



# What is the evidence for the effectiveness of interventions to reduce hepatitis C infection and the associated morbidity?

April 2005

## ABSTRACT

This is a Health Evidence Network (HEN) synthesis report on effective interventions to reduce hepatitis C infection. Prevalence is most common among injecting drug user populations, where up to 98% can be infected despite a low HIV prevalence.

Interventions are needed, particularly among injecting drug user populations. Behavioural interventions, distribution of bleach disinfectant and other injecting devices alongside clean needles and syringes, and supervised injecting centres are all promising interventions that merit further piloting and evaluation. Where opiate replacement therapy is provided for drug users, adequate dosing regimes should be used to minimize the risk of injecting practice. Cost-effectiveness analysis of current interventions aimed at primary prevention of hepatitis C infection shows additional benefits in reducing the prevalence of HIV.

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## **Summary**

### **The issue**

Hepatitis C infection has been declared a global health problem. Prevalence is most common among injecting drug user populations, where up to 98% can be infected despite a low HIV prevalence. Up to 20% of those infected with hepatitis C can clear the virus, though chronic infection can lead to significant hepatic morbidity and death.

### **Findings**

While needle exchange programmes reduce the prevalence of hepatitis C (HCV), prevalence remains high. Therefore, other interventions are required to complement exchange programmes. Whereas opiate maintenance treatment, most commonly with methadone, has significantly reduced the incidence of HIV, it is only marginally effective at reducing the incidence of HCV. In part this could be due to under-dosing. There is a paucity of research evaluating the effectiveness of either behavioural interventions or bleach disinfectants in reducing the transmission of hepatitis C infection among injecting drug user populations. The research that has been conducted would suggest that these interventions warrant implementation and evaluation. There is an emerging evidence-base for the effectiveness of supervised injecting centres at reducing the prevalence.

The transmission of hepatitis C infection from mother to child can be reduced by offering elective caesarean section in those co-infected with HIV. Optimal management of the intrapartum period can also reduce hepatitis C incidence. Breast feeding should only be avoided in those co-infected with HIV.

PEG interferon-ribavirin dual antiviral therapy is currently the most effective treatment at achieving a sustained virological response in those who are hepatitis C-RNA positive. Such treatment reduces the risk of developing chronic hepatic cirrhosis, or hepatocellular cancer. Dual therapy is also indicated in cases of co-infection, as long as HIV status is stable. Interferon monotherapy is indicated for those who develop acute infection after needle-stick injury.

Blood screening with NAT-technology is highly effective at reducing the transmission of HCV. However, NAT technology does not render careful donor selection unnecessary, nor does it allow blood or blood products to be used outside of pre-existing guidelines or in place of alternative manufactured infusions.

### **Policy considerations**

Interventions are needed, particularly among injecting drug user populations. Behavioural interventions, distribution of bleach disinfectant and other injecting devices alongside clean needles and syringes, and supervised injecting centres are all promising interventions that merit further piloting and evaluation. Where opiate replacement therapy is provided for drug users, adequate dosing regimes should be used to minimize the risk of injecting practice. Cost-effectiveness analysis of current interventions aimed at primary prevention of hepatitis C infection shows additional benefits in reducing the prevalence of HIV.

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The authors of this synthesis are:

Dr Nat M.J. Wright  
MBCChB DRCOG FRCGP  
Clinical Director Leeds Community Drug Services,  
Centre for Research in Primary Care  
Hallas Wing  
71-75 Clarendon Road  
Leeds LS9 8AA, United Kingdom  
Tel: +44 (0) 113 3436966  
Fax: +44 (0) 113 3434836  
Email: [n.wright@leeds.ac.uk](mailto:n.wright@leeds.ac.uk)

Dr. Charles E. Millson  
MD FRCP, Consultant,  
Renal and Liver Services,  
Liver Unit  
Merville Building  
St James's University Hospital  
Beckett Street  
Leeds LS9 7TF, United Kingdom  
Tel: +44 113 2066301  
Fax: +44 113 2066462  
Email: [charles.millson@leedsth.nhs.uk](mailto:charles.millson@leedsth.nhs.uk)

Charlotte N. E. Tompkins  
BA (Hons), MSc, Research Assistant,  
North East Leeds Primary Care Trust  
Centre for Research in Primary Care  
Hallas Wing  
71-75 Clarendon Road  
Leeds LS9 8AA, United Kingdom  
Tel: +44 (0) 113 3436966  
Fax: +44 (0) 113 3434836  
Email: [c.tompkins@leeds.ac.uk](mailto:c.tompkins@leeds.ac.uk)

## **Introduction**

Hepatitis C (HCV) is a blood borne virus (BBV) with potentially devastating hepatic complications (1). While approximately 20% of acutely infected people will clear the virus and recover, up to 80% will develop chronic hepatitis C (2). The World Health Organization (WHO) estimates that 3% of the world's population is infected (3) and hepatitis C has been declared a global public health problem. However, the majority of people when acutely infected do not display symptoms or signs in the early stages and may therefore be undiagnosed (4). There are a number of different genetic strains of the virus, classified using antibody characteristics. Nucleotide sequence analysis has highlighted six genotypes which can be further categorized according to subtypes (5). Differing genotypes are distributed differently by geographical region and route of infection, and have differing sensitivity to anti-viral treatment regimes (6). In Japan, North America and Western Europe the majority of genotypes are numbers 1, 2 and 3, whereas genotype 4 is more prevalent in the Middle East and in

North and Central Africa. Types 5 and 6 have been identified in South Africa and South East Asia, respectively (7).

While a number of risk factors have been identified, intravenous drug use is the major mode of HCV transmission (2,8). Other transmission risk factors include receiving a blood transfusion or blood products before the availability of heat-treated factors in the mid 1980s, using non-sterilized equipment in dental, surgical, skin piercing and tattooing procedures, clinical injuries, such as needle stick, vertical transmission (materno-fetal) and sexual spreading (though the efficacy of the latter is limited (1)).

### **Sources for this review**

This synthesis is based on a systematic review of the major electronic medical databases: Medline, EMBASE, PsycINFO, CINAHL and the Cochrane Library (Evidence Based Health). Selection of studies was based on criteria described in annexes 1 and 2. The terms “antibodies to HCV”, “HCV antibodies”, “anti-HCV positive” and “anti-HCV seroconversion” are used interchangeably throughout the synthesis to describe a positive antibody response to HCV infection. However, not all those who are anti-HCV positive are viremic. Active viral replication as evidenced by the presence of serum viral RNA means that the person is a carrier of HCV. Such a state is referred to as anti-HCV-RNA positive. The type of biochemical diagnostic test used to diagnose anti-HCV positivity is described whenever it is recorded in the literature. Successive generations of tests have led to an improved sensitivity and specificity of testing (9). Currently the most valid test for assessing anti-HCV seropositivity is a third-generation enzyme-linked immunosorbent assay (ELISA) test. Unless specifically stated otherwise, where anti-HCV seropositivity is reported, a third-generation ELISA test was used for diagnosis. In the synthesis, needle exchange programmes (NEPs) describe projects distributing sterile needles and syringes. Due to space restrictions, outcomes of reductions in the prevalence or incidence of human immunodeficiency virus (HIV) or hepatitis B (HBV) (in studies also examining HCV) are only reported in the sections relating to the cost-effectiveness of interventions, where it would be invalid to separate discussions of health economics by individual diseases.

## **Findings from research and other evidence**

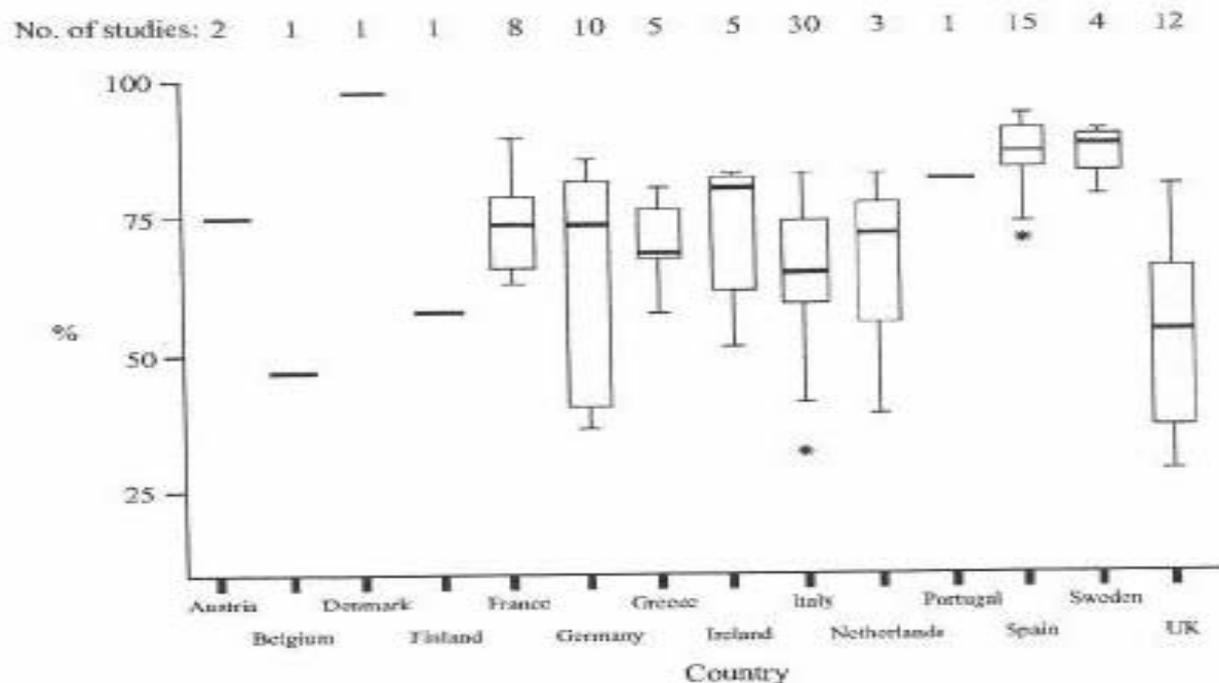
### **HCV prevalence and incidence**

A systematic review of HCV prevalence or incidence data for injecting drug users (IDUs) in European Union (EU) countries identified 98 studies (10). Prevalence ranged from 30% to 95% among males, 48% to 94% among females and 33% to 98% among those of unspecified gender. Figure 1 [reproduced from Roy et al.] shows a box plot of HCV prevalence by country (10).

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**Fig. 1.** Boxplot of hepatitis C virus prevalence by country of study.

The variability in the figure is confirmed by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (11,12), and concurs with a systematic review of seroprevalence of HCV markers among intravenous drug users (IVDUs) in western Europe (13). Associations among increasing age, increasing duration of IDU, imprisonment and anti-HCV seropositivity were described. However, caution should be exercised in considering these factors as the only reason for different prevalence rates between countries. Moreover, different countries use differing source types and some collect only local rather than national data. Additionally, in some situations, biochemical tests may underestimate prevalence. There are also warnings about comparing prevalence data with previous versions to follow changes over time, as inclusion of sources may vary according to data availability (12).

To further understand the epidemiology of HCV the international studies of anti-HCV incidence must be considered. The range of reported incidence of anti-HCV seroconversion is from 11 to 29 per 100 person-years (14-19). Independent risk factors for HCV seroconversion include a history of imprisonment, a history of needle or other paraphernalia sharing and polydrug use, in particular using heroin and cocaine together (speedballing) (14,15,18,19). While some incidence studies report younger age being an independent risk factor, others report older age (18). However, the latter is strongly confounded with the duration of the injecting career and this is arguably a greater independent risk factor than age for anti-HCV seroconversion. The difficulty of adequately controlling for confounders of age was highlighted in a review of prevalence studies which described a linear positive relationship between increasing age and prevalence of anti-HCV-RNA in anti-HCV positive injecting populations (13). The commentators offered possible explanations that HCV infection is more likely to resolve at a younger age, the natural history of the disease is characterized by frequent initial long periods of undetectable viral load levels, and age increases the risk of continuing exposure and re-infection. Similarly, there is no concordance between incidence studies as to whether gender is an independent risk factor, as some report a higher incidence in males (15), and others in females (16). It is therefore possible that gender is confounded with other independent variables. Among surgical workers, seroprevalence studies of anti-HCV have documented rates of 0.8% and 0.9% (20,21). Anti-HCV rates were higher among oral surgeons (9.3%) and dentists (0.97%) (22).

## **Effectiveness of needle exchange programmes in reducing HCV seroconversion**

Evaluating the effectiveness of NEPs in reducing the risk of blood-borne viruses has been difficult, as ethical and political considerations have hampered the design of intervention studies. There has also been difficulty in quantifying the direct effect of NEPs alone, since it may be their interaction with other factors, or the effect of secondary exchange (users obtaining needles and distributing to their peers) that have caused reductions (23). The limitations of observational research make it difficult to mitigate against selection bias toward the most high-risk users into NEPs. This has occasionally fuelled a debate as to whether needle exchanges cause an increase in blood-borne viruses. The international debate was perhaps at its most contentious following an outbreak of HIV in Vancouver, Canada in 1994, five years after the introduction of a NEP (24), that led to several observational studies exploring a possible causal link. A prospective cohort study tracked 1006 IDUs to assess HIV and HCV prevalence and incidence (25). Multivariate analysis of baseline data documented an independent association between HIV-positive serostatus and frequent (more than once a week) NEP attendance. NEPs were thus criticized for promoting unsafe injecting behaviour, or at the very least condoning IDU. These results were interpreted by some in the United States as evidence of a causal link between NEP use and HIV seroconversion, resulting in a ban of federal funding of NEPs (26-28). However, a 1999 multivariate analysis of HIV incidence among 694 subjects (28), while demonstrating a significantly elevated cumulative incidence among frequent attenders, also reported a range of confounders for the group (younger and more susceptible to unstable housing and hotel living, frequent injection cocaine, involvement in the sex trade, injection in shooting galleries or incarceration within the previous six months). Accounting for these confounders by Cox regression analysis demonstrated no independent causal link between NEP attendance and HIV seroconversion, and logistic regression modelling confirmed these findings.

## **Can needle exchange programmes reduce prevalence of HCV?**

A series of large observational studies conducted in Scotland in the mid-1990s compared prevalence of anti-HCV for the periods before during and after introduction of NEPs. The supporting data and full results are presented in a summary of relevant studies in table 1. Briefly, several methodologies were used, including retrospective analysis of prevalence data (29), analysis of residual sera from IDUs who had undergone named HIV testing (30,31), and annual cross-sectional surveys with saliva testing (32). Results showed a statistically significant reduction in anti-HCV prevalence in the early 1990s (shortly after the introduction of NEPs). Reduction was greatest in the under 25s. However, evaluation in the late 1990s showed that the declining trend in overall prevalence did not continue. There was only a reduction for those aged over 25. The authors concluded that the incidence of HCV decreased during the 1990s, but remained high. Such findings are confirmed by an Australian prevalence study showing a reduction in anti-HCV incidence from 63% in 1995 to 51% in 1996 to 50% in 1997 (33), a Swedish cohort study (34) and a Swiss longitudinal and cross-sectional survey (including serological testing) (35,36). The latter reported a reduction in anti-HCV prevalence after 1991 (when both needles and syringes were available) compared to 1988–1990 (when needles but not syringes were available) compared to before needle and syringe exchange in 1987. Two American studies failed to find a causal link between NEPs and HCV incidence. One case control study showed non-use of NEPs to be associated with a seven-fold greater risk of anti-HCV seroconversion (37). The other, a prospective cohort study, showed a statistically non-significant increase in HCV with NEP use (38). Large observational studies from the United States demonstrate that the introduction of NEPs leads to a self-reported reduction in sharing when independently confirmed by an increase in distribution. Such increase in distribution does not lead to an increase in injecting drug use or a switch from non-injecting to injecting (39,40).

## **Cost-effectiveness of needle exchange programmes**

One of the most comprehensive reports on the cost effectiveness of NEPs was published by the Commonwealth Department of Health and Ageing of Australia in 2003 (41). Employing ecological

study methodology, changes in HCV and HIV prevalence were compared in cities that had NEPs with those that did not. There were 190 calendar years of HCV seroprevalence data from 101 cities. Pre-NEP introduction HCV prevalence rates of 75% or 50% corresponded to a 1.5% or 2% decline in HCV prevalence per annum. The cost-effectiveness of NEPs is optimized by the combined effect of reduction in HIV and reduction in HCV. The financial return on government investment in NEPs regarding the impact on HIV and HCV combined was calculated at a lifetime saving to costs of treatment of \$3 653AUD million in treatment costs. A total gain of 170 279 Quality Adjusted Life Years (QALYs) were also calculated due to avoiding HCV and HIV. Fuller details regarding this study can be found in table 2. These findings concurred with American research that conducted a random mixing statistical model using sensitivity analysis to quantify the cost-effectiveness of NEPs in reducing the incidence of HCV (42), concluding that NEPs need to be integrated as part of broader interventions to reduce the population prevalence of HCV and thus maximize cost-effectiveness.

### **Effect of opiate replacement therapy on HCV seroconversion**

While buprenorphine and methadone are the two most common agents used for opiate replacement therapy, we could only locate studies relating to methadone maintenance therapy (MMT). The full results are also shown in table 1. In summary, whereas MMT has been successful in reducing the incidence of HIV, the evidence for its effectiveness in reducing HCV incidence is less convincing (17,43-47). However, only one study (44) reported the mean methadone doses that may affect the reduction in anti-HCV incidence. This may be important as some commentators have argued that under-dosing would reduce the effectiveness of MMT at reducing unsafe injecting behaviour (48,49). Additionally, it has been argued that while users are likely to contract hepatitis C early in their injecting, they do not present to MMT services until later years, when they are more likely to have contracted HCV (49). It should be noted that MMT is a safe intervention for those who are HCV-RNA positive, as it is not hepatotoxic. Neither does severe liver disease increase peak serum methadone levels, despite a prolongation of the apparent terminal half-life (50,51).

### **Effect of behavioural programmes on HCV seroconversion**

We were unable to identify any intervention studies evaluating the impact of behavioural programmes at reducing the incidence or prevalence of anti-HCV. Observational studies did not evaluate behavioural interventions separately from NEPs (see table 1 for full summary) (47,52). While some Spanish research noted a reduction in the prevalence of HIV after the introduction of preventive measures (condoms and safer injecting advice), no statistically significant reduction in HCV prevalence was reported (53). We conclude that the effect of behavioural programmes on HCV seroconversion be researched further.

### **Does bleach distribution reduce the risk of HCV?**

Some commentators argue that training drug users to clean syringes effectively gives false assurance, reduces the validity of admonishments to never share another person's injecting equipment and reduces the health policy imperative to ensure that sufficient needles are distributed (54). However, recent qualitative research has shown that needle sharing is not a fixed behaviour. The practice is more likely when a user is withdrawing and has obtained drugs but does not have access to clean injecting equipment (55). There appears to be limited evidence to inform best practice. One case control study nested within a prospective cohort study of 390 IDUs from five American cities reported a statistically non-significant reduction trend of lower anti-HCV seroconversion for those who used bleach all the time, compared to those who used it some of the time, to those who did not use it at all (56). It would appear that simple health education messages regarding cleaning needles have limited effectiveness. Bleach distribution alongside needle distribution, however, is an area that merits further pragmatic research activity.

## **Supervised injecting rooms and hepatitis C**

Supervised injecting rooms (SIRs) or medically supervised injecting centres (MSIC) are “legally sanctioned and supervised facilities designed to reduce the health and public order problems associated with illegal injection drug use” (57). Their purpose is to enable the consumption of drugs under hygienic, low-risk conditions. Trained health staff, while not physically helping users to inject illicit drugs, supervise injecting in order to avoid high-risk drug taking and to ensure hygienic practices. Part of their intended benefit is to reduce drug-related harm associated with transmission of blood-borne virus infections. Descriptive data from an early evaluation of an SIR in Australia did not report an increase in notifications of hepatitis C infections among local users during the 18-month trial period, despite an increase in notifications from neighbouring areas (58). The report acknowledges, however, that the low population prevalence of the infections in Australia may make it difficult to detect any statistically significant changes. A more recent report on drug consumption rooms concurred that few data are available regarding the impact of such centres on the incidence of drug-related infectious diseases (59). It is plausible that SIRs can contribute to a reduced incidence of HCV given that numerous surveys show that high-risk users use such centres and report significant reductions in BBV risk behaviour (60-64). Establishing causal relationships will continue to be problematic as it is difficult to distinguish the injecting centres from other harm-reduction interventions.

## **Management of occupational percutaneous injuries**

French research utilized statistical model-based estimates of the annual number of cases of HCV transmission from infected patients to uninfected surgeons or nurses due to percutaneous injury during invasive procedures (65). The estimated risk of HCV transmission during a single procedure ranged from 1 in 2 380 000 to 1 in 238 000. The estimated cumulative risk of acquiring occupationally-related HCV infection in one year ranged from 1 in 10 000 to 1 in 1000. This translated to between 2 and 21 of the 20 000 French surgeons acquiring occupationally-related HCV infection each year. The estimated cumulative risk for nurses of acquiring occupationally-related infection in one year ranged from 1 in 18 700 to 1 in 1870, between 16 and 167 of the 300 000 French nurses acquiring HCV each year. Assuming that the probabilities do not change over time, the estimated cumulative risk of acquiring occupationally-related HCV infection after 30 years of professional practice ranged from 0.3% to 3.1% for surgeons to 0.1 to 1.6% for nurses [based upon the assumptions that their level of clinical activity remains constant over the 30-year period and that risk of percutaneous injury does not alter with increasing experience (66,67)].

## **Management of needle-stick injuries to workers handling hepatitis C-positive blood**

The seroprevalence of HCV in hospital personnel is similar to the general population (as represented by blood donors) (68). While this implies that there is a low risk of HCV transmission in occupational exposure, it is also true that treatment is poorly tolerated and not universally successful. Following a needle-stick injury, the likelihood of a health care worker acquiring a blood-borne virus such as HCV depends upon several factors including the prevalence of infection in the specific population, the nature of the injury, mucosa versus skin penetration, depth and location of needle penetration, whether the needle is a hollow bore or solid, its thickness, the quantity of blood/fluid exposed, the duration of exposure, the viral load in the contaminating fluid and the availability and efficacy of pre-exposure and post-exposure prophylaxis.

## **Primary prevention of needle-stick injury**

Primary prevention of needle-stick injuries underpins all strategies for management of this entity. Health care workers must be trained to modify their behaviour to reduce risk (69). Strategies include educating workers about the existence and magnitude of risk, the use of “universal precautions” such as treating all patients as potential carriers, the use of gloves, goggles and gowns where procedures are likely to result in blood or body fluid contamination, handling sharps carefully and the designated

disposal of sharps and infected waste. Other risk management strategies include training health care workers to modify procedures that are associated with high risk, providing them with instruments that reduce risk and ensuring they are aware of post-exposure strategy.

General measures to reduce risk also include vigorously washing all contacted wound and skin sites with soap and water, including flushing the eyes with water as soon as the worker is aware of exposure. Caustic agents or disinfectants are not recommended nor is squeezing or manipulating the wound site excessively, which has no benefit in reducing transmission due to the potential for tissue damage. The source should be tested for HIV, HBsAg and HCV if the infective status is uncertain after counselling. Finally, medical records should document the event, including the nature and circumstances of the exposure and the worker's immune status.

### **Specific measures for exposure to hepatitis C**

The diagnosis of hepatitis C in the health care worker must be clearly defined. The two markers are the HCV antibody and the RNA, which appears in serum 10 days following exposure. False positive and negative RNA levels occur, so serial RNA-testing is valuable. HCV antibodies are detectable in serum a median of 50 to 70 days following exposure. Seroreversion of the antibody takes years, so most experts accept the absence of HCV antibodies and normal level of the liver enzyme alanine aminotransferase (ALT) at least six months after exposure as evidence of an absence of HCV infection. HCV testing should take place alongside testing for HIV and hepatitis B virus. All health care workers should be immunized against hepatitis B. There is a place for post-exposure management of HIV with anti-retrovirals.

The use of anti-viral drugs for health care workers exposed to HCV was not recommended until the remarkable data on treatment of acute HCV was published. In 2002, the National Institutes of Health Consensus on the management of Hepatitis C stated that treatment of people with acute HCV was warranted, but it was less clear when and how they should be treated (70). A recent meta-analysis (71) reported a highly significant effect for the treatment of acute hepatitis C with interferon monotherapy. This and other similar studies are summarized in table 3.

One of the few published studies evaluating the effectiveness of short course interferon therapy for occupational needle-stick injuries was performed in Japan. The results would support a full course of interferon treatment for those diagnosed anti-HCV positive. However, it would not support a prophylactic short course of interferon immediately after exposure (72). Retrospective analysis of medical records was undertaken of 279 personnel who were treated with 1 to 3 days of interferon within a few days of the needle-stick injuries. They were compared with 405 controls who received no treatment. One patient in the treated group and one in the untreated group developed chronic HCV infection, and both cleared the virus with further interferon treatment (the dose and duration were unspecified).

When to administer interferon therapy is important, as acute HCV infection will only progress to chronic infection in 80% of people. A prospective study (73) clearly demonstrated that any spontaneous HCV RNA clearance that occurs will be in the 8 to 12 weeks following onset. If facilities exist for the regular virological quantitative polymerase chain reaction (PCR), then the current evidence base would suggest that clearance can be predicted by the rate of viral load decline (74). In the meta-analysis mentioned above it was clear that delaying treatment for 60 days after the onset of symptoms did not reduce efficacy. The current guidelines (75) recommend the following specific measures post-exposure to HCV: First, an immediate HCV antibody (and/or PCR) test should be performed. This should be repeated after one and two months. If PCR is negative after month 1 and month 2, it should be repeated at months 3 and 4 to confirm that HCV has not been acquired. However, if PCR is positive at month 1 and negative at month 2, the patient is likely to have been exposed and cleared HCV spontaneously. If PCR is positive at month 1 and month 2, the patient

should be treated as “acute hepatitis C” with standard interferon monotherapy (with a daily induction dose during the first month).

A survey of United Kingdom clinical microbiologists/virologists demonstrated that despite the publication of guidelines the majority of hospitals did not follow them (76). Ten percent did not test the inoculation source and half only tested if the source was considered to be high risk. Three-quarters did not consider interferon of any value.

### **Reducing the incidence of HCV seroconversion from vertical transmission**

International evidence bases describe incidence rates of vertical transmission of HCV from anti-HCV seropositive mothers to children as 5%, with a range of 2.7% to 15% (77-80). Maternal co-infection with HIV increases the risk of vertical transmission (81,82) but does not increase the risk of sexual transmission. Additional risk factors for vertical transmission among vaginal deliveries include higher mean HCV load of mothers, a reduction in umbilical cord blood pH, the occurrence of perineal or vaginal laceration or prolonged rupture of membranes (83,84). However, for those HCV infected only, no statistically significant difference was found for HCV genotype, duration of drug use, duration of methadone use, methadone dose, history of alcohol abuse, past HBV infection, mode of delivery, maternal and gestational age, birth weight, incidence of breast feeding (83), mode of delivery (caesarean section vs. vaginal delivery or breastfeeding vs. non-breastfeeding (81). However, for the 35% who were co-infected with HIV, there was a 60% lesser probability of having an HCV infected child delivered by caesarean section, compared to those delivered vaginally. Mothers with HIV co-infection who breastfed were more than four times as likely to infect their children as those who did not. HIV infected children were also three to four times more likely to be HCV infected than children without HIV infection (81). The consensus among the recommendations is that there is an insufficient evidence base to recommend elective caesarean section to all anti-HCV seropositive pregnant women at term (77,81). However, elective caesarean section and advice against breastfeeding are recommended for mothers co-infected with HIV. These findings concur with a Canadian review that concluded that breastfeeding provides no important risk of HCV transmission if nipples are not traumatized and maternal hepatitis C is quiescent (85).

### **Monitoring the outcomes of vertical transmission of HCV**

An Italian literature review (86) recommended that for children born to anti-HCV positive, HCV-RNA negative mothers, alanine aminotransferase (ALT) and anti-HCV should be investigated at 18 to 24 months. If ALT levels are normal and anti-HCV is undetectable, follow up can be discontinued. In children born to HCV-RNA positive mothers, ALT and HCV-RNA should be investigated at 3 months. If the results of the test is positive and a further test within a twelve-month period is positive then the child should be considered HCV positive. HCV-RNA negative children with normal abnormal ALT should be tested again for viremia at 6 to 12 months and for anti-HCV at 18 months. HCV-RNA negative children with abnormal ALT should be tested for anti-HCV and ALT at 18 to 24 months and should be considered non-infected if ALT is normal and anti-HCV undetectable. Anti-HCV positivity beyond 18 months in a never viremic child with normal ALT is likely consistent with past HCV infection. The need for long-term follow-up of infected infants is further endorsed by a French review (87), arguing that because of the low rate of HCV vertical transmission pregnancy can be “allowed”. They urge, however, consideration of anti-viral treatment before pregnancy for those who are HCV-RNA positive. They and other commentators suggest offering antenatal screening only to those women with risk factors, since the prevalence of anti-HCV in pregnant women is less than 2% (88).

### **Evidence for the effectiveness of anti-virals at eradicating HCV and preventing chronic consequences**

Anti-viral therapy for HCV has evolved rapidly over the last 10 years. Initial therapy entailed the use of standard interferon monotherapy. However the current evidence base would suggest pegylated

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interferon (IFN conjugated to polyethylene glycol administered as a once-weekly injection) combined with ribavirin as the most effective therapy (89). Treatment for a period of either 24 or 48 weeks can achieve sustained viral responses of between 46% and 82% in trials using this PEG-ribavirin combination. Adverse effects are seen in up to 75% of recipients, causing up to 20% to fail to complete therapy (90,91).

The wide range of reported effectiveness is due to differing overall dosages, duration and schedules of treatment, heterogeneity of virological and clinical features of treated patients and different sensitivity of assays for detection of serum HCV-RNA (92). Italian commentators systematically reviewing the published literature reported a relapse of 13% (range 0-86%) in those achieving a sustained virological response (SVR) as defined by a negative virological test six months post completion. In reporting the heterogeneity of the studies they concluded that "it is possible to speculate that the eradication of HCV after antiviral treatment with combination therapy, especially if performed with highly active PEG-IFNs will remain stable in most patients over extended follow up" (92).

A recent meta-analysis has also demonstrated the effectiveness of interferon in achieving an SVR in the treatment of acute hepatitis C (71). The risk difference increased when trials were sorted by increasing weekly doses. Delaying therapy by 8 to 12 weeks after the onset of disease does not compromise the SVR rate. Chronic HCV infection progresses on to cirrhosis in at least 20% of people by the second decade of infection (93). A significant proportion of these people will develop end-stage liver disease, hepatocellular cancer and subsequently die. As a consequence, HCV is a major cause of death from chronic liver disease worldwide, even in those countries where liver transplantation is available. One of the aims of effective antiviral agents is to interrupt this disease progression. The next section examines the effect of antivirals on the laboratory parameters biochemistry and histology, as well as the clinical parameters described above.

*Does antiviral therapy improve biochemistry?*

The response to interferon treatment for people with chronic HCV was originally defined as normalization of serum ALT until the assays to detect HCV RNA became available. Despite the replacement of the biochemical definition by the virological definition of response, it is clear that up to 90% of those achieving a biochemical response will also have a virological response. However, not all "virological" responders will normalize their ALT (94-97). A meta-analysis of the sensitivity and specificity of ALT as a measure of histological response after interferon treatment for hepatitis C highlighted a number of difficulties with an ALT-based treatment response definition (98). First, a normalized ALT among people with improved liver histology was 4.8 times more likely than a normalized ALT among people without improved liver histology. Second, up to 17% of those without a normalized ALT may have improved histologically. Third, the range of sensitivity and specificity for ALT as a marker of histological improvement varied between 22% and 100% and 40% and 100% respectively. Fourth, some people with cirrhosis may never normalize their ALT regardless of their histological, or indeed virological response.

*Does antiviral therapy improve liver histology and reduce the incidence of cirrhosis?*

Investigations designed to explore regression of HCV-induced liver damage must be viewed cautiously as there can be variation between different clinicians in both sampling practice and histological interpretation. Furthermore, liver histology in chronic HCV may improve spontaneously. However, intervention and observational studies evaluating histological endpoints consistently demonstrate a reduction in necro-inflammatory activity in most people with chronic HCV successfully treated with interferon (IFN) (94,97,99-102). In those who manifest a sustained response – defined as six months post completion of anti-viral therapy, this histological improvement appears to be maintained (98,103).

Long term follow-up of 90 participants in Japan demonstrated a reduced incidence of cirrhosis in those randomized to receiving interferon therapy (104). Several observational and descriptive studies concur

that response to anti-viral therapy, leads to an improvement in fibrosis score relative to non-response/relapse, which in turn has a greater improvement in fibrosis scores compared to those who have not received anti-viral therapy (105-109). While early studies were all monotherapy-based, later studies evaluating dual therapy demonstrated reduced progression to fibrosis compared to those receiving monotherapy (103).

*Does antiviral therapy reduce the incidence of hepatocellular carcinoma (HCC)?*

A recently published Japanese randomized controlled trial specifically recruiting cirrhotic participants, while acknowledging the higher incidence of HCC in Japanese than in Caucasian populations, reported a lower incidence of HCC in the treated group (table 3) (104,110). These findings concur with an earlier systematic review (92) and a meta-analysis (111). The systematic review calculated a risk reduction of developing HCC in sustained responders compared with non-responders or relapsers (table 3). The meta-analysis also reported a pooled risk reduction of HCV incidence among sustained responders compared to untreated controls. These findings concur with those of large observational studies demonstrating a greater protective effect associated with sustained clearance of the virus (112-118). The studies concur that the difficulty in demonstrating the protective effect of ART against HCC should not be underestimated. Limitations include: probable limited effect of monotherapy compared to combination therapy; trials using types; a lack of combination therapy trials; the slow evolution of HCC as a late consequence of infection, when treatment is less effective; lack of control for the variables "alcohol intake" or "lead-time bias"; and some reporting of biochemical rather than virological responses.

The issue of whether the anticancer effect seen following successful viral eradication is due to the drug itself or due to removal of the viral stimulus has been the subject of debate. The tendency of the cancer to occur after successful treatment in older males with sustained biochemical derangement and alcohol excess, and the only partial abrogation of the risk in relapses would suggest that treatment response – not the treatment – influences the risk.

## **HIV/HCV co-infection**

Up to 30% of HIV-positive people in Europe and the United States are co-infected with HCV, and over 10% of HIV deaths are attributable to liver disease. Worldwide there are an estimated 40 million people infected with HIV and 170 million with HCV, of whom 10 million will be co-infected. HIV appears to accelerate HCV-related liver disease, but HCV does not appear to affect the rate of HIV disease progression. Up to 90% of HIV-positive haemophiliacs and 70% of HIV-positive intravenous drug users will also be HCV positive due to their shared transmission route (119). The international evidence base from independent epidemiological studies conducted in Asia, Europe and North and South America concurs that sexual transmission is rare (120-123). The risk factors for sexual transmission are higher in male-male encounters, where it is associated with promiscuity. The risk of transmission is also increased by sexual practices traumatic enough to result in overt bleeding or ulcerative sexually transmitted infections (124). Perinatal transmission is enhanced for both viruses in co-infected mothers, but highly active antiretroviral treatment (HAART) and caesarean section reduces this to under 1%.

*Diagnosis of HCV in HIV-positive individuals*

HCV antibody detection by ELISA is not reliable in advanced immunodeficiency, when the antibody may disappear yet the patient remains viraemic. RNA is detectable in approximately 80% of those anti-HCV positive, implying that a similar percentage of HIV positives will clear the virus as seen in the HIV-negative/HCV positive population. Hence, a single HCV antibody test does not exclude HCV co-infection and HCV PCR is necessary in all suspected people who have advanced HIV disease.

*Natural history of HIV/HCV co-infection*

The damaging effect of HIV on HCV-related liver disease is most clearly demonstrated by the haemophiliac cohort studies recently reviewed by German commentators (119). In an American cohort, 9% of multi-transfused, co-infected adult haemophiliacs developed liver failure (though they had no aids-defining illness or malignancy) compared with none in the HCV-positive HIV-negative haemophiliacs. The time to develop cirrhosis or hepatocellular cancer is shorter in co-infected individuals (125-128). Liver-related mortality in the post-HAART era is seen predominantly in intravenous drug users who drink even modest amounts of alcohol and manifest more HCC's and adhere poorly to HAART therapy. However, the evidence for the effect of HCV on HIV is still emerging. Modern anti-retroviral therapy that enables the restoration of immune defence has permitted extended follow up. Early studies demonstrated a lower CD4+ cell count (a sub-type of white cells important in fighting infection and therefore reflective of more severe immunodeficiency) one year after HAART in those with co-infection compared to those with HIV infection alone (129). However subsequent studies found no difference in mortality when multivariate analysis was applied to correct for use of HAART, baseline viral loads, CD4+ cell counts, age, race and risk factor for transmission of HIV (130,131).

The risk/benefit ratio of offering HAART to co-infected individuals has been debated. While HAART does not adversely affect HCV RNA (and may indeed cause some reduction), delays fibrosis, lowers rate of hepatic decompensation, and raises CD4+ cell count (132,133), there is a risk of hepatotoxicity. Additionally, the presence of HCV appears to confer an enhanced risk of hepatotoxicity independently. Hepatotoxicity is seen with ritonavir and nevirapine whereas the d-nucleosides (particularly didanosine and stavudine in combination) are best avoided in HAART regimens because they encourage hepatic steatosis in co-infected people (134,135).

*Efficacy and toxicity of HCV treatment in co-infected individuals*

Treatment trials of HCV in co-infected individuals using standard interferon monotherapy or interferon combined with ribavirin were characterized by sustained viral response rates under 40% and discontinuation rates of nearly 1 in 3 (136-140). There is an emerging evidence base from recent randomized control trials for the superior effectiveness of polyethylene glycol (PEG)-interferon in co-infected populations (compared to either standard combination therapy or PEG-interferon alpha-2a monotherapy) (141-144). Cohorts with genotypes 2 and 3 have a higher SVR than those with genotype 1 or 4 (141,143,144). There was also drop-out rate of up to 38% due to anti-viral therapy toxicity. A synthesis of the available evidence would suggest the following treatment algorithm:

1. Treatment should be biopsy based. Prior histology is required even with genotypes 2 and 3 as the treatment is far from universally effective, and indeed may be quite toxic.
2. Treatment should be considered where there is evidence of advancing fibrosis in a HCV RNA-positive individual.
3. Treatment should be considered alongside immunological status:
  - treat: CD4-count >350 cells/ul and plasma HIV RNA <50 000 copies/ml with or without HAART
  - caution, optimize HAART first: CD4-count<350 cells/uL
  - do not treat, initiate HAART: CD4-count <200 cells/uL.
4. Treatment should be combination therapy with pegylated interferon and ribavirin.
5. Treatment duration should be 48 weeks for genotype 1 and 4 and perhaps 2 and 3 as well.
6. Treatment should stop at 12 weeks in those people who fail to demonstrate a reduction in viral load of >2 log.
7. Careful monitoring of treatment side-effects and drug interactions is required.
8. Avoid ribavirin and didanosine, due to the risk of pancreatitis and mitochondrial toxicity.
9. Ribavirin may enhance toxicity with zidovudine and stavudine.

10. Consider liver transplant in end-stage liver disease. The results of liver transplantation in the pre-HAART era were dismal, but now that HIV can be controlled after liver transplant, one year survival is close to that of transplant recipients for HCV alone.

## **Treatment of Haemophilia and HCV**

After exposure, approximately 10% of infected haemophiliacs clear the virus spontaneously, usually within 12 months. This occurs in younger people with milder forms of haemophilia who do not require particularly frequent transfusions (145). For the majority of people who do not clear the virus, the range of liver disease is broad, incorporating those who are PCR-positive but who have persistently normal liver transaminase values, to those people with cirrhosis and HCC. However, the results of prospective cohort studies would suggest that the disease progression is less aggressive than in the non-haemophiliac population (146,147). More severe disease progression is associated with genotype 1 (148), and the age at infection (though this is confounded by duration of infection) (149). Treatment of HCV disease in haemophilia is identical to that advised in non-haemophiliac populations (150). PEG-IFN and ribavirin is the standard for 6 months in non-genotype 1 and 12 months in genotype 1 disease. Response rates, however tend to be poorer as the patients are almost exclusively males, with high viraemia, infected with the most resistant virus sub-type, genotype 1. The decision to treat in haemophiliacs is hampered by the difficulties in obtaining liver histology, and must be a compromise based on biochemical and virological factors, patient preferences and likelihood of disease progression.

The risk of hepatic decompensation 20 years after first exposure to clotting factors is around 10% but the incidence rates of HCC are high (390 per 1000 person-years), and tumours almost invariably present as multicentric, which are not eligible for curative treatment. The effectiveness of tumour surveillance has yet to be demonstrated (151).

## **HCV/HIV co-infection and haemophilia**

With the reduction in mortality from HIV infection by HAART, the potentially life-threatening effects of chronic HCV infection have become apparent. A European study (152) examined a large cohort of co-infected haemophiliacs over a 20-year period and showed that while there was no increase in the rate of HCV related deaths, HCV accounts for an increasing proportion of deaths in recent years due to a reduction in HIV related deaths after HAART. HIV co-infection increases the risk of hepatic decompensation and HCC (147,149).

The outcome of HCV in HIV patients with haemophilia is related to the following factors: degree of immunocompetence at the time of initial HCV infection, the magnitude of HCV inoculation, the duration of the infection, more advanced HIV infection (but not degree of viraemia), previous infection with hepatitis B and alcohol excess (153). The detrimental role of the hepatitis B virus in the course of hepatitis C in haemophiliacs warrants vaccination in those not exposed.

HCV treatment strategy in HIV co-infected people is the same as in immunocompetent people. In addition, progression of hepatitis C towards cirrhosis is delayed by HAART and hepatic decompensation rates are reduced in co-infected haemophiliacs under antiretroviral therapy compared to untreated people. Anti-viral treatment is indicated in those co-infected individuals not on HAART, with stable HIV and with well preserved CD4 counts. Risk of hepatotoxicity from HAART appears to be higher in those co-infected with HBV, HCV and HIV. Currently there is no consensus regarding the most appropriate drug combination. Close monitoring is required regardless of which therapy is used.

The place of liver transplantation in the treatment of haemophilia is now well-established. The transplant will cure the underlying coagulation disorder and patient and graft survival are comparable to non-haemophilia recipients. HIV co-infected people stable on HAART can be considered for liver transplant if indicated by severity of liver disease (154).

## **Thalassaemia and hepatitis C**

Patients with thalassaemia major require large amounts of red cell products, rendering them vulnerable to transfusion-acquired viruses such as hepatitis C. While modern screening of donated samples has reduced the transmission rate considerably, nearly three quarters of thalassaemic patients over the age of 25 are infected with hepatitis C (155). With improved clinical care, thalassaemia patients are living longer and hence complications of chronic hepatitis C such as cirrhosis and hepatocellular cancer are being seen more frequently. Clinicians have been cautious with the use of standard antiviral therapy because the data sheets for ribavirin preclude use in heamaglobinopathies, and exacerbation of the iron overload is also possible, so careful evaluation of potential treatment recipients is necessary. Hence initial enthusiasm for interferon monotherapy has, at last, given way to combination therapies where clearance rates approach those expected for non-thalassaemic hepatitis C positive patients, but adequate trial data are lacking (156).

## **Effectiveness of blood screening procedures prior to transfusion and organ or tissue screening before transplantation**

The potential for transmission of tissue and blood-borne pathogens by either transfusion or transplantation causes alarm among both the general public and policy-makers. Over the last ten years major changes have been implemented to improve the safety of blood and tissue products. A brief overview is presented below.

### *Development of Testing*

Reports from the early 1940s describe jaundice following blood transfusion (157). However it was not until the 1960s that donor screening for elevated ALT was introduced in some countries as a means of identifying people with hepatitis. In the 1970s the introduction of donor testing for hepatitis B surface antigen led to a reduction in post-transfusion hepatitis. It also alerted transfusion services to the fact that the majority of post-transfusion hepatitis was not caused by hepatitis B (158). The discovery of hepatitis C in 1989 and the subsequent introduction of donor antibody screening in the USA setting resulted in a substantial reduction in post-transfusion hepatitis from 448 per 100 000 to 1.25 per 100 000 (159).

Antibody (or serological) tests for hepatitis C require a period of time for the patient to acquire the virus, incubate it and subsequently manifest an antibody response. During this "window period", the patient will be negative for the antibody, but will be infective. This window period is approximately 60 days. While the actual risk to the blood/blood product recipient is small, the theoretical risk prompted blood services worldwide (FDA, European Agency for the Evaluation of Medicinal Products) to recommend the introduction of nucleic acid amplification technology (NAT) testing for both single donor and pooled donations. It identifies actual viral RNA in the blood that appears as rapidly as 10 days after infection has been acquired. NAT reduces the risk of HCV transmission to 0.27 per 100 000 (160). French data demonstrates a similar level of risk reduction (161). NAT can either be applied to samples individually and processed separately or 'pooled' and tested in batches. In the latter case, if the pool tests positive individual donor samples can be further tested. Such pooling measures can speed the processing of samples without affecting identification accuracy.

### *Quality Control in Testing*

Worldwide, many transfusion services have introduced NAT technology to screen blood donors for HCV. The introduction of such technology makes additional demands on the blood services including the need to carefully collect and store samples, to avoid contamination in the amplification process and to cope with delays in blood and product availability because of PCR processing time. Laboratories report the need for additional technician training, strict and vigorous cleaning of the PCR machine with ultraviolet irradiation to reduce false positive results (162). The introduction of TaqMan or real-time PCR technology reduces contamination risk, shortens processing and increases sensitivity compared to the older PCR technology.

The availability of World Health Organization (WHO) international viral RNA standards permits standardisation and ongoing performance monitoring for laboratories (163). The Australian Red Cross Blood Service introduced NAT screening of all donors in 2000. Over an 18-month period, 1.5 million blood donations were collected in 5 centres and tested either singly or in pools of 24 donors. Critical examination entailed careful investigation of run failures (when the internal NAT controls – known positives placed to check accuracy – fail to be returned as positive), use of internal and external controls and comparison with other laboratories. Results showed pooled testing to be more efficient but also more prone to frequent minor performance defects. One-hundred ninety-four (0.01%) donations were positive on NAT testing for HCV, of which 190 were antibody positive. The remaining four were antibody negative (from the original pool of 1 439 765 donations). The method was to compare three sites using both individual and pooled testing with two sites using individual testing alone. NAT was used to check NAT insofar as the PCR technology (which is what NAT is) is the benchmark for identification of virus in blood. Hence the purpose of this trial was to see whether pooled NAT testing was as efficient as pooled testing. The assay specificity was 100%. There were 66 donors who were antibody positive but RNA negative, implying they had spontaneously cleared the virus. The sensitivity was 74.6%, is similar to 76% from American data (164). Run failure rates were 4.2% for pooled sites compared with 2.9% for single sites, although there was a tendency for this to reduce with time, suggesting that familiarity with the techniques improved efficiency and accuracy.

#### *Cost-effectiveness of donor testing*

Optimizing recipient safety includes measures to reduce the number of donations a recipient receives by means such as autologous transfusion, use of cell-savers at surgery, or erythropoietin. A systematic review of the cost-effectiveness was undertaken in the Netherlands (165), concluding that antibody testing alone is cost-saving as it reduces the risk of transmission. However the addition of NAT testing requires a considerable budget reallocation for a very small additional health gain. It is argued that transfusions are given to an aging population who will take many years to manifest disease from any associated viruses transmitted during blood transfusion. In such a population, either death or other serious illness can precede the manifestation of viral illness. (166). Thus, antibody testing is cost-saving, whereas NAT testing is associated with a cost-utility ratio (life-years gained adjusted for quality of life) that exceeds US\$ 1.5 million dollars per QALY. While this figure is high, political commitment remains in most high-income countries due to the need to maintain public confidence in the safety of blood transfusion (167).

### **Improving data monitoring of HCV prevalence and incidence**

There is a need for improved data sources of HCV incidence and prevalence to monitor the future societal burden of the chronic consequences of HCV infection. American research has demonstrated that in services employing physicians and/or nurses, attendees are more likely to be screened for HCV (168). Barriers to offering HCV screening services to clients include concerns about lack of educational and training materials for providers and clients, funding and medical coverage, the need for a screening facility and difficulty arranging treatment with outside HCV providers. Commentators in the United Kingdom have proposed possible data sources for monitoring HCV incidence and prevalence (see annex 3) (169).

## **Conclusions**

In summary, reducing the prevalence of HCV continues to present a considerable political and public health challenge. In the absence of an immediate prospect of a vaccine against HCV (170), over-reliance should not be placed on any one primary or secondary intervention. Due to the significant health morbidity associated with the long-term consequences of HCV infection, wider availability of the full range of interventions described in this synthesis is likely to lead to significant health and economic savings. Some interventions such as needle exchange programmes in prisons, safe injecting

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rooms or provision of bleach as disinfectant alongside clean needle exchange have the potential to be contentious. Controversy can arise from the absence of an international consensus and the need to balance health, legal and political agendas as well as public confidence in the management of the complex drugs agenda. Renewed political will to address the HCV agenda is welcome and provides an opportunity to work with the full range of stake-holders with a common aim of successful control of the global health problem of high HCV prevalence (171,172).

## **Annex 1: Quality assessment criteria of papers considered for the synthesis**

The protocol for the systematic review entailed devising a checklist to assess the quality of the papers:

- clear case definition of anti-HCV positivity (type of biochemical test used)
- location (city, country, number and type of treatment settings)
- years of recruitment (and total duration of recruitment)
- number of participants (and breakdown by age, gender, ethnicity, sexual orientation, type of drug used, mean length of illicit drug use, employment status, housing status)
- percentage of those identified recruited into study
- percentage follow-up of participants.

For randomized controlled trials:

- randomization clearly described and whether open, single blind, or double blind
- concealment process clearly described
- steps taken to avoid contamination
- steps taken to ensure independence of data analysis
- use of intention-to-treat analysis.

For quasi-experimental or case-control studies:

- baseline data reported
- potential for selection bias described and accounted for in the analysis
- potential for confounders described and accounted for either by multivariate analysis or stratification
- steps taken to ensure independence of data analysis.

For observational cohort studies:

- probabilistic sampling methods to select participants
- use of a control group
- potential confounders described with an attempt made to quantify the effect either by multivariate statistical analysis or stratification
- potential for loss to follow-up bias described and accounted for in the analysis (minimally a description of any difference in baseline demographics between those followed up and those lost to follow-up).

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## **Annex 2: Levels of Evidence & Strength of Recommendations**

*Categories of evidence for causal relationships and treatment:*

- Ia: evidence from meta-analysis of randomized controlled trials
- Ib: evidence from at least one randomized controlled trial
- II: evidence from at least one controlled study/other type of quasi-experimental study
- III: evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies
- IV: evidence from expert committee reports or opinions and/or clinical experience of respected authorities.

*Proposed categories of evidence for observational relationships:*

- I: evidence from large representative population samples
- II: evidence from small, well designed, but not necessarily representative samples
- III: evidence from non-representative surveys, case reports
- IV: evidence from expert committee reports or opinions and/or clinical experience of respected authorities.

*Strength of Recommendation*

- A directly based on category I evidence.
- B directly based on category II evidence or extrapolated from category I evidence
- C directly based on category III evidence or extrapolated from category I or II evidence
- D directly based on category IV evidence or extrapolated from category I, II or III evidence.

### **Annex 3: Proposed data sources for monitoring HCV incidence and prevalence (source: Bird et al., 2001)**

Registration of confirmed hepatitis C infections and information on HCV-test uptake:

- a registry of confirmed HCV infections including the individual's first name initial, a soundex of the surname, date of birth, gender, postcode, district of residence, health board of residence, risk factor, source of referral and previous HCV test history<sup>1</sup> (If injecting drug use is the risk factor, then "year of starting to inject" should be recorded since this marks the likely start of an individual's seroconversion interval.);
- surveys of HCV test-uptake by injectors and others, which are currently unavailable in the United Kingdom and other countries;
- documentation of pregnancy and its outcome in HCV-infected women, including paediatric surveillance for HCV infections;
- anonymous testing for HCV antibodies in blood or saliva for at risk groups (including new blood-donors, pregnant women, patients awaiting kidney transplantation, non-injector prisoners, health care workers, or non-injector heterosexuals attending genitourinary medicine clinics, injectors in the community undergoing testing at drug treatment centres, or injectors undergoing testing in the prison environment);
- historical data on HCV prevalence in injectors;
- HCV incidence studies in injectors;
- uptake of harm-reduction measures by injectors (frequency of needle sharing and methadone substitution).

Data sources for monitoring the late consequences of hepatitis C carriage, its investigation and treatment:

- linkage surveillance (for example by master index to identify deaths, hospitalization or cancer registrations among confirmed HCV infected people);
- surveys of HCV status among patients attending *Hepatology* services (including those who undergo liver biopsy, are newly diagnosed with cirrhosis, or are newly diagnosed with liver cancer);
- surveys of liver biopsy rate in HCV-infected injectors and others;
- uptake and outcome of anti-viral therapy in the treatment of HCV carriers;
- cohort studies of HCV progression;
- sample surveys of genotype in HCV-infected persons;
- acute hepatitis B infections and uptake of hepatitis B immunization by injectors;
- liver transplantation in HCV-infected patients;
- HCV status and other risk factors in deaths from cirrhosis or liver cancer (to determine whether they are HCV-related or injector-related).

Potential data sources for quantifying the scale of the underlying injector epidemic:

- drug misuse databases analysed using capture-recapture methods to assess the number of injectors
- drug-related deaths by region to assess number of injectors
- number of HIV-infected injectors
- HIV progression in injectors
- overdose and other causes of death in injectors

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<sup>1</sup> To this minimum dataset we would argue that "ethnicity" should be added.

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- expert opinion on injector incidence combined with survey information on age-distribution at initiation and the duration of injecting careers
- injector incidence historically inferred from HCV-infected blood donors
- age distribution of current injectors, and at initiation (to validate the assumptions behind statistical modelling of HCV population prevalence data made from local surveys)
- mortality of former injectors
- general population (or other) survey ratios of surviving ever-injectors to injectors in (for example) the last five years, last year, and currently.

**Table 1: Summary of observational studies exploring the impact of primary prevention measures upon HCV prevalence and incidence among IDUs**

Author, year	Setting	Participants (number, age, gender, ethnicity & drug use)	Methods (including inclusion/exclusion criteria & quality of methodology)	Duration of study	Outcomes	Results
Broers et al. 1998	Methadone maintenance treatment clinic, Geneva, Switzerland.	706 drug users, 540 men, 166 women. Average age at entry 27 years (range 17.4-48.4 years).	Prospective cohort study between 1988 and 1995.	Those in programme for 3 months compared with new clients.	Effect of HIV health promotion interventions on HCV incidence and prevalence for pre 1988 (drug use before HIV health promotion interventions); from 1988-1991 (mixed drug use and health promotion); 1991 onwards (drug use started post HIV health promotion interventions). Antibodies for HCV were assayed in 1989-1991 using a 1st generation HCV antibody ELISA system (Ortho-Diagnostics, Raritan, New Jersey, USA) and a 2nd generation test from June 1991 (HCV EIA, Abbott). Stored sera were re-tested with the second test where available.	Prevalence at entry into treatment declined dramatically over time for HCV. The prevalence of HCV among drug users entering treatment before 1988 was 91.6%, compared to 29.8% in those entering treatment after 1993. HCV incidence was 4.2% per person-year of follow up (95% CI 2.2-7.4).
Goldberg et al. 1998	Regional Virus Laboratory, Glasgow, UK.	342 serum samples 1990 and 414 samples 1995 taken from IDUs presenting for HIV testing. Serum residues were stripped of patient information except for age and sex.	Retrospective longitudinal study.	2 cohorts – one tested in 1990 & one tested in 1995.	Prevalence of HCV in 1995 compared with 1990. Specimens reacting to ELISA (Ortho 3rd generation, Chiron) were retested by a second ELISA (Sanofi Pasteur) hepatitis C test. Discrepant results tested by a recombinant immunoblot assay (RIBA 3rd generation, Chiron).	Prevalence of anti-HCV fell significantly between 1990 and 1995 from 90% to 77% in IDUs of all ages (95% CI 73-81), from 92% to 29% in IDUs aged 15–19 (95% CI 1-56), and from 91% to 65% (95% CI 54-75) in IDUs aged 20–24. No significant reduction for those aged 25-29, 30-34 or those over 35. No significant differences between males and females in 1990 or 1995.
Goldberg et al. 2001	Scottish Centre for Infection and Environmental Health, Glasgow.	IDUs who had undergone named HIV testing HIV in Edinburgh and Glasgow were identified, linked to age band and gender information, and tested anonymously for HCV.	Retrospective longitudinal study.	Changes in anti-HCV prevalence in Glasgow over 1995-1997 and in Edinburgh for 1989-1990 and 1995-1997.	Changes in HCV prevalence. Residual sera specimens which tested reactive by a 3 <sup>rd</sup> generation ELISA assay (Ortho, Chiron) were retested with an ELISA assay (Sanofi Pasteur). Only specimens reacting to both tests deemed antibody positive.	Significant decreases in anti-HCV prevalence in Edinburgh IDUs from 69% (95% CI 65-74) in 1989/90 to 13% (95% CI 8-21) in 1997 in those <25. Significant decrease in 25 years or over from 80% in 1989/90 (95% CI 76-83) to 54% in 1997 (95% CI 48-61). The $\chi^2$ test for trend over 1989-97 showed the reducing trend to be more pronounced amongst those <25, (186.5, p<0.0001) than those 25 or over (54.6,

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						p<0.0001). In Glasgow, a significant decrease, in prevalence from 91% (95% CI 85-95) to 43% in 1997 (95% CI 34-51) in those aged <25 ( $\chi^2$ test for trend 73.9, p<0.0001). For 25s and over, the decreasing trend was of borderline significance (3.7, p=0.06). Of both cities' 17% of 15-19 year olds sampled during 1995-1997 were anti-HCV positive.
Hagan et al. 1995	Tacoma syringe exchange, USA.	28 IDUs (60.7% male, 82.1% white) were cases with acute HBV and 20 (70% male, 85% white) IDUs with acute HCV. Controls were 38 (50% male, 73.7% white) IDUs with no HBV markers and 26 (42.3% male, 73.1% white) with no HCV markers. 3 age groups, less than 25, 25-35 and 35 years or older.	Case control study	1991-1993	Association between syringe exchange use/non use and hepatitis B and C in IDUs.	After adjusting for demographic characteristics and duration of injecting drugs, non-use of the exchange associated with a seven fold greater risk of anti-HCV seroconversion (AOR = 7.3, 95% CI=1.6-32.8).
Hagan et al. 1999	6 drug treatment programs and from social service, corrections and drug-use assessment agencies Seattle, USA.	353 anti-HCV negative IDUs from a larger cohort of 2,728 IDUs recruited into an earlier study. Age ranged from 14, ethnic background was described as English or Spanish speaking. Recruitment by probabilistic sampling methods of every nth person as they entered the agency, or appeared on client lists. A control group was established.	Prospective cohort	June 1994 and January 1996.	HCV incidence measured by 3 <sup>rd</sup> generation immunoassay (Abbott laboratories, Chicago, Illinois).	No statistically significant differences between those lost to follow up and those retained in the study with respect to baseline characteristics 187/241 had injected during the follow-up period (mean of 408.9 days). From this cohort 39 IDUs seroconverted (a cumulative incidence rate of 20.8% per year). Relative to non-users, regular users had a slightly higher incidence (adjusted relative risk 1.31, 95% CI 0.79-2.19), which was lower than the incidence amongst sporadic users (adjusted RR 2.59 (CI: 0.79-8.5). Both effects statistically non-significant.
Hernandez-Aguado et al. 2001	3 AIDS prevention & information centres, Spain.	5473 volunteers of which 3238 had an HCV test. Average age 27.4 years, 77.4% male.	Prospective longitudinal study	1990-1996	Effect of HIV prevention measures upon the trends in prevalence of antibodies to HCV measured by a 1st generation EIA test during 1990-1991, a 2nd generation EIA from 1992 onwards (Organon Teknika, Holland). A second confirmatory test (Recombinant Immunoblot Assay RIBA-2, Ortho Diagnostic systems, Raritan, New Jersey, USA) was done on the positive EIA tested serums.	No statistically significant reduction in prevalence of HCV over the study period. 84.5% (1990-92 (RR=1); 84.1% 1993-94 (RR=0.99, 95% CI: 0.969-1.03); 87% 1995-96 (RR=1.03, 95% CI: 0.99-0.07). Chi-squared test for trend NS (P=0.13).
Hutchinson et al. 2002	Edinburgh, Glasgow, Tayside & Grampian, Scotland.	Residual sera from IDUs who had undergone named HIV testing were tested anonymously for anti-HCV.	Retrospective longitudinal study.	Prevalence measured over 1989-2000.	Changes in anti-HCV prevalence since 1997 as tested by an ELISA assay (3rd generations Ortho, Chiron, or Abbott, AxSYM). Reactive samples were retested	No significant prevalence changes among those aged <25 during the late 1990s (Glasgow 1997-09/00: 43-41%; Lothian 1997-1999: 13-17%; Tayside 1997-1999: 45-35%; Grampian

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					by either a recombinant immunoblot assay (3rd generation RIBA, Chiron) or Monolisa (Sanofi Pasteur).	1996-1999: 28-29%). The Tayside 1993-1999 reducing trend of anti-HCV prevalence was significant for the under 25s (57%-35%, $\chi^2$ 3.9, $p=0.05$ ) and for those 25 or older (76% to 61%, $\chi^2$ 6.6, $p=0.01$ ). Among those 25 years or older, significant decreases in prevalence were observed during the late 1990s in Glasgow [1997-9/00: 79% (95% CI 74-83) to 72% (95% CI 67-76)] and Lothian [1997-9: 54% (95% CI 48-61) to 45% (95% CI 39-51)].
Kapadia et al. 2002	Recruitment through 6 sites in 5 US cities.	468 recruited. 390 persistently seronegative controls. 78 anti-HCV seroconverters. Age range 18-30.	Case control survey nested within a prospective cohort study.	Data collected at baseline and 6 & 12 months.	Effect of bleach disinfection of syringes on anti-HCV seroconversion.	OR for anti-HCV seroconversion for participants who reported using bleach all the time = 0.35 (95% CI 0.08-1.62), OR anti-HCV seroconversion for those using bleach some of the time = 0.76 (95% CI 0.21-2.70) when compared to those not using bleach.
Mansson et al. 2000	Syringe/needle exchange program, Malmö, Sweden.	698 IVDUs, follow up possible for at least 6 months for 515. 76% male, median age 32 (range 20-58), ethnicity not stated. 70% amphetamine users, 16% heroin users, 14% both.	Prospective cohort study.	At least 6 months of the 2 year follow period.	Effect of NEP upon incidence of HCV. Baseline sera samples tested for anti-HCV using licensed immunoassays. 1st generation screening used until April 1991, when replaced by 2nd generation test. Seroconversion to anti-HCV confirmed by 2nd or 3rd generation recombinant immunoblot assay.	HCV 26.3 seroconversions per 100 person years at risk. HCV seroconversion correlated with imprisonment during study (OR 2.2 95% CI 1.04-4.74), absence of drug free periods (OR 5.7 95% CI 1.44-22.3), and frequent needle, syringe exchange OR 1.31 95% CI 1.02-1.7).
MacDonald et al. 2000	Needle and syringe programs (NSPs) in Australia. 21 NSPs in 1995, 20 NSPs in 1996 and 23 NSPs in 1997.	4141 attendees at the NSPs (979 in 1995, 1463 in 1996 & 1699 in 1997). Age range 13-58, median age 28 and 66% male.	Repeated annual cross-sectional surveys for 1995, 1996 & 1997.	1995-1997	Prevalence of HCV as determined by capillary blood collected on blotting paper by finger prick and tested by 3rd generation enzyme immuno-assay.	Prevalence declined significantly from 63% in 1995 to 51% in 1996 and 50% in 1997 ( $P<0.001$ ). Remained significant when odds ratio adjusted for age, gender, duration of injecting, last drug injected, frequency of drug injection and health service contact (AOR 0.5, 95% CI, 0.4-0.7).
Patrick et al. 2001	Vancouver, Canada.	1345 subjects (66% male, 34% female, median age 34 years, range 15-58, 60% white, 25% aboriginal, 15% other).	Prospective cohort study	December 1996 to November 1999.	Effect of NEPs upon incidence of HCV as measured with a 3rd-generation ELISA containing recombinant antigens (HCV 3.0, Ortho Diagnostics Systems, Rochester, NY)] at enrolment was 81.6% (95% CI 79.6%- 83.6%).	Multivariate analysis by Cox proportional hazards identified the following independent predictors for HCV seroconversion: female gender [adjusted hazard ratio 2.29 (95% CI 1.35-3.89)], injection of cocaine alone or as a component of speedballs [adjusted hazard ratio 2.42 (95% CI 1.22-4.79)], frequent injection (at least once per day) [adjusted hazard ratio 2.02, (95% CI 1.09-3.77)] and frequent attendance at a needle exchange programme (at least once per week) [adjusted hazard ratio 2.56 (95% CI 1.37-4.79)]. Insufficient power to determine a reducing trend in HCV

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						incidence over the study period.
Rezza et al. 1996	Three drug treatment centres in Naples, Italy.	746 injecting heroin users. 263 IDUs were HCV negative at baseline and 40.3% were re-tested. Total follow up time 73.4 person years.	Nested case control study within a prospective cohort study.	Between 1991 and 1993.	Effect of MMT upon incidence of HCV, measured by EIA – Abbot laboratory test and confirmed by RIBA 2 test (Chiron, Corporation, Emeryville, California).	21 individuals sero-converted, an incidence rate of 28.6/100 person years (95% CI 17.8-43.4). The AOR for “lack of methadone treatment” (in the 6 months prior to testing) was of borderline significance (2.9, 95% CI 0.9-9.7).
Selvey et al. 1997	Methadone clinic in Brisbane, Australia.	106 HCV negative clients (who had previously undergone testing) taking MMT identified from perusing drug treatment records of 319 users. No statistically significant differences in age, gender or duration of heroin use between those tested for HCV and those not. Median age 28 years (range 17 to 52), 61% male, 29% employed and median duration of heroin use was 7 years (range <1-27). The median duration since initial registration was 1 year (range 1 month to 5 years).	Prospective cohort study	November 1994 to March 1995.	Incidence of HCV for a cohort of IDUs taking methadone maintenance treatment at time of recruitment. Testing kits used to assess HCV status described as “the first negative test of all participants was performed by a 2nd- or 3rd-generation HCV ELISA, except in one instance, in which the result was later confirmed by 3rd-generation testing”.	Five seroconversions (14%) were recorded over 47 person-years, a seroconversion rate of 11 per 100 person-years (95% CI 2-20). Univariate analysis only conducted: time in methadone treatment was reported as “not associated with seroconversion”. However, relative risk and supporting confidence intervals were not reported. Further univariate analysis described anti-HCV positivity associated with duration of heroin use at the time of the test (for duration 5-9 years RR 1.53, 95% CI 1.16-2.01, P<0.01 and 10+ years RR 1.96 95% CI 1.55-2.48, P<0.01) and being female for those cases whose duration was less than five years (RR 1.71, 95% CI, 1.08 to 2.71, P<0.05).
Smyth et al. 1999	Addiction treatment centre in Dublin, Ireland.	353 injecting drug users with an injecting history of less than 24 months. Heroin 78%, morphine sulphate 21%, benzodiazepines 1%. Age range or mean age not stated, 68% male. Ethnicity was not stated.	Repeated cross-sectional surveys.	New attenders between July 1993 & December 1996.	Effect of “expanded harm reduction programme” on prevalence of anti-HCV (confirmed by 3rd generation enzyme linked immunosorbent assay) for those who injected pre August 1993, August 1993-July 1994 and those commencing after July 1994.	Statistically significant reduction in those commencing injecting post 1994 (AOR 0.43, CI 0.27-0.67, P-value < 0.001) compared to those commencing injecting pre-1994. Statistically significant reduction in prevalence in those injecting less than 13 months (adjusted OR 1.0) compared to those injecting > 13 months (adjusted OR 1.76, CI 1.10-2.80, P=0.017). Statistically significant reduction in anti-HCV prevalence over time for those injecting less than 13 months (P< 0.003), but not those injecting > 13 months (P=0.33) – confidence intervals not reported.
Somani et al. 2000	Four clinics offering opiate substitution in Zurich, Switzerland.	603 drug users, mean age 30.7 years (SD 6.2), 62% male. Ethnicity was not stated. All but one had a history of heroin use and 80% reported a history of cocaine use. 75% gave a history of injecting drug use.	Cross sectional study	6 months from July 1997-January 1998.	Associations between NEPs and HCV prevalence. Exact serological testing procedures were not stated and differed in the clinics.	Protective effect in “the order of 80% for those starting to IDU after 1991 as opposed to those starting before 1987”. Statistical analysis was not presented. Data presented as descriptive in graphical form.

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Taylor et al. 2000	Glasgow, Scotland.	1949 saliva specimens from injectors from both in treatment and out of treatment settings. Age range 16-49, median 26 and median length injecting career 7.4 years, 72% male.	Prospective study of annual cross sectional survey data between 1990-1994 and 1996.	1990-1996	Effect of NEPs on the annual prevalence of antibodies to HCV among IDUs as determined by a modified ELISA assay (Monolisa Anti-HCV-Sanofi Pasteur, France) to detect antibodies in saliva.	1189/1949 (61%) were anti HCV positive (95% CI-59%-63%). Prevalence rates per year ranged from the highest of 67% in 1990 (95% CI 62%-72%) to the lowest of 56% in 1996 (95% CI 49%-63%). Overall estimated seroprevalence of anti HCV was 72%. In multiple regression model, length of injecting career, year commenced injecting, number of times in prison since injecting and place of residence were significantly more likely to test positive. Those who began injecting after introduction of needle and syringe exchange were significantly less likely to test HCV antibody positive than those who started before.
Thiede et al. 2000	4 methadone treatment centres, Washington, USA.	716 participants (83% participation rate from a systematically selected sample of 999). One year follow-up rate was 84%. Age > 14 years; median age 38 years; 51% male, 77% white; 74% started injecting 10 or more years before study enrolment.	Prospective cohort study of incidence.	Between October 1994 and January 1998. Baseline data collected and follow-up data at 12 months.	Effect of methadone maintenance treatment on the incidence of HCV for those who "left methadone treatment", "disrupted methadone treatment" or "continued treatment for the follow up period." Testing for anti-HCV was by a 3rd generation enzyme immunoassay (EIA; Abbott Laboratories) with repeat testing to confirm positive results.	Statistically non significant reduction in HCV seroconversion for those who remained in treatment AOR 0.4 (95% CI 0-4.2).
Van Ameijden et al. 1993	Low-threshold methadone programs and an STD clinic for drug using prostitutes, Amsterdam, The Netherlands.	305 heterosexual drug users who had an intake visit and at least 1 follow up visit between December 1985 and September 1989. 46% males, 69% Dutch, 21% German. Mean age 31.2 years (SD 5.8) for males and 27.2 years for females (SD 5.2). At intake 88% had ever injected.	Observational cohort study with 4 monthly follow-up with standardised questionnaire, medical examination and blood test for HBC, HCV & HIV.	December 1985-September 1989.	Effect of "NEPs, information campaign, free distribution of condoms and methadone maintenance upon the incidence of HCV. Antibodies for HCV were assayed by a 1st-generation HCV antibody ELISA system (Ortho Diagnostics, Raritan, NJ).	No statistically significant reduction in annual incidence rate/100 person years over the four year study period (1986: 16.9; 1987: 4.0; 1988: 12.5; 1989: 11.2) chi-squared test for trend, P=0.79).

Note: some studies report incidence/prevalence for HBV and HIV. Only the data for HCV is presented in this table

**Table 2: Statistical Modelling Studies**

Author, year	Setting	Methods	Outcome	Assumptions informing the statistical model	Conclusions
Commonwealth Department of Health and Ageing, 2002.	International HCV prevalence studies (where sample size greater than 50) to compare changes in HCV prevalence from 9 cities that implemented needle exchange programmes (NEPs) between this study and completion of an earlier study, 51 cities that already had NEPs when the studies were carried out, and 41 that did not.	Ecological study	The effectiveness of NEPs in preventing transmission of HIV and HCV. Cost effectiveness of NEP interventions in Australia.	Between 1991 and 2000, an estimated \$141million (\$150 million in 2000 prices) was expended on NEPs across Australia (excluding pharmacies that sell needles and syringes). Treatment costs avoided based on lifetime costs of HIV or HCV treatment regimes by disease stage were calculated and applied over the projected lifetime of cases. Standardised costs reported for each component of health care used year 2000 prices. Major factor influencing the cost profile is the number who progress to liver failure. While this number is relatively small, the cost of treatment is extremely high. The costs of HIV treatment avoided are approximately ten times those of HCV, which reflects a combination of the number of cases avoided in the first instance (25,000 for HIV compared to 21,000 for HCV), a higher diagnosis rate for HIV compared to HCV, and higher average annual treatment costs for HIV than for HCV. Calculations on the financial return on government investment discounted future cash flows associated with the investment in the NEP and treatment costs avoided by an agreed discount rate, conventionally 5% per annum for government expenditure. Quality adjusted life years (QALYs) gained calculated by incorporating both quantity and quality of life gained by avoiding HIV and HCV (incorporating the 5% discount rate described above).	Median HCV prevalence 75% (range 24% to 96%) in studies without NEPs and 60% (range 17% to 98%) in cities with NEPs (NPtrend p=0.01) Results indicated little change in HCV prevalence before NEPs were introduced, followed by a decline after the introduction of NEPs. Pre-NEP introduction HCV prevalence rates of 75% or 50% corresponded to a 1.5% or 2% decline in HCV prevalence per annum. Total HCV treatment costs avoided over the lifetime of cases were estimated at \$783 million (undiscounted). Overall, treatment costs avoided over the life of the cases of HCV and HIV due to NEPs were calculated at \$7,808 million (before discounting). Financial return on government investment in NEPs regarding the impact on HIV and HCV combined was calculated at a lifetime saving to costs of treatment of \$3,653 million. Total of 170,279 QALYs were gained [calculated as net present value (1991)].
Yazdanpanah et al. 1999.	France	Statistical model-based estimates of the annual number of cases of HCV transmission from	Estimate the risk of transmission of hepatitis C from an infected patient to an uninfected health care worker.	The model derived from previous French multi-centre studies documenting the incidence of percutaneous injury <sup>2 3</sup> , that 1% to 10% of the general population are seropositive for HCV. Probability of viral transmission was derived from the pooled results of 9 international prospective studies <sup>4</sup> which estimated the	Estimated risk of HCV transmission during a single procedure ranged from 1 in 2,380,000 to 1 in 2,38000. Estimated cumulative risk of acquiring occupationally-related HCV infection in 1 year ranged from 0.01% (1 in 10,000) to

<sup>2</sup> Johanet H, Antona D, Bouvet E. [Risks of accidental exposure to blood in the operating room. Results of a multicenter prospective study. Groupe d'Etude sur les Risques d'Exposition au Sang]. [French]. *Annales de Chirurgie* 1995; 49(5):403-410.

<sup>3</sup> Abiteboul D, Antona A, Fourrier A, Brücker G, Deschamps J, Leprince A, et al. Exposition accidentelle au sang du personnel soignant. Résultats d'un an de surveillance du risqué pour les infirmières dans 17 hôpitaux. *Pathol Biol* 1992; 40:983-989.

<sup>4</sup> Puro V, Petrosillo N, Ippolito G, Jagger J. Update on occupational HCV Infection Incidence Studies: Literature Review (Abstract) 1er Colloque International sur les Infections Transmissibles par le Sang, Risque Professionnels et Prévention, 1995, Paris: A8.

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		infected patients to uninfected surgeons or nurses.		probability of HCV transmission after percutaneous exposure. 1.2%-3.4%). However, these estimates were derived from studies of injuries mostly caused by hollow bore needles and involved nurses who did not wear gloves. Therefore model further refined from the findings of an animal tissue study in which a combination of using gloves and suture (rather than hollow bore) needles reduced the volume of blood transferred by 86% <sup>5</sup> . A ten-fold decrease in the probability of HCV transmission was estimated due to wiping effect of gloves prior to percutaneous injury.	0.1% (1 in 1000). This translated to between 2 and 21 of the 20,000 French surgeons acquiring occupationally-related HCV infection each year. The estimated cumulative risk for nurses of acquiring occupationally-related infection in 1 year ranged from 0.0054% (1 in 18700) to 0.054% (1 in 1870). This translated to between 16 and 167 of the 300000 French nurses acquiring HCV each year. Assuming that the probabilities do not change over time, the estimated cumulative risk of acquiring occupationally-related HCV infection after 30 years of professional practice ranged from 0.3% to 3.1% for a surgeon to 0.1 to 1.6% for a nurse.
Pollack 2001.	USA	Statistical random mixing model.	Cost effectiveness of NEPs at reducing the prevalence of HCV and HIV.	Assumes random mixing of infected users and therefore does not account for the possibility of social networks. Assumes steady state of HCV transmission and therefore has limited application to slowly changing epidemics.	Needle exchange programmes (NEPs) have limited cost effectiveness at reducing HCV infection. Cost per averted infection exceeds \$250,000 and \$1,000,000. Cost effectiveness is optimised when considering the cost per averted infection of HIV. They are more effective at reducing HIV infection due to the lower reproductive rate of infection.

<sup>5</sup> Mast S, Woolwine J, Gerberding J. Efficacy of gloves in reducing blood volumes transferred during simulated needlestick injury. *Journal of Infectious Diseases* 1993; 168:1589-1592.

**Table 3: Intervention Studies Evaluating the Effectiveness of Anti-Viral Therapy**

Author, Year	Setting	Methods	Participants, inclusion criteria and period of recruitment	Intervention	Outcomes	Results
Almasio et al 2003.	Palermo, Italy	Systematic review of all English and non-English articles identified on MEDLINE for the period 1987-december 2001	Studies included if report data on chronic HCV and SVR (defined as persistently undetectable serum HCV RNA by PCR at six month follow-up after ART.	Anti-viral therapy for chronic HCV	Risk reduction (as calculated by Der Simonian and Laird random effects model) of <ul style="list-style-type: none"> <li>• Cirrhosis</li> <li>• HCC</li> </ul>	Risk reduction of developing cirrhosis or HCC in sustained responders of -0.22 (95% CI -0.36/-0.08) or -0.097 (95% CI -0.13/-0.08), respectively compared with non-responders or relapsers
Bonis et al 1997	Boston, USA	Meta-analysis. Data source - English and non-English studies retrieved from Medline (from 1966 to December 1995).	Studies included which used interferon alpha for chronic hepatitis C and biopsies had been performed before and after therapy. Included data from all studies in which stratification of the histological response according to ALT or RNA responses was possible. (15 studies) If data were insufficient for quantitative analysis, qualitative evaluation was conducted (42 studies).	Interferon alpha used for treatment of chronic HCV (with liver biopsies performed before and after therapy)	Sensitivity and specificity of ALT as a measure of histological response after interferon treatment for hepatitis C	Normalized ALT among patients with improved liver histology was 4.8 (95% CI 3.1-7.4) times more likely than a normalized ALT among patients without improved liver histology. Strict definitions of histological response were considered histology improved in 28% (95%CI 17-43%) of patients post interferon treatment. Sensitivity and specificity of ALT for determining histological change were 55% (95% CI 44-65%) and 75% (95% CI 67-81%) respectively
Camma et al 2001	Palermo, Italy	Meta analysis of 3 randomised controlled trials and 15 non randomized trials of IFN for prevention of HCC identified from MEDLINE search (1985-1999)	Studies included if an RCT or (non randomised control trial) NRCT comparing IFN-treated and untreated patients with cirrhosis with a specific outcome measure of incidence of HCC	Anti-viral therapy for chronic HCV	Risk difference (as calculated by Der Simonian and Laird random effects model) of HCC incidence in SVRs compared to untreated controls	Pooled risk difference in incidence of -19.1% (95% CI -13.1/-25.2, p<0.00001) among sustained responders compared to untreated controls.
Chung et al 2003	10 hospitals in Japan	Non-randomised controlled clinical trial	684 anti-HCV negative personnel who sustained occupational needle-stick injury during March 2001	Short course (median 1 day, range 1-3 days) intramuscular interferon alpha treatment	Anti-HCV seroconversion as assayed by a second generation kit	1/279 in treated group and 1/405 in untreated group developed HCV (descriptive data only reported). Both "treated with interferon after developing acute hepatitis, and HCV was subsequently cleared"
Chung et al 2004. ACTG trial	Adult AIDS Clinical Trials Group sites in the USA.	Randomised control trial	133 patients co-infected with HIV and HCV	48 weeks treatment of either: peginterferon alfa-2a (180microg per week), or interferon alfa-2a (6 million IU three times weekly for 12 weeks followed by 3 million IU	SVR (as defined by SVR less than 60 IU per ml) 24 weeks after completion of therapy. Histological response in those who underwent liver biopsy (those who did not have a SVR at week 24 of treatment)	Pegylated interferon plus ribavirin associated with significantly higher rate of SVR than treatment with interferon plus ribavirin (27% vs 12% P = 0.03. 14% of genotype 1 had a SVR vs 73% SVR in those infected with other genotypes. Histological responses

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				three times a week for 36 weeks. Both groups received ribavirin according to a dose escalation schedule		observed in 35% of participants with no SVR who underwent liver biopsy
Laguno et al 2004. CLINIVIC study	Specialised HIV unit at hospital clinic in Barcelona, Spain	Randomised control trial	95 previously untreated (for HCV) patients co-infected with HIV and HCV who received care between April 2001 and October 2002.	Peg interferon subcutaneously (at a dose of 100mcg for body weight <75kg or 150mcg for weight >75 kg) plus daily oral ribavirin vs standard therapy (interferon alpha 2b plus daily oral ribavirin). Genotypes 1 and 4 received 48 weeks of treatment whilst 2 and 3 received 24 weeks only	SVR (defined as undetectable serum HCV RNA at the end of follow-up i.e. 24 weeks post treatment)	44% patients treated with PEG Interferon alpha 2b combination manifested a SVR compared with 21% for standard Interferon combination (p=0.017). Difference remained when accounted for by multivariate analysis (AOR:0.3, 95% CI 0.1-0.85, P=0.025). For genotypes 1 and 4 38% in the PEG-INF arm manifested an SVR vs 7% in the INF arm (P=0.007). No stat significant difference for genotypes 2 and 3.
Licata et al 2003	Palermo, Italy	Meta-analysis of 16 controlled trials identified by MEDLINE search from 1985-2002. Supplemented by manual searches of reference lists	Studies included if they were controlled trials comparing IFN to no treatment and if they included patients with either post-transfusion or sporadic hepatitis. In total data pooled on 640 patients (403 transfusion and 237 sporadic)	IFN vs no treatment for the treatment of acute hepatitis C	SVR (defined as negative HCV RNA post treatment follow-up)	Statistically significant pooled estimate of treatment effect. Risk difference of SVR 49%; 95% CI: 32.0-65% for treatment compared to no treatment, P < 0.00001; NNT = 2. Pooled risk difference 66% (95% CI 16.4-43.3) in studies with a high weekly dose of IFN and 29.9% (95% CI 16.4-43.3) in those with a low weekly dose of IFN. Risk difference of interval of disease onset to therapy not statistically significant: 49.9% (95%CI 7.6-93.3%) for starting treatment within 60 days of onset and 45.4% (95% CI 25.4-65.4) in those who received treatment after 60 days from disease onset.
Nishiguchi et al 2001	Treatment settings in Osaka, Japan	Randomized controlled trial of interferon alpha versus symptomatic treatment	90 patients with chronic HCV and compensated cirrhosis	Interferon alpha	<ul style="list-style-type: none"> <li>Decompensated liver disease.</li> <li>Hepatocellular carcinoma</li> <li>Death.</li> </ul>	HCC detected in 33 (73%) of the 45 controls and 12 (27%) of the 45 treated patients (P<0.001, CI not reported). Risk ratio (by multi-variate analysis) of IFN versus symptomatic treatment 0.250 (95% CI 0.124-0.440) for progression to Child-Pugh B; 0.256 (0.125-0.522) for development of HCC; and 0.135 (0.049-0.372) for death, respectively
Perronne et al 2004 - RIBAVIC study	France	Randomised multi centre, open label,	412 patients (40 years old, 74% male, 79% IDU) co-infected with	PEG-Interferon alpha 2b plus ribavirin versus	SVR	27% with PEG combination versus 18% with standard combination therapy

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		controlled trial	HIV and HCV	standard combination therapy: interferon alfa-2b and ribavirin		
Poynard et al 2000	Paris, France	3 randomised controlled trials reproduced with permission of principal investigators	1,509 patients who had paired biopsies available from an original cohort of 2089 participants (no statistically significant differences between the two populations)	Interferon alpha 2b plus ribavirin versus interferon alone	Progression of liver fibrosis in pre-treatment and post-treatment biopsies. Fibrosis progression and regression rates between biopsies calculated by the Kaplan-Meier method and by the fibrosis progression rate per year.	Percentage of patients without significant fibrosis (stage 0 or 1) at 96 weeks was 68 +/- 4% (mean +/- SE); when treated by combination regimen for 48 weeks; 64 +/- 4% by interferon alone for 48 weeks; 42 +/- 7% by combination regimen for 24 weeks (lower than both 48-week regimens P <.001), and 24 +/- 9% interferon alone for 24 weeks (lower than the combination regimen for 24 weeks; P =.02).
Torriani et al 2004. APRICOT study	95 centres in 19 countries	Randomised control trial	868 co-infected with HIV and HCV who had not previously been treated with interferon or ribavirin	48 weeks treatment of either: peginterferon alfa-2a (180microg per week) plus ribavirin (800mg per day), peginterferon alfa-2a plus placebo, or standard therapy i.e. interferon alfa-2a (3 million IU three times a week plus ribavirin)	SVR [defined as serum HCV RNA level below 50 IU per ml at the end of follow-up (week 72)]	SVR significantly higher among recipients of peginterferon alfa-2a plus ribavirin compared to standard therapy (40% vs 12% odds ratio 5.40; 97.5% CI: 1.83-4.58;p<0.001), or PEG-interferon alpha-2a monotherapy (40% vs 20%; OR 2.89, 97.5%CI 1.83-4.58, p=0.008,).

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