributing to discrimination, these institutions are key stakeholders and as such contribute to decisions on issues affecting people with hepatitis C. This means that rational public health efforts to reduce the impact of hepatitis C, including measures such as needle and syringe programs, may be controversial among some segments of the community (Crofts 1997). This form of discrimination has a serious impact on people who inject drugs.

The stigma and discrimination experienced by people who inject drugs is due, in part, to the association of injecting drug use with perceived deviant behaviour and self-inflicted harm. The behaviour of people who inject drugs is often regarded as perverse, or abnormal. As a result, they often experience infringements of their civil liberties. Negative images of people who inject drugs as dysfunctional, addicted, desperate, unstable and untrustworthy are a constant theme in media and society (McCarthy 1994). The media frequently uses emotive, judgemental language to describe the world of drug use. This makes education and promotion to reduce discrimination against people who inject drugs extremely difficult.

The increased social isolation, stress and generally poorer health of people with hepatitis C, who also inject drugs, makes them more vulnerable to the effects of discrimination (Lawless et al. 1996, Pietrobon 1995, Wood 1997).

Lawless et al. (1996) suggest that the stigma associated with using illicit drugs increases the fear of being discriminated against, and adds to stress associated with interactions with health care workers and obtaining medical attention. In some instances, fear and stress contribute to an individual avoiding contact with health care services, even those that they previously accessed.

Conversely, other people with hepatitis C who inject drugs do not accept discrimination and seek remedies for these experiences. Assuring confidentiality and providing assistance and support is essential in these cases (NUAA 1995). It must be considered how the outcome of these people's experiences in addressing discrimination is communicated to other injecting drug users with hepatitis C, as this will influence the uptake of legal remedies.

Currently, anti-discrimination legislation across all Australian jurisdictions offers no protection to injecting drug users who have experienced discrimination on the grounds of injecting drug use (McCarthy 1994). Given that anti-discrimination legislation can also act as a disincentive by preventing overt discrimination, the absence of protection for injecting drug users provides further justification for individuals and institutions to continue discriminatory practices.

NUAA identified a range of complaints of discrimination in service provision experienced by people who inject drugs. These included:

- being refused goods and/or services
- breaches of confidentiality
- unauthorised access to information and medical records
- accusations of 'scamming' or lying to service providers
- inhumane, undignified and unethical treatment
- invasion of privacy
- restricting freedom of movement
- having needs ignored or trivialised
- denial of the same rights as other consumers
- exclusion from treatment based on stereotypical attitudes to drug users
- denial of access to information on service options, and
- sexual, physical and verbal harassment.

A report from the New South Wales Anti-Discrimination Board (1992) revealed that it is in the provision of health care services that discrimination is reported most consistently and extensively. At the same time, education measures are viewed as the most effective means to reduce transmission and prevent discrimination against injecting drug users with hepatitis C. This was reinforced recently at the Parliamentary Legislative Council Standing Committee on Social Issues Inquiry into Hepatitis C in New South Wales (1998).

Numerous forms of discrimination in health care can be demonstrated. Health care professionals can discriminate overtly, for example, by refusing to provide health care. Providing a discriminatory standard of care or adopting unnecessary or excessive infection control procedures has also been reported frequently (NUAA 1995). Other more subtle forms of discrimination can occur in circumstances where people are tested for hepatitis C without their consent, and when confidentiality regarding health status is breached.

Similarly, Herdman (1994) suggests that the most insidious and deep-rooted discrimination is located within health care settings. Examining the discourses apparent in the universal precautions model of infection control reveals how structural factors can stimulate and sustain discrimination. For example, the universal precaution model of infection control states that all health care workers assume that all people are potentially blood-borne virus (BBV) positive. Theoretically, the precaution model is ideal, protecting both the health care professional and the client without discriminating against individuals or groups. The failure to ensure that education is provided to support the adoption of the universal precautions model of infection control by all staff is, in itself, a form of institutional discrimination. The lack of such education programs further produces and maintains discriminatory practices against people with blood-borne viruses such as hepatitis C.

In health care settings, an individual's 'infection' status and drug use is usually noted in medical files so those health care professionals can ascertain the most suitable treatment and care. The onus and responsibility to maintain client confidentiality resides directly with health care professionals, who are bound both legally and ethically by the various Health Acts and professional codes of conduct. However, there is no guarantee that this confidentiality will be maintained, largely due to the inability to enforce legislative requirements and/or seek redress under such legislative frameworks. In addition, ethical governance resides with individual health care workers and their values and attitudes. Codes of conduct are unenforceable, particularly where breaches of conduct cannot be brought before any professional board or peer review assessment by complainants who are largely disenfranchised by both their health status and illicit use of injectable drugs.

> *Currently policies are meant to ensure information regarding an individual's medical treatment remains confidential, however it has proved extremely difficult to ensure that health workers follow them (NUAA 1995).*

Some people with hepatitis C who inject drugs claim to have received second-class medical treatment. These experiences result in injecting drug users attempting to conceal either their injecting drug use or sero-status from health care professionals to avoid stigmatisation. The implications of such practices are that people with hepatitis C who inject drugs illicitly are unlikely or unwilling to access health care. Parallels can be drawn with people living with HIV and their experiences of discrimination in health care settings. For example, a French study in 1994 found that HIV positive drug users rarely sought medical attention until they were close to death, due to the attitudes of doctors and nurses towards them and their previous health care experiences (Tellier and Sobel 1994).

The experience of discrimination and stigmatisation appears to increase a fear of discrimination and affects the willingness and ability of people with hepatitis C to access essential health and support services (Lawless et al. 1996).

Fear of discrimination also results in their failure to disclose drug use to health professionals. The potential for signs and symptoms of conditions to be misdiagnosed, misinterpreted or go untreated remains high. Many people with hepatitis C who inject drugs will choose not to access health services in order to avoid discrimination (NUAA 1995).

Pietrobon (1995) reported that women who inject drugs illicitly did not appear to access mainstream health and welfare services because of past experiences of discrimination, maltreatment and breaches of confidentiality. Women's expectations of prejudice and discrimination in mainstream health and welfare services lead to limited opportunities to access to education and information.

NUAA advocates that any real sustainable change in negative attitudes towards injecting drug users needs to begin with service providers. This need is reinforced in the Burrows and Basset report (1996).

Human rights, anti-discrimination and the law

For the purposes of anti-discrimination legislation in Australia, hepatitis C infection is regarded as a disability. Theoretically, discrimination on the basis of perceived or real hepatitis C sero-status is covered by the Commonwealth under the *Disability Discrimination Act (DDA) 1992* and the *Human Rights and Equal Opportunity Commission (HREOC) Act 1986*. Anti-discrimination laws are designed to ensure that people are not treated less favourably than others because of a characteristic that does not warrant such treatment. The DDA applies to discrimination in employment, accommodation, education, the provision of goods and services, and club memberships.

The definition of disability under the DDA includes:

- Total or partial loss of a person's bodily or mental functions...
- A disorder, illness or disease that affects a person's thought processes, perceptions of reality, emotions or judgement; or that results in disturbed behaviour.

Disability discrimination is defined under the DDA as:

> *A person ('discriminator') who discriminates against another person ('aggrieved person') on the grounds of a disability of the aggrieved person and, because of the aggrieved person's disability, the discriminator treats or proposes to treat the aggrieved person less favourably, than in circumstances that are the same or are not materially different, the discriminator treats or would treat a person without the disability.*

The HREOC Act provides the HREOC with the power to investigate breaches of the Declaration on the Rights of Disabled Persons and defines 'disabled person' as:

> *Any person unable to ensure by himself or herself, wholly or partly, the necessities of normal individual and or social life, as a result of deficiency, either congenital or not, in his or her physical or mental capabilities.*

Furthermore, the Declaration proclaims that:

> *Disabled persons shall be protected against all exploitation, all regulations and all treatment of a discriminatory, abusive or degrading nature.*

Infringements of the Declaration are not, of themselves, necessarily unlawful. The Commission may hold inquiries into complaints of discrimination or violation of human rights, but has no power to conduct formal hearings. HREOC is also empowered under the DDA to hear complaints. This makes discrimination on the grounds of disability unlawful in the areas of employment, accommodation, education, access to premises, club memberships, participation in sport and in the provision of goods, services, facilities and land.

People who experience discrimination are often reluctant to use existing complaint procedures and arrangements. Reasons for this may include the belief that disclosure will lead to public identification, that extensive delays would be likely, that the process would be associated with considerable stress and distress, and that there would be no beneficial outcomes (Cabassi 1999).

Seeking redress for discrimination is difficult and not a priority for many people with hepatitis C. Often people with hepatitis C have more immediate concerns such as maintaining confidentiality, surviving in relative isolation, parenting and custody issues, maintaining their health, and economic independence (Wellings 1994).

The right to health care originates in the Australian Government's determination to adopt the 1948 Geneva Universal Declaration of Human Rights. The United Nations enunciated in full the right to have a living standard sufficient to ensure an individual's and any dependents' health and well-being in relation to food, clothing, medical care and social services (Moulin 1993).

The acceptance of human rights emphasises the worth of the individual and, perhaps more importantly, recognises the individual's rights within society. In Australia, the Federal Government defines human rights in the following way:

> *...the term 'human rights' covers the series of often disparate rights and freedoms asserted by many to be universally accepted and essential prerequisites for peoples' enjoyment of a life based on the centrality of human dignity (Department of Foreign Affairs and Trade 1993).*

Currently, there is no international human rights instrument that raises the issue of discrimination towards people who use drugs, nor are drugs mentioned in any broader context. There are a number of international conventions specifically related to drug trafficking and the international illicit drug trade, however, these instruments are not designed to promote and protect the rights and human dignity of drug users, or better understand drug use as an aspect of human activity (NUAA 1995).

An Anti-Discrimination Tribunal or Equal Opportunity Commission may hear complaints, conduct investigations, and undertake information and education programs. Following the 1996 report of the Victorian Equal Opportunity Commission, the Commission has provided a resource dealing specifically with discrimination on the basis of hepatitis C sero-status. It is a publication that sets out current remedies available to address discrimination.

Anti-discrimination legislation covers assumed or imputed impairments. Many people report experiencing discrimination because they are assumed to have hepatitis C, even though this assumption may be unfounded. Much of the discrimination to which people who inject drugs are subjected is related to assumptions. The DDA covers assumed disabilities, thereby ensuring that all Australians have access to this protection (Leach 1994). Whether this protection prohibits, or even restrains, discrimination towards people living with hepatitis C, can be argued at length.

Discrimination that is prohibited in one State or Territory may be not accepted in another jurisdiction. Altogether there are seven different State and Territory Acts attempting to prohibit discrimination across Australia (Leach 1994). Differences between these Acts are reflected in their time of creation, the success or failure of various lobby groups and community prejudices, values and attitudes. It is therefore apparent that a review of these Acts should incorporate a broader definition of discrimination to provide coverage to people who inject drugs and/or are hepatitis C positive.

Existing public health laws in Australia include a range of regulations to protect the health of the general community, including public health orders that are primarily aimed at recalcitrant individuals suspected of subjecting those around them to significant public health risk. However, these laws are generally punitive and directed at specific categories of people considered at risk, particularly sex workers.

Where to from here?

The discussion and issues raised in this paper have highlighted that discrimination against people with hepatitis C is extensive and largely ignored. It is apparent that additional factors, such as injecting drug use and assumptions about transmission, impacts upon the types of responses that health care professionals and other service providers have towards a client presenting with hepatitis C infection. Such a response guarantees unequal access to treatment and care, which further perpetuates stigmatisation and isolation.

In order to address the discrimination experienced by people with hepatitis C, a multi-faceted approach must be adopted, which incorporating education and training as well as legislative initiatives and other mechanisms to remedy discrimination.

Legislative mechanisms to address discrimination are imperative for several reasons. According to the NSW Anti-Discrimination Board (1992), legislation can be viewed as a relatively efficient means of addressing social problems. Anti-discrimination legislation is an important part of any strategy to address discrimination, both by its educational impact and its provision of some forms of protection for those whose rights are violated (NSW Anti-Discrimination Board 1992). However, hepatitis C-related discrimination cannot be dealt with effectively within a legislative framework alone.

Education must be a key component in any response to discrimination against people with hepatitis C. However, information alone, without educational and promotional components, may increase fear and prejudice rather than reduce it. The NSW Anti-Discrimination Board (1992) asserts that education also needs to address the facts of hepatitis C transmission, and the bases of pre-existing prejudice, stereotypes and discrimination against those identified with and discriminated against because of injecting drug use and/or perceived or real hepatitis C status. Education must be based on this model rather than focus solely on those affected by hepatitis C.

Broader community understanding of hepatitis C is fundamental in reducing the stigma associated with the infection. Hepatitis C-related discrimination affects individuals, their families and associates and the broader Australian community. Failure to address discrimination against people with hepatitis C will impact on Australia's ability to address the complex challenges posed by the epidemic. Clearly, it will be difficult to meet such challenges without a dedicated commitment to legislative reform, comprehensive anti-discrimination campaigns and education of the broader Australian community.

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Australian Commonwealth Legislation

Disability Discrimination Act (DDA) 1992

Human Rights and Equal Opportunity Commission Act (HREOC) 1996

Hepatitis C Virology

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Contents

Introduction

There has been rapid progress in understanding the molecular biology of hepatitis C virus (HCV) since the initial description of the molecular cloning of the virus genome, but progress in our knowledge of the basic virology has not kept pace. This is due to the same difficulties that frustrated efforts to discover the virus in the past, namely, the lack of a reproducible cell culture system and the low levels of viraemia in naturally infected individuals. In addition, humans and chimpanzees are the only species that can be infected with HCV. There is no suitable small animal model. These problems have hindered progress, but have also led to innovative approaches.

The basic virology

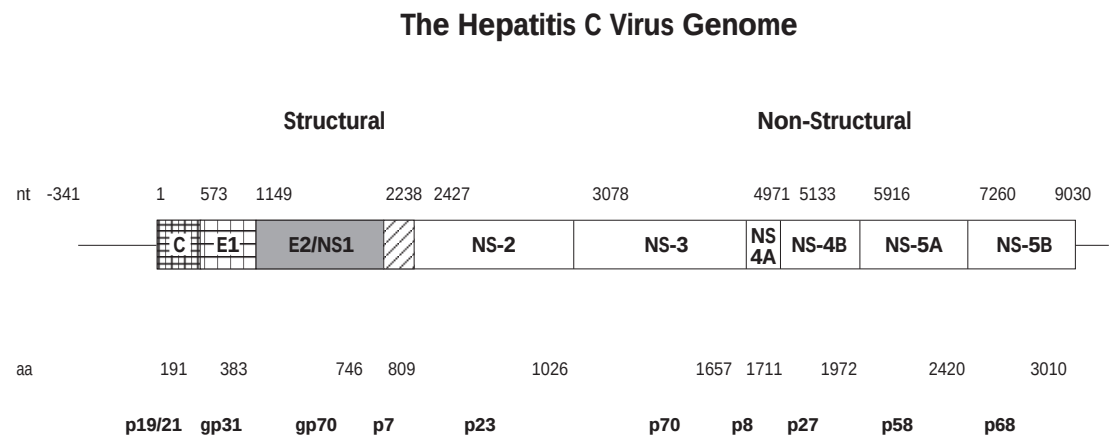
Before the discovery of HCV in 1989 and based on its filter-passing abilities, the NANB agent was considered to be a 30–60 nm particle with a lipid envelope, since infectivity was abolished by treatment with chloroform (Feinstone et al. 1983). More recent electron microscopic studies of virions purified from the serum of HCV-infected individuals confirmed HCV to be an enveloped virus of approximately 60 nm (Prince et al. 1996). Treatment of the virus with detergent resulted in an increase in the particle's density consistent with the removal of a lipid-containing glycoprotein envelope and the release of a 33 nm nucleocapsid (Takahashi et al. 1992). The level of viraemia is normally too low to permit detection of the viral antigens by conventional immunoassays. Consequently, viraemia is recognised by detecting viral RNA using nucleic acid amplification procedures, usually reverse transcriptase-polymerase chain reaction (RT-PCR). However, detergent treatment of the virus in serum samples permits the detection of the nucleocapsid (core) antigen with core-specific antibodies, (Aoyagi et al. 1999, Dickson et al. 1999, Komatsu and Takasaki 1999) but this procedure is not in general use, presumably due to reduced sensitivity compared with that of PCR. The low level of viraemia indicates the level of virus replication *in vivo* and the study of naturally infected tissue samples has failed to provide data on the mechanism of virus replication (Gowans 2000).

Physicochemical studies identified two HCV populations with different densities in the serum of infected individuals. The low-density population contained infectious virus associated with low-density lipoproteins (LDL). The high-density fraction contained non-infectious virus that was coated with antibody (Hijikata et al. 1993) and could be precipitated with anti-human immunoglobulin. These results explained a discrepancy in the infectivity of different serum samples containing a similar viral load (by RT-PCR). They are consistent with immune complex formation that is often associated with persistent HCV infection. Thus some HCV-positive blood is of low infectivity. Nevertheless, parenteral transmission is efficient and generally results in a subclinical acute infection. For this reason, it is difficult to study patients with acute hepatitis C infection. Approximately 80% of infected individuals develop persistent infection that often results in chronic liver disease. It is not clear why such a high proportion of individuals develops persistent infection. Although no specific factors have been identified, several studies have indicated that particular HLA class II haplotypes are more likely to clear the infection and thus are resistant to persistent infection (Minton et al. 1998, Tibbs et al. 1996, Congia et al. 1996). This suggests that antigen presentation, which is required for an effective immune response, may be defective in the majority of individuals who develop persistent infection, although the mechanism for this has not been defined. It has also been suggested that increased quasispecies complexity in the acute phase of the infection is associated with the development of persistent infection (Ray et al. 1999). This is consistent with the finding that a rapid antibody response to the HVR1 region in the virus envelope (see below) is associated with self-limited infection (Zibert et al. 1997). However, no consensus has emerged to explain the high incidence of

persistent infection, which is most likely to be a virus strategy that has evolved to ensure survival. Given that most persistently infected individuals fail to develop clinical symptoms of infection for many years despite shedding infectious virus, the strategy is most successful. There are no data to suggest that mutations lead to the emergence of less virulent strains of virus.

Studies of the dynamics of virus production showed that the half-life of virus particles was 2.7 hours and highlighted that the viral load is the net result of the steady state virion production and the rate of virion clearance (Neumann et al. 1998). It was calculated in the patients studied that 1.3×10^{12} virions were produced per day, a figure that equates to approximately 10–100 virions per infected hepatocyte, if it is assumed that most of the hepatocytes are infected. This figure reinforces the low level of virus replication. It also highlights the large viral burden resulting from infection of a large organ like the liver, by comparison with the daily HIV production, which has been estimated to be around 1×10^{10} (Perelson et al. 1996)

Figure 1. The organisation of the hepatitis C virus genome



Numbers above the box depicting the position of the structural and non-structural proteins represent nucleotides. Numbers below the line represent amino acid positions of the various proteins. The numbering begins with the start site of the core protein. The bold numbers represent the molecular weight of the mature polypeptides.

The virus genome

The genome is a single strand, positive sense RNA molecule of approximately 9500 nucleotides (nt). It contains a single, long, open reading frame (gene) that encodes a polyprotein of 3008–3037 amino acids, depending on the genotype (see below), and is flanked by untranslated regions (UTR) at the 5' and 3' ends (Figure 1). Consequently, the HCV genome has several similarities with the genomes of the *Flaviviridae* and as a result, HCV was classified as a separate genus—the *Hepacivirus* genus—in the *Flaviviridae*. The order of the genes in the genome is 5'UTR-core, E1, E2, p7, NS2, NS3, NS4A, NS4B, NS5A, NS5B, 3'UTR. The core and envelope (E1 and E2) proteins are structural proteins that comprise the virus particle, while the remainder, the non-structural (NS) proteins, are required for virus replication, although it is not clear if p7 is a structural or non-structural protein. The nucleotide sequence of the genome of different isolates has been shown to differ. On this basis, six genotypes, each containing a number of subtypes, have been described (Simmonds et al. 1994) although it was suggested that there is sufficient diversity to constitute 12 genotypes (Bukh et al. 1993). More recently, however, it was recommended that the different isolates of HCV be classified into clades 1–6, which encompass the previous known genotypes (Robertson et al. 1998). However, HCV is typical of many RNA viruses, and the virus population that circulates in the blood of an infected individual usually includes a major proportion of closely related viruses and a minor proportion of variants derived from a common ancestor. The variants are produced because the RNA polymerase used to replicate the viral genome has no proofreading capacity and consequently, errors (mutations) are introduced into the nascent genomes. Thus the total virus population is described as a quasispecies. There are no data to suggest that a specific genotype is more or less pathogenic than others, although genotype distribution has been shown to differ with the average age of the cohort that was studied. The genome also contains a region at the 5' endof the E2 gene, known as hypervariable region 1 (HVR1). This has been shown to accumulate mutations at a rapid rate. The HVR1 of the E2 protein is an important antibody target and is discussed below.

The 5' and 3'UTR are the most conserved regions in the genome; the 5'UTR is recognised to be 341 nt and the 3'UTR varies between 200–250 nt. The conserved region in the 3'UTR is limited to the 98 nucleotides at the extreme terminus. The 5' and 3'UTR are thought to be important for the control of RNA transcription and virus replication, although few data are available to confirm this other than the finding that the 98 nt region is required for infectivity in chimpanzees (Yanagi et al. 1999). The 5'UTR contains an internal ribosome entry site (IRES) that permits the translation of proteins from the genome in a cap-independent manner, in contrast to the cap-dependent mechanism used by most cellular mRNA molecules. Consequently, the IRES represents an attractive target for antiviral agents (see below). A recent report showed that nt 20371 represented the likely 5' and 3' boundaries of the IRES (see Hwang et al. 1998 for review) and confirmed an earlier finding that the IRES encompassed a short region of the gene for the core

protein (Reynolds et al. 1995). Thus the 30 nt region at the 5' end of the core gene has two functions. This situation was thought to be unique among RNA viruses, but more recently, similar overlapping functions have been detected in the pestiviruses, which are closely related to HCV and proposed in two members of the *Picornaviridae*-hepatitis A virus and encephalomyocarditis virus (Tang et al. 1999). Unlike the IRES of some members of the *Picornviridae,* which can be complemented *in trans*, the HCV IRES is only able to function *in cis* (Tang et al. 1999).

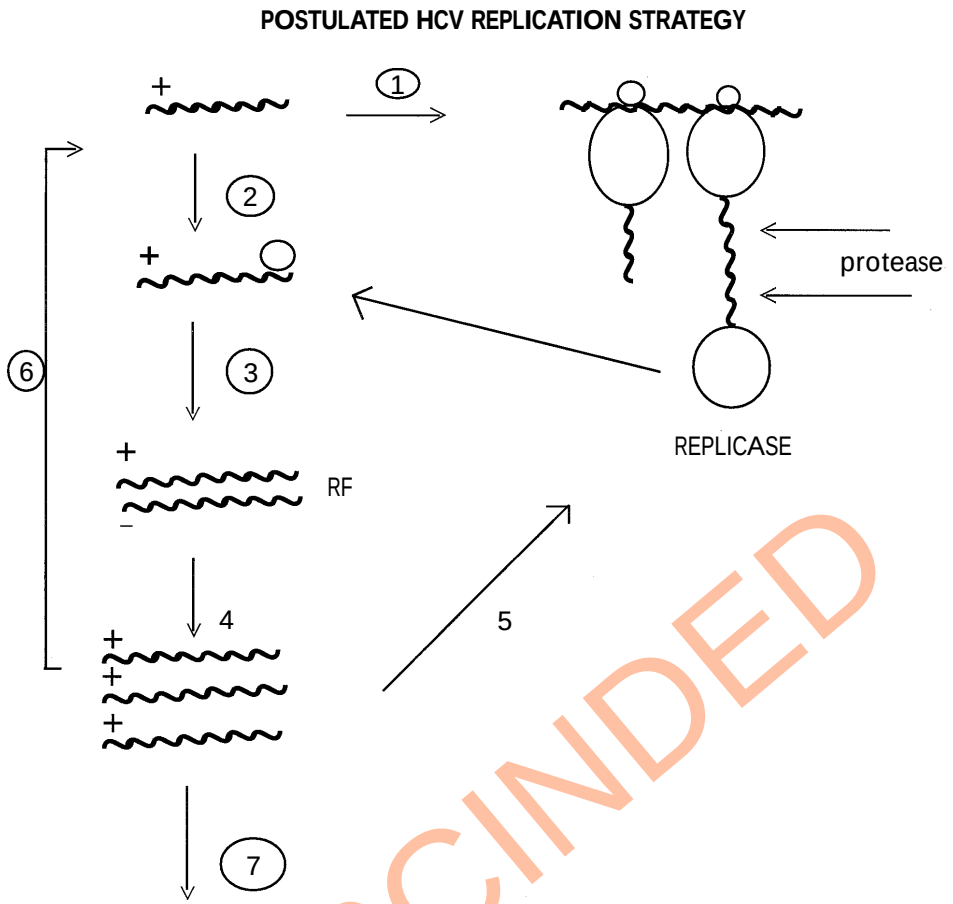
A number of cellular proteins, namely polypyrimidine tract binding protein (PTB), La protein, hnRNP L, and eIF3, interact with the 5'UTR (Tang et al. 1999, Ito and Lai 1997, Sizova et al. 1998, Hahm et al. 1998), but only eIF3 appears to be involved in IRES function, although it is not absolutely essential (Sizova et al. 1998). The lack of a requirement for the canonical initiation factors eIF4A, eIF4B and eIF4F emphasises the unique nature of the HCV IRES translation initiation process. PTB also binds to the 98 nt region and the poly (U) tract in the 3'UTR (Luo 1999), a process that was reported to enhance HCV IRES-directed translation (Ito et al. 1998), presumably by facilitating an interaction between the 5' and 3' ends of the genome. This is not without precedent, as the poly (A) tail of normal cellular mRNA binds Pab1p, which interacts with the 5' end of the RNA in an indirect reaction with other cellular factors, and results in the circularisation of the mRNA (Wells et al. 1998).

Virus replication

In the absence of a reproducible cell culture system for HCV, few details of the virus replication process are known. However, by analogy with other members of the *Flaviviridae*, particularly the pestiviruses, it is possible to construct a model (Figure 2). Several steps of the putative replication cycle, for example, polyprotein processing, IRES-directed protein synthesis, have been examined in isolation using recombinant DNA technology The results from these studies have confirmed the analogy with pestivirus replication. After virus entry into the target cell, the input viral RNA acts as mRNA for the synthesis of the virus polyprotein, which is processed to produce the mature viral proteins. The input RNA is then used as a template for the synthesis of nascent RNA in a replicative complex that is thought to contain NS5B and other NS proteins. Initially, this occurs by the synthesis of a negative strand that then base pairs with the input plus strand to form a double strand replicative form (RF), and then by the production of nascent plus strands from the RF. The nascent plus strands can then be used in one of three ways: (i) as a template for further translation of viral proteins, (ii) as a template for transcription of negative strand viral RNA, or (iii) encapsidated and exported from the cell as progeny virus. It is thought that virus morphogenesis in the last step depends on a critical mass of virion components, but the controls for these processes have not been defined.

The detection of negative strand HCV RNA is considered to be a marker of virus replication, although the detection of negative strand RNA by strand specific RT-PCR is fraught with technical difficulties (McGuinness et al. 1994) and can often lead to inaccurate results. This has caused difficulties, particularly in the interpretation of HCV of *in vitro* infectivity experiments, and resulted in clear guidelines for the specific detection of negative strand RNA (Sanger and Carroll 1998).

Figure 2. A model for the replication of hepatitis C virus RNA



The positive sense input virus RNA is used as a messenger RNA (mRNA) in the synthesis of the viral polyprotein, which is co- and post-translationally processed into the mature virus polypeptides (step 1). The resulting replicase then uses the input vRNA as a template (step 2) for the transcription of negative strand vRNA (step 3) to produce the double-stranded replicative form RNA (RF), which in turn is used as the template for the production of nascent positive sense vRNA (step 4). This can be re-cycled as a template for translation (step 5), re-cycled as template for transcription (step 6) or incorporated into mature virions and exported from the cell (step 7).

It has been suggested that HCV may bind to the hepatocyte as a consequence of the LDL component of the envelope binding to the cellular LDL receptor (Agnello et al. 1999 and Monazahian et al. 1999). However, the virus has also been shown to bind to the CD81 molecule through the interaction of CD81 with E2, and antibody to the HVR1 region is able to inhibit this binding. Consequently, it has been proposed that CD81 represents the cellular receptor for the virus (Pileri et al. 1998). After entry and uncoating, events that are not defined, the IRES directs the synthesis of the viral proteins as discussed above. The polyprotein is co- and post-translationally processed into the mature individual polypeptides by host and viral proteases. The structural (S) proteins are cleaved into the mature polypeptides by a cell signalase that is probably located in the lumen of the endoplasmic reticulum, while the NS proteins are cleaved by one of two virus-specific

proteinases. The NS2/3 site is cleaved *in cis* by the NS2/3 metalloprotease, which is independent of the major viral protease activity contained in NS3. The NS3 protease, a trypsin-like protease, cleaves at the downstream NS3/4A, NS4A/4B, NS4B/5A and NS5A/5B sites. Cleavage at NS3/4A and the NS4B/5A sites depends on a co-factor activity provided by NS4A, while cleavage at the NS4A/4B and the NS5A/5B sites is enhanced by the cofactor (Urbani et al. 1999). The NS3 protein also contains a helicase activity and NS5B contains an RNA polymerase activity, both of which are thought to be part of the replication complex. The nature of the replication complex is still to be defined, but a simplistic view is to suggest that all the NS proteins, along with specific cellular proteins, are components. Specific functions have been assigned to each of the proteins except p7, NS4A and NS5A (Table 1).

Table 1. Properties of HCV proteins

Protein	*Size (kD)*		*Putative function*
	Predicted	*Actual*	
Structural			
C	20.8	p22	Capsid
E1	20.9	gp35	Envelope
E2	47.0	gp72	Envelope
p7	7.0		Unknown
Non Structural			
NS2	24.0	p23	Zn^{+} dependent protease component
NS3	67.3	p70	Protease/helicase
NS4A	5.8	p 6	Protease co-factor
NS4B	27.2	p27	? Membrane assoc. replicase component
NS5A	49.1	p56/58	? Replicase component
NS5B	65.4	p65	RDRP

The envelope glycoproteins E1 and E2 are thought to be type I transmembrane proteins with a C terminal membrane anchor that targets and retains the proteins in the endoplasmic reticulum (ER) (Cocquerel et al. 1999). E1 and E2 form a heterodimeric complex believed to be a precursor of the mature virion envelope that accumulates in the ER. E2 interacts with the cellular chaperone calnexin, which promotes authentic folding in the absence of E1 (Choukhi et al. 1998). E2 is also required for E1 to fold into the proper configuration. It has been proposed that E1 contains a putative fusion domain located between amino acids 264–290 in the polyprotein that may have a role in virus entry into the host cell, but fusion activity has yet to be demonstrated (Flint et al. 1999). Expression of the core E1 and E2 proteins in recombinant baculovirus resulted in the formation of large cytoplasmic cisternae, thought to be derived from the ER, and led to the formation of HCV virus-like particles (Baumert et al. 1998). The formation of these particles can be considered to be a model for HCV morphogenesis.

The lack of an authentic cell culture system resulted in a greater emphasis on a molecular approach to replication. This has resulted in the synthesis of full-length cDNA clones of the genome, with the potential to direct the transcription of infectious HCV RNA (Kolykhalov et al. 1997, Yanagi et al. 1997, Yanagi et al. 1998, Hong et al. 1999, Beard et al. 1999). Each of these studies reported HCV replication after direct injection of *in vitro* transcribed RNA into the liver of chimpanzees, which resulted in authentic hepatitis C infection. Analogous studies in cell culture have proved much more difficult. More recently, however, an HCV replicon from which the structural gene region was deleted was shown to replicate in a stable cell line that was selected using G418 encoded in the replicon (Lohmann et al. 1999). Intriguingly, the NS2 protein was not necessary for replication of the replicon. The stable cell lines produced levels of HCV RNA that were detectable by Northern blot hybridisation, and represent the most authentic model yet in which to study details of the HVC replication process, despite the fact that whole virus was not synthesised.

Interferon treatment and other anti-viral therapy

Until relatively recently, the only licensed treatment for HCV infection was interferon alpha. However, although interferon (IFN) can often reduce the viral load quite dramatically, only a small proportion of patients show a long-term response followed by recovery (Conjeevaram et al. 1995). The major predictors of response to IFN are viral genotype and viral load. Patients who are infected with genotype 1 or who have a high viral load are most refractory to treatment. Although the mechanism of IFN action against HCV is not well defined, it has been suggested to block virion production or release from the infected cell (Neumann et al. 1998). Studies to investigate the IFN-resistant nature of some HCV strains determined that the NS5A protein contains a region of 40 amino acids, termed the Interferon Sensitivity Determining Region (ISDR), which is thought to influence the response of the virus to treatment with interferon (see Pawlotsky et al. 1998 for review). Virus genomes with the wild type sequence in this region were resistant to IFN treatment, whereas genomes that contained mutations leading to three or four alterations in the amino acid sequence in the ISDR were sensitive to IFN. However, the importance of the ISDR has not been universally confirmed, although it appears to be an important determinant in Japanese patients, and it is thought that interferon resistance may be multifactorial in other populations (Pawlotsky et al. 1998, Duverlie et al. 1998). Nevertheless, NS5A interacts with and inhibits the double-stranded RNA-induced protein kinase, PKR, which is a component of the cell signalling pathway leading to the production of interferon (Gale et al. 1997). More recently, a motif in E2 (PePHD) that is highly conserved in genotype 1 isolates (IFN resistant) but less so in other genotypes (IFN sensitive) was also shown to interact with PKR and inhibit the kinase activity of the molecule (Taylor et al. 1999). It has been proposed that this may represent an alternative explanation for IFN resistance.

More recently, combination therapy with IFN-alpha and ribavirin, a nucleoside analogue, has been shown to be more effective than IFN alone (Davis 1999). Ribavirin is known to inhibit the replication of a range of RNA viruses, including the flaviviruses, and although the mechanism of action is not well defined, it is thought to also have some immunomodulatory activity (Patterson and Fernandez-Larsen 1990). It is unclear if virus that is resistant to the combination therapy contains wild type ISDR sequences. Amantadine in combination with IFN-alpha was shown to reduce the level of HCV replication *in vitro* (Martin et al. 1999) and showed promising results in a clinical trial (Smith 1997). The mechanism of amantadine action is not known.

The rational design of antiviral agents depends on a clear understanding of the virus replication cycle to permit targeting of specific steps in the cycle. This permitted the development of protease inhibitors for HIV and the influenza virus neuraminidase inhibitor, developed in Australia by Biota (Varghese et al. 1998). The following

discussion on the development of potential anti-viral agents highlights potential targets resulting from our current knowledge of the HCV replication cycle. Based on an earlier observation that lactoferrin is able to bind to E1 and E2 (Yi et al. 1997), a preliminary clinical trial showed that lactoferrin was able to reduce the viral load in carriers with a pre-existing low viral load, but had no effect on carriers with higher levels of viraemia (Tanaka et al. 1999). Nevertheless, the study provides some encouragement that the approach of binding virus may be useful, and it may be possible to improve the binding efficiency by chemical alteration of the lactoferrin molecule or by designing peptides that mimic the cellular receptor for the virus. This represents another reason for the intense interest in the role of CD81 in HCV binding and entry.

The IRES element represents a virus-specific target. Ongoing work in the SASVRC hepatitis C laboratory has identified two compounds that can inhibit IRES-directed but not cap-directed protein synthesis (unpublished data). A yeast RNA molecule has also been shown to inhibit HCV IRES function. The mechanism for this is thought to result from competition for critical cellular polypeptides (Das et al. 1998), and this study further illustrates the potential to inhibit HCV replication by inhibiting IRES function. It is also possible to inhibit IRES function by ribozymes. These RNA molecules have been reported to inhibit the replication *in vitro* of a chimeric HCV-poliovirus containing the HCV IRES (Macejak et al. 2000). Delivery to the infected cell may inhibit the usefulness of this and the yeast RNA approach. The helicase/protease and polymerase functions of the NS3 and NS5B proteins respectively represent logical targets for antiviral agents. In particular, the protease activity of NS3 is a suitable target in view of the outstanding success of the protease inhibitors, which have revolutionised treatment of HIV infection. The design of protease inhibitors normally depends on knowledge of the crystal structure of the protease itself. Although this has been described for the HCV protease (Kim et al. 1996 and Love et al. 1996), the development of specific inhibitors has been extraordinarily difficult, due to the shallow nature of the cleft into which the target protein is inserted. This has resulted in a change of emphasis for several research groups. An alternative approach identified an RNA aptamer that bound NS3 and resulted in a 20% reduction in NS3 activity *in vitro* (Urvil et al. 1997). It is possible that this will form the basis for the design of improved NS3 inhibitors.

The aim is to develop a range of specific inhibitors to permit combination therapy and thus avoid the emergence of resistant mutants. Provided the new generation of HCV-specific anti-virals that will be developed show reduced levels of toxicity compared with the compounds currently in use, they could be used to treat healthy carriers in a bid to reduce the viral load before the emergence of liver disease. However, the lack of a useful animal model means that optimal dosage schedules will have to be determined in HCV-infected individuals. The above approaches represent only a few of the potential approaches. The full range must wait for details of the replication cycle to materialise.

The development of an effective vaccine

Since it is difficult to culture HCV *in vitro*, it is not possible to develop a conventional vaccine based on virus attenuation. Live attenuated vaccines have the capacity to elicit a humoral and a cell mediated response, although the role of each in protection after vaccination has not been clearly defined. However, it is generally accepted that while a humoral immune response is important to prevent virus infections, a cellular immune response, particularly a cytotoxic T lymphocyte (CTL) response, is necessary to ensure clearance of virus infection by eliminating virus-infected cells (Oldstone 1997). Thus one might predict that antibodies to the E1 or E2 proteins of the HCV envelope would result in protection against infection. Indeed, vaccination of chimpanzees with E1/E2 protected five out of seven animals against challenge with homologous virus (Choo et al. 1994), although the dose of challenge virus was very low. However, as the HVR1 region in E2 is thought to represent a major neutralising antibody target, the quasispecies nature of a natural challenge virus will be resistant to homologous antibody. More recent data from the same group was consistent with the hypothesis that vaccination to induce a humoral immune response to the virus envelope proteins was unlikely to provide protection against challenge with heterologous virus. Indeed, passive vaccination of chimpanzees with high titre immune globulin, prepared by cold ethanol fractionation to inactivate residual HCV, failed to protect the animals, although it did delay the onset of acute hepatitis (Krawzynski et al. 1996). This is consistent with the fact that individuals who recover from HCV infection can be re-infected.

This also leads to the realisation that the development of a vaccine represents a huge challenge, since natural immunity after HCV infection is poor. Thus there is general pessimism about the development of a vaccine designed to elicit a humoral antibody response. More recently, however, it has been recognised that the HVR1 contains several highly conserved amino acid residues (McAllister et al. 1998 and Puntoriero et al. 1998) and that specific HVR1 sequences have been shown to induce antibodies that are recognised by a range of HVR1 sequences (Puntoriero et al. 1998 and Shangh et al. 1999). This provides hope that an antibody-based vaccine approach may be feasible.

Nevertheless, although generating an effective CTL response is technically more difficult, many view this as the more likely approach to a successful HCV vaccine. CTLs recognise viral antigens that are synthesised intracellularly, processed by the cell proteasome, and presented on the cell surface in conjunction with HLA class 1 molecules. CTLs can kill virus-infected cells that express viral antigen in this way by direct contact (or in close proximity), through the action of perforin and granzymes, or they can eliminate virus from the cells in a non-cytolytic manner through the action of interferon and tumour necrosis factor. Although CTLs can be detected in the peripheral blood and liver of HCV carriers, it is thought that these are quantitatively insufficient to eliminate the HCV-infected hepatocytes. However, because there is no direct correlation between intrahepatic HCV RNA levels and hepatic injury (McGuinness et al. 1996), it is

thought that this abortive CTL response results in the ongoing hepatitis. Since some studies have shown an inverse correlation between viral load and CTL response (e.g. Nelson et al. 1997), this has led to the corollary that a vigorous CTL response may protect naïve individuals or eliminate virus in carriers. Several methods are available to elicit a CTL response by vaccination, either by ensuring endogenous protein expression for eventual entry into the MHC class 1 pathway or by delivering exogenous proteins directly to the class 1 pathway. These methods include recombinant live virus vectors, virus-like particles (VLPs), antigen or peptide formulated in appropriate adjuvants and DNA immunisation. Several of these approaches may present licensing problems, and ongoing work in the SASVRC laboratory has focused on the use of VLPs that have been shown to elicit a CTL response against other viruses. Progress and problems associated with the development of an HCV vaccine have been reviewed recently (Houghton 2000).

Developing an HCV vaccine will be difficult and costly, and there is no consensus yet on the optimal approach and formulation. Nevertheless, the potential benefits are great and in the event of success, it is likely that the considerable effort will be judged worthwhile.

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