

Management of Chronic Hepatitis C: Consensus Guidelines

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Hepatitis C

Epidemiology of Hepatitis C in Canada

Chronic hepatitis C continues to be a significant medical and economic burden to Canadians. It is associated with an excess mortality that will continue to increase for many years into the future (Figure 1). Infected individuals may have a diminished quality of life.

There are no large-scale representative studies to determine the prevalence of chronic hepatitis C in Canada. However, sophisticated modeling techniques suggest that the prevalence is about 0.8-1%, and increasing over time (1). The annual estimated hepatitis C-related mortality and the rate of cure on therapy is exceeded by the number of new infections, and infected immigrants coming to Canada, so that the prevalence of HCV infection is increasing, and will continue to increase for the foreseeable future (see Table 2). Currently about 65% of the estimated cases in Canada have been identified. Predictions are that by 2022 the number of hepatitis C-related deaths will increase by a third (Figure 1)(1).

Approximately 20% of hepatitis C in Canada occurs in the immigrant community, where access to health care may be less than optimal (1). Countries with high prevalence rates for hepatitis C, and that provide Canada with immigrants include Egypt, Somalia, Pakistan, Bangladesh and Vietnam. In addition, immigrants from Southern Europe (mainly Italy, Greece and Spain) who came to Canada years ago also have a high prevalence of hepatitis C, related to silent epidemics in their home countries between the end of World War 2 and about 1975. Hepatitis C infection from transfusion of blood products accounts for only about 13% of all cases. Injection drug use - current or past, accounts for more than 65% of all hepatitis C infections in Canada (Table 3).

Almost all new hepatitis C infections acquired in Canada are related to injection drug use, with sharing of injection equipment. However, immigration now contributes about 33% of all new cases of hepatitis C (1).

Given the alarming estimates of future disease burden more accurate information about the incidence and prevalence of hepatitis C and its complications are urgently required to inform health care planning and resource allocation.

- 1. Recommendation: A large scale population-based seroprevalence survey should be mounted to accurately assess the prevalence of hepatitis C in Canada. The design of the study should take into account the known risk factors and should specifically sample populations with known high endemicity (III).**
- 2. Recommendation: The current surveillance and data collection/reporting process needs to be expanded to better capture the incidence of new cases (III).**
- 3. Recommendation: Steps must be taken to reduce the incidence of hepatitis C infection among injection drug users and users of crack cocaine. These may include expansion of safe injection sites, needle exchange programs, provision of single use**

injection or crack-smoking equipment. Legal impediments to such programs must be removed. This is not a crime issue. This is a public health issue, as injection drug users are more and more becoming the reservoir for new infections (III).

4. **Recommendation:** Programs should be established to identify the 35% or so of hepatitis C infected individuals who are unaware of their infection, since there is curative therapy, and for those for whom cure is not possible lifestyle modifications to reduce the rate of disease progression can be advised (III).

Acute hepatitis C

Most cases of acute hepatitis C are asymptomatic and are seldom diagnosed. Nonetheless, acute hepatitis C represents an opportunity to offer effective therapy. Acute hepatitis C is diagnosed usually under three circumstances – documented seroconversion, known exposure (e.g., needle stick exposure), and acute clinical hepatitis.

There is a high rate of spontaneous clearance of virus following acute hepatitis C, which in some studies may be more than 50% (2). The younger the age of infection, the more likely is spontaneous clearance of virus. Icteric hepatitis predicts spontaneous clearance with a high accuracy. Clearance usually occurs within 14 weeks of exposure. Most patients clear virus within 12 weeks. However, a single negative HCV RNA is insufficient to confirm clearance, and the test should be repeated at least once.

Because seroconversion is unpredictable, treatment should be considered in all patients. Treatment is most effective if started before 12 weeks (3,4). SVR rates of better than 90% have been described using pegylated interferon monotherapy (5-7).

5. **Recommendation:** Patients with acute icteric hepatitis C can be observed for up to 12 weeks to determine whether spontaneous clearance occurs. If clearance has not occurred treatment should be initiated by 12 weeks (II-2).
6. **Recommendation:** In patients with acute non-icteric hepatitis C the likelihood of spontaneous clearance is lower, so treatment could start soon after diagnosis (II-2).
7. **Recommendation:** Treatment is with pegylated interferon alpha monotherapy. Genotype 2 and 3 should be treated for 12 weeks and genotype 1 for 24 weeks (I).

Chronic Hepatitis C

Selection of patients for treatment

Testing for hepatitis C should be undertaken in patients with abnormal aminotransferases and/or with risk factors for contracting hepatitis C. These include past or active injection drug use (IDU), blood transfusion prior to the introduction of second generation anti-HCV assays in 1991 and immigration from countries of high prevalence where medical procedures may have been dispensed using improperly sterilized needles or unscreened blood products (8,9).

The initial test should be an antibody test against HCV (3rd generation enzyme-linked immunoassay). A sensitive HCV RNA assay can be used for confirmation.

8. Recommendation: All patients with chronic hepatitis C should be assessed to determine whether they might benefit from therapy (III).

Whether treatment is offered or not should be decided by the weighing risks and benefits for a particular patient. This decision is complex and should consider risk of disease progression to end stage, probability of a favorable response to therapy, risks of adverse effects with therapy and co-morbid conditions. The patient's wishes must also be taken into consideration. Although patients with advanced liver disease are those most in need for therapy; those with early disease are most likely to clear virus.

The assessment for suitability for therapy should include a review of the patient's history for past or current psychiatric disease, seizures, cardiac or renal disease, autoimmune disease and alcohol or drug addiction.

Further laboratory testing includes HCV genotyping and viral load, TSH, ANA, serum or urine β -HCG (for women of reproductive age) and an ECG (if >50 years of age or history of heart disease). A fundoscopic exam to rule out retinopathy in patients over 50 years of age, high blood pressure or diabetes mellitus is advisable. Although IFN can induce a retinopathy there are no data to suggest that the risk is higher or that retinopathy is more severe in patients with pre-existing retinopathy. The retinopathy resolves on withdrawal of interferon.

Liver biopsy is the most sensitive measure of severity of liver damage. Although not mandatory, it is recommended prior to the initiation of therapy. In patients who elect not to be treated a biopsy showing mild disease is helpful to support that decision.

9. Recommendation: Sensitive qualitative HCV RNA, HCV viral load testing and genotype testing are essential to the management of these patients. Results should be reported in IU/mL, and should be available in a timely manner (III).

Because of the theoretical risk of teratogenicity associated with ribavirin, male or female patients must use effective contraception while on therapy and for 6 months after completion of therapy. However, no associated fetal abnormalities have been described in pregnancies where either parent was taking ribavirin at the time of conception or in early pregnancy.

Despite more effective and tailored therapy it appears that less than a third of patients in large hepatitis C clinics have been treated (10). The most common reasons for ineligibility besides patient refusal include a high likelihood of non compliance, low blood counts, advanced age, psychiatric conditions, substance abuse, coronary disease, cerebrovascular disease, retinopathy, uncontrolled diabetes, autoimmune disorders, serious pulmonary disease.

Contraindications

There are very few absolute contraindications to treatment (see table 4). There are anecdotal reports of successful therapy in patients who might have been excluded from therapy for most of the previously defined contraindications. Therefore, most contraindications are considered to be relative rather than absolute. In most cases treatment of these patients requires a high degree of expertise, and therefore patients with relative contraindications should be treated in expert centers. Past histories of substance abuse are not contraindications to therapy. Stable patients on a methadone maintenance program can be treated successfully (11). Patients who do not achieve complete abstinence from alcohol can also be treated successfully (12). Recent alcohol use reduces the likelihood of completing treatment, but for those who complete treatment the response is similar to non-drinkers. Patients with prior alcohol or other substance abuse should undergo a period of abstinence prior to initiating therapy to allow the abstinence to become more stable. In most cases this should be at least 6 months, although this can be individualized.

Low blood counts can often be corrected prior to therapy. Patients with normal ALT should be considered for treatment; some will have significant histological liver disease. They respond to therapy in the same manner as those with elevated ALT (13). Older patients can be treated successfully (14).

Generally, in patients with substance abuse, alcoholism and psychiatric conditions the prime factor determining whether treatment is feasible is the likelihood of poor adherence. Patients who are likely to be non-adherent for any reason are generally not good candidates for treatment. However, adherence can be greatly enhanced when therapy is provided in a supervised and multidisciplinary setting.

Patients with a history of depression are not at necessarily higher risk for depression on therapy. However, patients who are depressed at the start of therapy are at higher risk for worsening of symptoms. Onset of depression during therapy is not a reason to discontinue treatment, as there are many antidepressants that can be used to successfully treat these symptoms. However, suicidal ideation or the development of mania are treatment-related medical emergencies, and must lead to complete withdrawal of therapy.

Some conditions such as severe cardiac disease or other causes of reduced life expectancy due to comorbid disease, or organ transplants (other than liver transplant) still represent contraindications to therapy but generally many of the contraindications are modifiable or treatable and thus a patient currently deemed ineligible for therapy should be reevaluated at a later date.

Therapy for HCV

The best results obtained have been with combination pegylated interferon and ribavirin (15,16). There are 2 formulations of pegylated interferon available, interferon alpha-2a and pegylated interferon alpha-2b. They differ by virtue of the size and configuration of the polyethylene glycol molecules bound to the

interferon molecule. The two formulations of pegylated interferons have not been compared head-to-head but appear to be equivalent choices for therapy.

The definitions of response at different time periods during therapy are given in Table 5:

Ribavirin Dose

Pegylated interferon and ribavirin remains the mainstay of hepatitis C therapy. It is clear that optimizing the ribavirin exposure (17,18) particularly during the first 12 weeks of therapy is critical for achieving a good response to therapy.

Unfortunately, in Canada the ribavirin is bundled with the interferon, reducing the discretion of the physician to give additional ribavirin if considered necessary. Ribavirin is dosed by weight. However, in genotype 1 infection it is not certain that patients weighing less than 74 kg will achieve the optimal results using 800 mg of ribavirin, nor that patients heavier than 88 kg will have better outcomes on 1400 mg of ribavirin than 1200 mg. It is also not certain that heavier patients with genotype 2 infection need more than 800 mg of ribavirin.

Standard treatment of hepatitis C

Standard and modified (see later) treatment algorithms are given in Figures 8 and 9.

10. Recommendation: Genotypes 1,4, 5, and 6 should be treated with either;

a) PEG IFN alpha-2a 180 µg subcutaneously once weekly and ribavirin 1000-1200 mg daily given orally in 2 divided dosages. The choice of the dose of ribavirin dose depends on whether the patient weighs more or less than 75 kg (I); or

b) PEG IFN alpha-2b 1.5 ug/kg subcutaneously once weekly and ribavirin 800-1200 mg daily given orally in 2 divided dosages. The choice of the dose of ribavirin dose depends on the patient weight targeting a daily dose of ribavirin greater than 13.5 mg/kg daily given orally in 2 divided doses (I).

11. Recommendation: Therapy is given for 48 weeks for genotype 1,4, 5 and 6. In patients who do not achieve an early virological response (EVR) or are still viremic after 24 weeks, therapy should be discontinued, as the likelihood of SVR is negligible (I).

12. Recommendation: Genotype 2 or 3 infection should be treated with either;

a) pegylated interferon alpha-2a 180 µg subcutaneously once weekly and ribavirin 800 mg daily given orally in 2 divided dosages. There are data from randomized controlled studies and from other sources showing that for genotype 2 or 3 infection 800 mg/day of ribavirin is sufficient (I); or

b), pegylated interferon alpha-2b 1.5 µg/kg subcutaneously once weekly with ribavirin. The manufacturers suggest that ribavirin be dosed by weight in this group as well, but the evidence that more than 800 mg/day is required is not convincing (I).

13. Recommendation: The standard duration of therapy for patients with genotype 2 or 3 infection is 24 weeks (I).

SVR rates for genotype 1 infection ranges from 42-46% (15,16,18). SVR rates for 72-80% have been achieved for treatment of genotype 2 and 3 infections (15,16,18). Although infections with genotypes other than 1, 2 and 3 are less common and results of treatment are less well defined, they appear to be better than for genotype 1 but not as good as genotypes 2 and 3. .

New regimens for treatment of hepatitis C

There is increasing evidence that the standard duration of therapy is not optimal for many patients with chronic hepatitis C infection. Modifying the duration of therapy based on viral kinetics can maximize SVR rates while limiting the toxicities and costs associated with treatment. An essential component in the decision to shorten therapy is an assessment of rapid virologic response (RVR)(see Table 5).

14. Recommendation: Week 4 HCV-RNA testing must be available in a timely manner to all clinicians treating chronic hepatitis C (III).

Genotype 1

In those who achieve RVR and in whom there are no predictors of poor response (advanced fibrosis, high viral load, high BMI, older age, African American race, HIV co-infection, immunosuppression) therapy may be shortened to 24 weeks. In this subgroup, SVR rates of 88-89% can be achieved (19-21).

15. Recommendation: Patients with genotype 1 infection and no predictors of poor response who achieve a rapid virological response may be treated to 24 weeks (II-3). Before terminating treatment at 24 weeks the patient should be aware that if relapse occurs retreatment for 48 weeks will be necessary. Early withdrawal of therapy should not be undertaken unless funding is available for a second more standard course of therapy (III).

Some patients may achieve a 2 log drop in HCV RNA by week 12 but do not achieve undetectable HCV RNA. This is defined as partial virological response (PVR) or viremic EVR. They may then clear HCV RNA by week 24. Such patients have been termed “slow responders”. A preliminary study suggested prolonging therapy to 72 weeks might be of benefit in this subgroup (22). Subsequently several studies comparing 48 to 72 weeks of therapy in genotype 1 patients suggest a benefit of prolonged therapy in slow responders (23-26). Some published studies however, used 800 mg of ribavirin, and the benefit of prolonged therapy if weight based ribavirin is used remains uncertain.

16. Recommendation: -Prolonged therapy to 72 weeks may be considered in genotype 1 patients with PVR who are HCV RNA negative at week 24 (I). Funding for prolonged treatment should be supported by provincial drug formularies under appropriate circumstances (III).

Genotype 2 and 3

In patients who have an RVR 12-16 weeks of therapy results in SVR in 80-100% of genotype 2 and 77-85% of genotype 3 patients (27-32). However, in a large randomized trial 24 weeks of therapy was superior to 16 weeks in those with RVR in both genotype 2 (91% vs 80%) and genotype 3 (89% vs 84%)(32). This study used 800 mg of ribavirin however and although the optimal dose of ribavirin has not been adequately defined, higher doses of ribavirin may be required in shortened regimens (33).

17. Patients with genotype 2 or 3 infection who achieve rapid virological response may have therapy withdrawn at 12 or 16 weeks if they have been receiving weight-based ribavirin dosing (I). Before terminating treatment early the patient should be aware that if relapse occurs retreatment for 24 weeks will be necessary. Early withdrawal of therapy should not be undertaken unless funding is available for a second more standard course of therapy (III).

RVR is the best predictor of SVR. In those who fail to achieve RVR, SVR rates with 24 weeks of therapy are disappointing particularly in genotype 3 (41-58%) but also in genotype 2 (50-89%)(27-32). It is possible that prolonging therapy may produce a higher SVR, however to date no study of prolonged therapy in this population has been carried out. Further data are needed to establish the role of prolonged therapy (greater than 24 weeks) in patients with genotype 2 or 3 infection who fail to achieve an RVR. There was no consensus as to whether prolonged treatment should be offered to this group of patients.

Treatment algorithms for genotypes 1, 2 and 3 incorporating treatment decisions based on RVR are given in Figures 2 and 3.

Genotype 4

The standard duration of therapy in patients with genotype 4 C infection is 48 weeks. This results in an SVR of 40-79% (34-36). The week 12 HCV RNA can be used to predict response and as in genotype 1, the lack of an EVR has a high negative predictive value and treatment should be discontinued. In those with fibrosis scores of 0-2 on liver biopsy and a viral load at baseline less than 800 000 IU/mL, treatment duration can be shortened to 36 weeks (36).

Maintenance Therapy

In addition to its antiviral action, interferon has many other properties including antiproliferative and antiangiogenic activity that may reduce the rate of complications in patients with advanced fibrosis who fail to achieve an SVR. Three large trials are ongoing to evaluate the role of long-term low dose (maintenance) therapy in this population. At the present time there is insufficient evidence to recommend maintenance therapy in non-responders.

Re-treatment of previous treatment failures

Compared to the currently available PEG IFN and ribavirin combination products, the previous anti-viral therapies of standard interferon monotherapy and standard interferon and ribavirin combination therapy were associated with more treatment failures. The exact number of previous treatment failures in the community is unknown but given the number of patients treated before the licensure of the PEG IFN and ribavirin products, it is likely that the pool of standard interferon treatment failures is not inconsequential. Although the limited intrinsic potencies of the previous anti-viral therapies contributed substantially to treatment failure, other secular factors including sub-optimal dosing in response to monitoring laboratory blood-work or adverse clinical effects, non-adherence because of lack of nursing support, inadequate patient education, and physician inexperience may have contributed. It must also be appreciated that the contemporary recommendations for dose reduction and drug withdrawal are not as restrictive and cautious compared to previous years given the additional years of experience with HCV interferon-based therapies in general. Thus, among the patients who failed previous therapy there are likely to be significant proportion who failed because of early withdrawal, overly aggressive dose reductions and missed doses, rather than for true non-response or true relapse.

There are presently seven studies (37-43), evaluating re-treatment of both relapsers and non-responders and another large study has been reported in abstract form (44). Of these studies, two have been randomized clinical trials (37,43) that have compared two doses of PEG IFN α -2b plus ribavirin and the others have been single-arm observational studies that have administered PEG IFN α -2b plus ribavirin or PEG IFN α -2a plus ribavirin.

In general, relapsers to previous interferon-based therapy have a superior response to PEG IFN and ribavirin combination therapy (34-55%) than non-responders to previous therapy (8-26%). Genotype 1 relapsers respond less well to PEG IFN and ribavirin combination therapy (34%-53%) compared to non-genotype 1 patients (i.e., mostly genotype 2,3)(42-70%). Amongst non-responders to previous standard interferon therapy, the SVR of genotype 1 patients ranged from 5-8% to 17-22%, whereas non-genotype 1 non-responders ranged from 19-20% to 37-57%. The maximum response reported for genotype 1 non-responders to previous combination therapy is 19-20%. Most studies reported that response is inversely proportional to fibrosis score. The largest study with 1046 patients reported that amongst genotype 1 non-responders to previous interferon-based therapy, SVR ranged from 23% for those with bridging fibrosis and a platelet count $>125 \times 10^9/L$ to 9% for those with cirrhosis and a platelet count of < 125

$\times 10^9/L$. Failure to achieve EVR at week 12 of therapy has also been reported to be 100% predictive of failure to achieve SVR in genotype 1 patients. In the two studies that randomized PEG IFN α -2b plus ribavirin based on weight-based dose (ie. 1.0 vs. 1.5 $\mu\text{g}/\text{kg}$ of PEG IFN (1) and 0.5 vs 1.5 $\mu\text{g}/\text{kg}$ of PEG IFN (218), a non-statistically significant trend was reported in favour of the higher weight-based dose.

Consensus interferon has also been shown to improve the response rates in previous treatment failures, including previous failures on pegylated interferon and ribavirin (45). The treatment regimens used require daily doses of interferon, and ribavirin was not part of the regimen. What role consensus interferon should play in re-treating patients is not clear.

- 18. Recommendations: Patients who were relapsers to previous standard interferon-based therapies respond well to pegylated interferon and ribavirin combination therapy regardless of genotype and should be offered therapy (II-2).**
- 19. Recommendation: Given the uncertainty of treatment dose and duration at the time and its general inferiority to combination regimens with ribavirin, patients who were previous treatment failures with standard interferon monotherapy should be offered treatment with pegylated interferon and ribavirin combination therapy regardless of whether the treatment failure was due to non-response or relapse and regardless of genotype (II-2).**
- 20. Recommendation: Patients who were non-responders to previous standard interferon and ribavirin combination therapy may be considered for treatment with pegylated interferon and ribavirin combination therapy. If treatment is offered, a quantitative HCV RNA determination at base-line and week 12 of therapy should be performed. Failure to achieve EVR should lead to treatment withdrawal (I).**

Monitoring while on therapy

Therapy with pegylated interferon and ribavirin is associated with numerous possible side-effects. Some adverse events can be severe, even life-threatening and irreversible. Thus close patient monitoring by the treating team is imperative. Laboratory monitoring during therapy involves: CBC at weeks 1, 2, 4, 6, 8 and monthly thereafter; AST, ALT, alkaline phosphatase, bilirubin, INR, albumin, glucose, creatinine, urinalysis; TSH every 3 months and pregnancy testing periodically (48). RVR is assessed by qualitative HCV RNA at week 4. EVR is assessed by quantitative HCV RNA at week 12 in those with genotype 1 infection. Failure to achieve EVR should lead to treatment withdrawal. In those who achieve an EVR, but who did not achieve undetectable viral load a qualitative HCV RNA should be done at week 24 and a positive test should result in treatment withdrawal.

Management of hepatitis C in special circumstances

Renal failure

HCV infection is more frequent in dialysis patients than in the general population (49). Anti-HCV may not be positive, even in the presence of HCV RNA. ALT elevation does often not reflect disease severity in this population. Liver biopsy may be necessary to establish disease severity, despite the potential additional bleeding risk. Transjugular biopsy can also be considered. HCV infection adversely affects patient and graft survival after kidney transplantation. However this is not a contraindication to transplantation. Overall outcomes in HCV-infected individuals remain within an acceptable range with poor outcomes generally seen in those with advanced fibrosis at transplant. Interferon-based therapy prior to transplantation improves post-transplant outcomes (50). Interferon-based therapy increases the risk of rejection and is generally contraindicated after solid organ transplantation (except for liver transplantation).

Pegylated interferon alpha 2b and ribavirin are excreted by the kidneys. Ribavirin is not dialyzable. Both carry therefore the risk of accumulating, resulting in an increased risk of increased toxicity, in patients with renal failure, in particular on dialysis. However, both pegylated interferon alpha-2a and 2b have recently been used in small series of HCV infected hemodialysis patients (51-53), in combination with very low dose ribavirin. The ribavirin dose was controlled by ribavirin blood level monitoring. Despite reported SVR rates of 20-70% and an acceptable tolerability (except for an increase in erythropoietin requirements), the database is too small to allow general recommendations. At this point, patients with advanced renal failure should only be treated with pegylated interferon and ribavirin in specialized centers able to perform ribavirin blood level monitoring. In patients with end stage renal disease hepatitis C treatment should generally be reserved for those who are candidates for renal transplantation. Interferon is poorly tolerated in this population and response rates to treatment are low. Competing risks for mortality in this population also reduce the likelihood of benefit to hepatitis C treatment

21. Recommendation: Treatment of hepatitis C in renal failure is best undertaken in conjunction with a nephrologist, and should be reserved for experts (III).

Decompensated liver disease

Pegylated interferon and ribavirin have limited efficacy and a poor safety/tolerability profile in this patient population (54-56). Anti-HCV treatment in patients with decompensated liver disease should never delay referral for transplant evaluation. This should only be carried out at a liver transplant or other expert center.

22. Recommendation: Treatment of these patients should be conducted in conjunction with a liver transplant team and by physicians familiar with the management of these diseases (III).

Solid organ Transplantation

Interferon is usually contra-indicated after solid organ transplantation, because of the risk of exacerbating rejection. Loss of kidney grafts have been reported after interferon use. . In those with life sustaining organ transplants (e.g. heart or lung), interferon should be avoided given the risk of rejection and graft loss. In renal transplant recipients, interferon-based therapy may be considered in those with progressive HCV-related liver disease or HCV-induced renal disease if the benefits are felt to outweigh the risks (rejection, graft loss, return to dialysis) and after discussion with the patient.

However, interferon can be used post-liver transplantation for treatment of hepatitis C. Rejection may occur in this setting but is generally easily treated if detected early.

Treatment of hepatitis C in transplant recipients should only be conducted in expert centers

Cryoglobulinemia

Mixed cryoglobulinemia type II is present in up to 50% of patients with HCV infection and may lead to symptomatic vasculitis in a minority of patients. SVR rates of 44-78% have been achieved with pegylated interferon and ribavirin in small series of patients (57-59). SVR was associated with clinical improvement of the vasculitis in the majority of, but not all patients (60). Patients with symptomatic type II cryoglobulinemia vasculitis may benefit from antiviral combination therapy, even if viral eradication is not achieved. The optimal therapeutic scheme remains to be defined. There is insufficient information to make any specific recommendations.

Chronic anemia

Antiviral therapy with standard dose pegylated interferon alpha and ribavirin of HCV infected patients with thalassemia major has been shown to be effective, but increases transfusion requirements (61). As in other patients, co-morbidities and the likelihood of their HCV-related liver disease ever reaching relevant morbidity and mortality during their life expectancy has to be taken into account when deciding on therapy in these patients. Similar considerations apply to patients with other forms of chronic anemia. These patients may need to be supported by transfusion during therapy, rather than by the use of erythropoietin.

23. Recommendation: patients with chronic anemia can be treated with interferon and ribavirin. This requires collaboration between hematologist and the physician treating the hepatitis C (II-2).

Lymphoma

HCV infection can be associated with some forms of non-Hodgkin's Lymphoma (NHL) although a causal relationship has not always been documented (62-64). In small uncontrolled series, interferon based anti-HCV therapy has been reported to lead to a complete hematologic response in >50% of patients when

associated with HCV suppression (65,66). Optimal drug dosage and duration of therapy remains to be defined. There is insufficient information to make any specific recommendations.

HCV Infection in Hemophiliacs

Hemophilia is not a contraindication for antiviral therapy with the current regimens of pegylated interferon and ribavirin. Except for liver biopsy, the same criteria for indication and conduct of therapy apply, as in HCV infected patients without hemophilia. Liver biopsy is unpopular in the hemophilia population, but can be safely carried out by the transjugular route with appropriate clotting factor support.

Hepatitis C/HIV co-infection

Approx. 20% of HIV infected patients are co-infected with HCV (67). HCV-related end-stage liver disease has become the leading cause of death in these patients, accounting for 50% of all deaths in one study. (68). Anti-retroviral therapy slows down fibrosis progression and decreases liver-related mortality in HCV/HIV co-infection; (69). The indications for treatment in HIV co-infected patients are similar to that in mono-infected patients. Whether anti-HCV and anti-HIV therapy should be performed sequentially or at the same time needs to be decided on an individual basis depending on the stage of HIV disease (as measured by CD4 count). Treatment with pegylated interferon and ribavirin results in acceptable SVR rates, with toxicity that is not much different than in HCV mono-infected patients. SVR rates of 43% to 62% in genotype 2 and 3 infection have been reported after 48 weeks of treatment. Studies evaluating pegylated interferon plus ribavirin treatment of HCV genotype 2 and 3 in the HIV-co-infected have reported relapse rates of 32 to 35% when the treatment duration is 24 weeks and the ribavirin dose is 800 mg daily (70,71), although one study using weight based ribavirin plus peginterferon reported a relapse rate of 9% with 24 weeks of treatment (72). In contrast, the relapse rate after 48 weeks of therapy with pegylated interferon plus ribavirin 800 mg daily is 3 to 12% (73-75). In genotype 1 infection the SVR rates were between 16 and 38%. The dose of ribavirin used was 800 mg/day. Patients who fail to achieve either a 2 log drop in viral load after 12 weeks of therapy or undetectable virus have a negligible chance of clearing virus. Therapy is best provided in close collaboration between an infectious disease specialist and a hepatologist. Simultaneous therapy with ribavirin and ddI or d4t increases the risk of mitochondrial toxicity (pancreatitis, hyperlactatemia) and should be avoided (76). The combination of zidovudine and ribavirin increases the risk of anemia (77). Therefore, patients on zidovudine who need treatment for hepatitis C should have their HIV therapy changed to eliminate zidovudine if possible.

24. Recommendation: Anti-HCV therapy should be considered in all HCV/HIV co-infected patients. Patients should be treated with standard doses of interferon and ribavirin for 48 weeks (I). Patients who fail to achieve EVR should be withdrawn from therapy (I).

Hepatitis C in Children

HCV infection seems to progress more slowly to fibrosis and cirrhosis in childhood acquired disease than in adult-acquired disease (78,79). Standard interferon 3MU/m² TIW with ribavirin 15 mg/kg/day for 48 weeks yields an SVR of 40-60% overall, and 70-100% in genotype 2 or 3 infection (80). Pegylated interferon 2a or 2b and ribavirin have been used in small numbers of HCV infected children with SVR rates of 43-59% (higher in genotype 2/3 than genotype 1/4) (81,82). Whether EVR can be used, as in adults, to stop therapy early in patients destined to be non-responders is not clear. The tolerability/side effect profile in children and adults seems similar except for transient growth inhibition.

While the medical need for therapy seems limited in the majority of HCV infected children, antiviral therapy may be warranted in selected patients with rapidly progressive fibrosis. The exact indications for therapy remain to be better defined. Therefore decisions about treatment are best taken in specialized centers. A pretreatment liver biopsy should show significant inflammation and/or fibrosis. Because there is as yet only limited data on the use of pegylated interferon and ribavirin currently treatment in children remains standard interferon alpha 3 MU/m² sc TIW combined with ribavirin 15 mg/kg/day po. This leads to practical problems of ribavirin dosing with the available preparations in children <8-10 years of age, since ribavirin is only available in 200 mg tablets. Whether antiviral therapy in children carries long-term side-effects remains to be seen. Children under 3 years should not be treated because of concerns of potential neurotoxicity of interferon on the developing brain. Furthermore, spontaneous viral clearance occurs with high frequency in this age group.

There is insufficient information to make any specific recommendations about treating children with hepatitis C.

Injection Drug Users

The prevalence of HCV infections is highest in injection drug users (IDUs) across Canada (>50%)(1,83-87). With over 2/3 of new HCV infections today occurring through IDU, the relative importance of this patient population for HCV disease and related public health issues will further increase in the future. IDUs are difficult to reach with traditional medical care structures and are often psychosocially unstable with ongoing addiction problems. They frequently have multiple medical and psychiatric co-morbidities and social issues (homeless, no supports), are highly mobile and fear prosecution. Given the high prevalence of HCV infection among IDUs and the central role of this population in the HCV epidemic today, it is not justifiable to automatically exclude HCV infected IDUs from antiviral therapy. Although the limited data available indicate that only about 10% of HCV infected IDUs who are potential candidates for HCV therapy actually get treated, (88-89), other data suggest that 70-80% express an interest in being treated. (89). The low rate of uptake of therapy was due to a multitude of medical co-morbidities and social problems, rather than a reluctance on the part of physicians to treat these patients. Data on treatment outcome is largely lacking.

- 25. Recommendations:** An appropriately funded, multidisciplinary effort is required to improve care strategies for HCV infected IDUs. Antiviral therapy should be considered in selected patients in whom HCV-related morbidity or mortality will likely become relevant (II-2). This requires an integrated multidisciplinary approach reaching beyond traditional care structures.

Hematopoietic Growth factor Support in the Management of Hepatitis

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Maximizing response rates to HCV therapy requires full treatment adherence with both pegylated interferon and ribavirin. However, anemia due to ribavirin-induced hemolysis is often a limiting factor. Treatment associated anemia requiring a reduction in ribavirin dose occurs in 25% of patients, often in the first 1-2 months of therapy and negatively impacts SVR. Ribavirin induced anemia is more frequent with the higher doses of ribavirin used to treat non genotype 2 and 3 infection. The use of erythropoietin to stimulate red cell production has been investigated. The data clearly shows that erythropoietin does stimulate a rise in hemoglobin, and allow a higher overall ribavirin doses to be given (92-94). These studies have recently been extended and show that the use of erythropoietin allows higher ribavirin dosing, and thereby improves SVR compared to a group in which erythropoietin is not used (95).

Treatment with erythropoietin can be considered if the hemoglobin falls more than 40 gm/l, or falls below 110 g/l, or if patients become symptomatic from anemia (weakness, dyspnea, angina, etc.). The initial dose should be between 20000-40000 IU SQ/weekly, increasing to a maximum dose of 60000 IU/week if required. Erythropoietin dosing is maintained to keep the hemoglobin at or above 110 g/L, but it is not necessary to aim for a return to baseline hemoglobin. Ribavirin-induced anemia also results in an increased consumption of red cell production factors, so that supplementation with iron, folic acid and vitamin B12 can be considered. Other causes of anemia need to be ruled out by laboratory testing (i.e. iron, folate, B12) before attributing the anemia to medication.

Although erythropoietin can be useful there is insufficient data to recommend routine use in all patients.

Between 30-50% of patients will experience a fall in neutrophil counts within the first 2 weeks of therapy (ref), and neutropenia is the most common cause of interferon dose reduction. Although dose reductions or the addition of G-CSF is commonly recommended when the neutrophil count falls to $<0.5 \times 10^9/L$, this does not seem to be associated with an increased risk of infection (96). Although the package inserts for both pegylated interferons suggest dose reductions if the neutrophil count falls below $0.7 \times 10^9/L$ and recommend discontinuation if the neutrophil count falls below $0.5 \times 10^9/L$, experts suggest that dose reductions are not necessary until the neutrophil count falls below $0.5 \times 10^9/L$, with discontinuation if the neutrophil count falls below $0.3 \times 10^9/mL$. Since less than optimal doses of interferon have a negative impact on SVR rates granulocyte colony stimulating factor (G-CSF) has been used to maintain interferon dose (97). However, there is insufficient data to recommend the use of this agent as standard of care.

Although the package inserts for both pegylated interferons suggest dose reductions if the platelet count falls below $75 \times 10^9/L$ and recommend discontinuation if the platelet count falls below $50 \times 10^9/L$ experts suggest that dose reductions are not necessary until the platelet count falls below $30 \times 10^9/L$, with discontinuation if the platelet count falls below $20 \times 10^9/mL$.

26. Recommendations: Erythropoietin can be used to support hemoglobin levels in patients on treatment with PEG IFN and ribavirin. However, there is insufficient evidence to recommend its use for all patients (III).

Table 1. Levels of evidence according to study design (98)

Grade	Definition
I	Randomized controlled trials
II-1	Controlled trials without randomization
II-2	Cohort or case controlled studies
II-3	Multiple time series, dramatic uncontrolled experiments
III	Opinion of respected authorities. Descriptive epidemiology

Table 2. Estimated HCV prevalence in Canada, July 1998 to December 2002

HCV prevalence, July 1998	240,000
Annual new infections	6,600
HCV immigration	2,000
Annual mortality	4,700
<hr/>	
HCV prevalence	250,500

Table 3. HCV prevalence by exposure category, Canada, 2002

	Population	HCV prevalence rate	HCV prevalence number	Proportion
IDU	91,000	55%	49,900	20%
Ex-IDU	181,400	49%	89,400	36%
IDU, total	272,500		139,300	56%
Transfusion	2,748,200	1.2%	32,900	13%
Hemophilia		57%	1,200	0.5%
Other	<u>28,023,900</u>	<u>0.26%</u>	<u>73,800</u>	<u>30%</u>
Total	31,046,600	0.80%	247,200	100%

Table 4. Contraindications for treatment with pegylated interferon and ribavirin

Conditions that are no longer contraindications	<p>Normal ALT</p> <p>Stable methadone maintenance</p> <p>Neutropenia, anemia or thrombocytopenia</p> <p>Controlled seizure disorder</p> <p>Age over 65</p> <p>Alcohol use</p>
Relative contraindications	<p>Major Depression</p> <p>Major psychosis</p> <p>Autoimmune disease</p> <p>Injection drug use</p> <p>Renal failure (including dialysis)</p>
Strong, but not absolute contraindications	<p>Alcohol abuse</p> <p>Hepatic decompensation</p> <p>Coronary artery disease</p> <p>Solid organ transplantation (except liver)</p>
Absolute contraindications	<p>Pregnancy</p>

Table 5. Definition of Treatment Responses

Rapid Virologic Response (RVR)	HCV RNA negative (< 50 IU/mL) at week 4
Early Virologic Response (EVR)	≥ 2 log decline in HCV RNA at week 12 (EVC plus PVR) or HCV RNA negative at 12 weeks
Aviremic or Early Virologic Clearance (EVC)	HCV RNA negative (<50 IU/mL) at week 12
Viremic or Partial Virologic Response (PVR)	≥ 2 log decline in HCV RNA at week 12, but HCV RNA still positive
Sustained Virologic Response (SVR)	HCV RNA negative 24 weeks after end of treatment

Figure 1. Modeled prevalence of HCV sequelae, Canada, 1962-2022 (after Remis R).

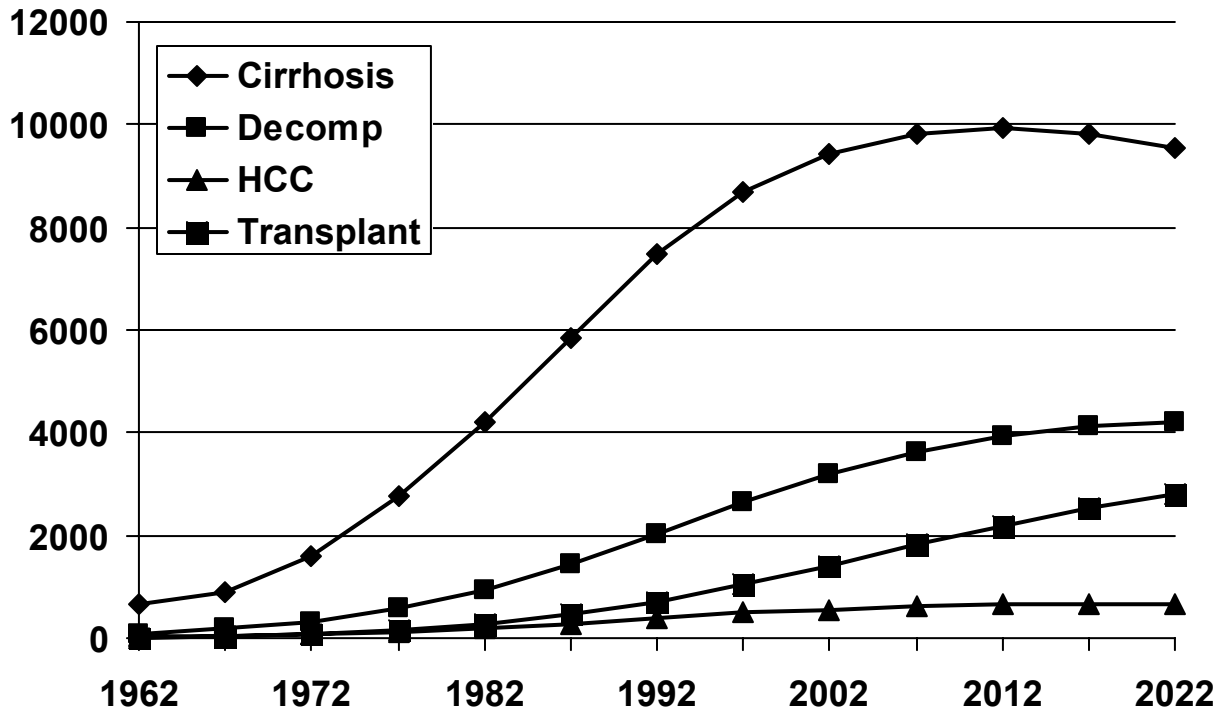
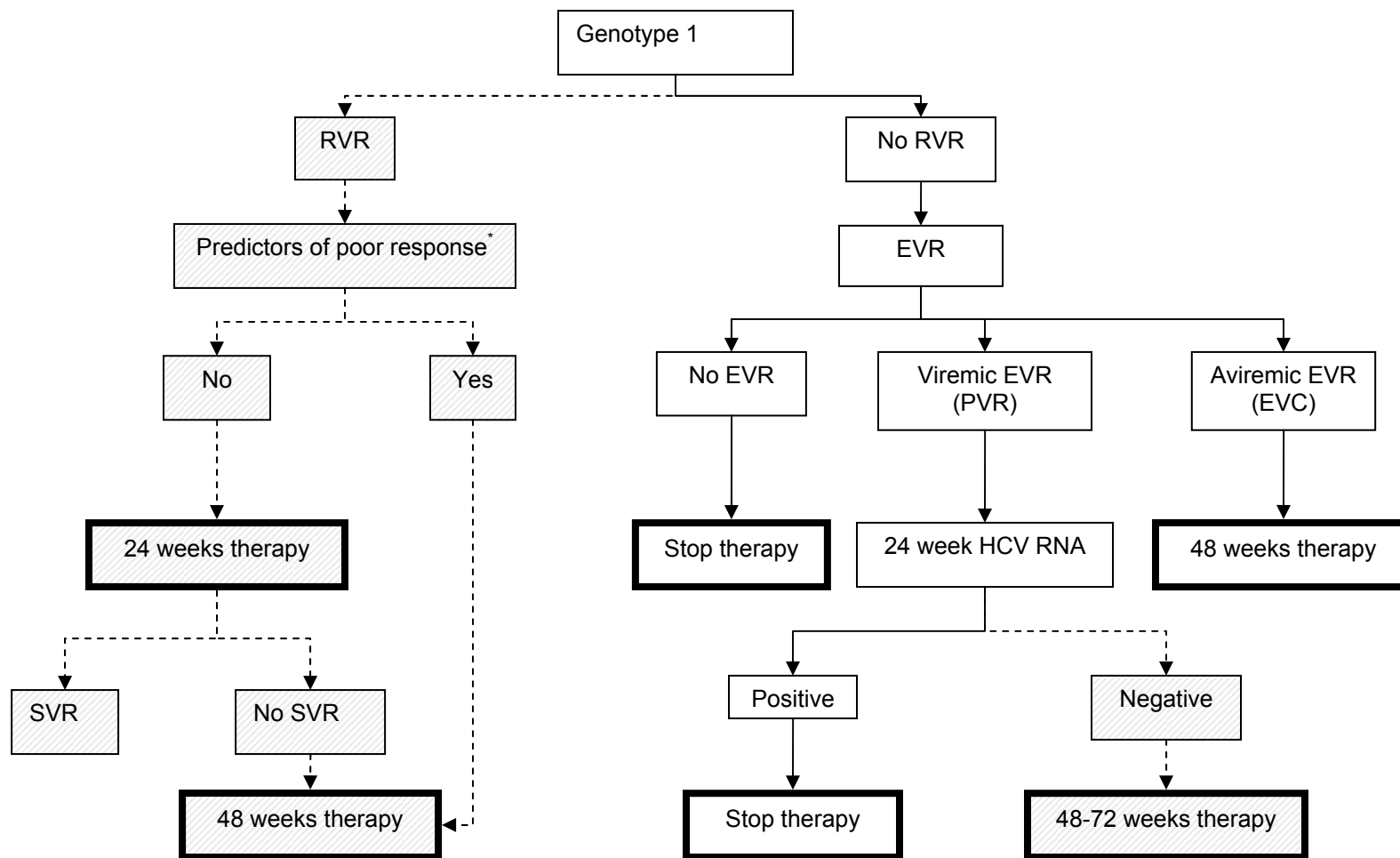
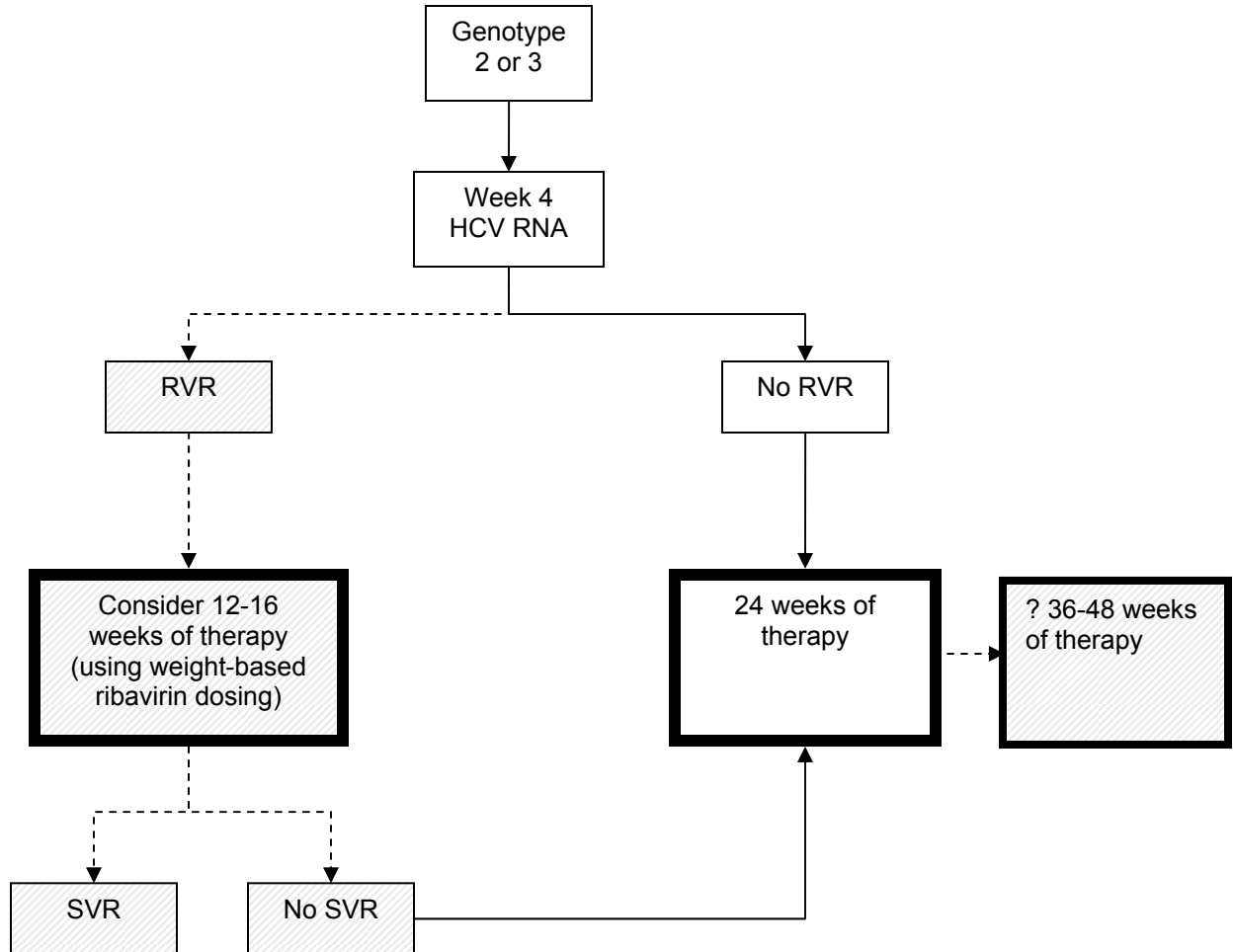


Figure 2. Algorithm for the management of patients with hepatitis C genotype 1 infection on therapy with pegylated interferon and ribavirin. The dotted arrows and shaded boxes represent new treatment algorithms based on viral kinetic. The solid arrows and clear boxes represent the standard algorithms.



*Advanced fibrosis, high viral load, high BMI, older age, African American race, HIV co-infection, immunosuppression

Figure 3. Algorithm for the management of patients with hepatitis C, genotype 2 or 3, on therapy with pegylated interferon and ribavirin. The dotted arrows and shaded boxes represent new treatment algorithms based on viral kinetic. The solid arrows and clear boxes represent the standard algorithms.



References

1. Remis R. Estimating the Number of Persons infected with Hepatitis C in Canada: Submitted to the Health Canada 2005.
2. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. *J Viral Hepat.* 2006 Jan;13(1):34-41.
3. Jauncey M, Micallef JM, Gilmour S, Amin J, White PA, Rawlinson W, Kaldor JM, van Beek I, Dore GJ. Clearance of hepatitis C virus after newly acquired infection in injection drug users. *J Infect Dis.* 2004 Oct 1;190(7):1270-4.
4. Wiegand J, Buggisch P, Boecher W, Zeuzem S, Gelbmann CM, Berg T, Kauffmann W, Kallinowski B, Cornberg M, Jaeckel E, Wedemeyer H, Manns MP; German HEP-NET Acute HCV Study Group. Early monotherapy with pegylated interferon alpha-2b for acute hepatitis C infection: the HEP-NET acute-HCV-II study. *Hepatology.* 2006 Feb;43(2):250-6
5. Kamal SM, Fouly AE, Kamel RR, Hockenjos B, Al Tawil A, Khalifa KE, He Q, Koziel MJ, El Naggar KM, Rasenack J, Afdhal NH. Peginterferon alfa-2b therapy in acute hepatitis C: impact of onset of therapy on sustained virologic response. *Gastroenterology.* 2006 Mar;130(3):632-8.
6. Jaeckel E, Cornberg M, Wedemeyer H, Santantonio T, Mayer J, Zankel M, Pastore G, Dietrich M, Trautwein C, Manns MP; German Acute Hepatitis C Therapy Group. Treatment of acute hepatitis C with interferon alfa-2b. *N Engl J Med.* 2001 Nov 15;345(20):1452-7
7. Kamal SM, Moustafa KN, Chen J, Fehr J, Abdel Moneim A, Khalifa KE, El Gohary LA, Ramy AH, Madwar MA, Rasenack J, Afdhal NH. Duration of peginterferon therapy in acute hepatitis C: a randomized trial. *Hepatology.* 2006 May;43(5):923-31.
8. Maio G, d'Argenio P, Stroffolini T, Bozza A, Sacco L, Tosti ME, Intorcia M, Fossi E, d'Alessio G, Kondili LA, Rapicetta M, Mele A. Hepatitis C virus infection and alanine transaminase levels in the general population: a survey in a southern Italian town. *J Hepatol.* 2000 Jul;33(1):116-20.
9. Comandini UV, Tossini G, Longo MA, et al. Sporadic hepatitis C virus infection: a case-control study of transmission routes in a selected hospital sample of the general population in Italy. *J. Infect. Dis.* 1998;30:11-15
10. Falck-Ytter Y, Kale H, Mullen KD, Sarbah SA, Sorescu L, McCullough AJ. Surprisingly small effect of antiviral treatment in patients with hepatitis C. *Ann Intern Med.* 2002 Feb 19;136(4):288-92.
11. Mauss S, Berger F, Goelz J, Jacob B, Schmutz G. A prospective controlled study of interferon-based therapy of chronic hepatitis C in patients on methadone maintenance. *Hepatology.* 2004 Jul;40(1):120-4.
12. Anand BS, Currie S, Dieperink E, Bini EJ, Shen H, Ho SB, Wright T; VA-HCV-001 Study Group. Alcohol use and treatment of hepatitis C virus: results of a national multicenter study. *Gastroenterology.* 2006 May;130(6):1607-16.
13. Shiffman ML, Diago M, Tran A, Pockros P, Reindollar R, Prati D, Rodriguez-Torres M, Lardelli P, Blotner S, Zeuzem S. Chronic hepatitis C in patients with persistently normal alanine transaminase levels. *Clin Gastroenterol Hepatol.* 2006 May;4(5):645-52
14. Nudo CG, Wong P, Hilzenrat N, Deschenes M. Elderly patients are at greater risk of cytopenia during antiviral therapy for hepatitis C. *Can. J. Gastro.* 2006;20:589-592.
15. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, Goodman ZD, Koury K, Ling M, Albrecht JK. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet.* 2001 Sep 22;358(9286):958-65
16. Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FL Jr, Haussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Lin A, Hoffman J, Yu J. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med.* 2002 Sep 26;347(13):975-82.
17. Bain VG, Lee SS, Peltekian K, et al. Exposure to ribavirin (RBV) predicts EVR and SVR in patients with HCV genotype 1 infection: analysis of the Canadian Pegasys expanded access program (EAP). *Hepatology* 2006;44:335°
18. Hadziyannis SJ, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, Ramadori G, Bodenheimer H Jr, Bernstein D, Rizzetto M, Zeuzem S, Pockros PJ, Lin A, Ackrill AM; PEGASYS International Study Group. Peginterferon alfa-2a and ribavirin combination therapy in hepatitis C. *Ann, Intern. Med.* 2004;140:346-355

19. Ferenci P, Fried MW, Shiffman ML, et al. Smith CI, Marinos G, Goncalves FL Jr, Haussinger D, Diago M, Carosi G, Dhumeaux D, Craxi A, Chaneac M, Reddy KR. Predicting sustained virological responses in chronic hepatitis C patients treated with peginterferon alfa-2a (40 KD)/ribavirin. *J Hepatol* 2005;43:425-33
20. Jensen DM, Morgan TR, Marcellin P, Pockros PJ, Reddy KR, Hadziyannis SJ, Ferenci P, Ackrill AM, Willems B. Early identification of HCV genotype 1 patients responding to 24 weeks peginterferon alpha-2a (40 kd)/ribavirin therapy. *Hepatology*. 2006 May;43(5):954-60.
21. Zeuzem S, Buti M, Ferenci P, Sperl J, Horsmans Y, Cianciara J, Ibranyi E, Weiland O, Noviello S, Brass C, Albrecht J. Efficacy of 24 weeks treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C infected with genotype 1 and low pretreatment viremia. *J Hepatol* 2006;44:97-103
22. Buti M, Valdes A, Sanchez-Avila F, Esteban R and Lurie Y. Extending combination therapy with peginterferon alfa-2b plus ribavirin for genotype 1 chronic hepatitis C late responders: a report of 9 cases. *Hepatology* 2003;37:1226-7
23. Berg T, von Wagner M, Nasser S, Sarrazin C, Heintges T, Gerlach T, Buggisch P, Goeser T, Rasenack J, Pape GR, Schmidt WE, Kallinowski B, Klinker H, Spengler U, Martus P, Alshuth U, Zeuzem S. Extended treatment duration for hepatitis C virus type 1: comparing 48 versus 72 weeks of peginterferon-alfa-2a plus ribavirin. *Gastroenterology*. 2006 Apr;130(4):1086-97
24. Ferenci P, Lafen H, Scherzer TM, et al. Customizing treatment with peginterferon alfa-2A (40KD) (Pegasys(R)) plus ribavirin in patients with HCV genotype 1 or 4 infection. *Hepatology* 2006;44:336A (abstract 390)
25. Pearlman B, Ehleben C and Siafee S. Improved virologic response rates with treatment extension to 72 weeks of peginterferon alfa-2B plus weight-based ribavirin in a difficult to treat population of genotype 1 infected slow responders. *Hepatology* 2006;44:318A (abstract 343)
26. Sanchez-Tapias JM, Diago M, Escartin P, et al. Enriquez J, Romero-Gomez M, Barcena R, Crespo J, Andrade R, Martinez-Bauer E, Perez R, Testillano M, Planas R, Sola R, Garcia-Bengoechea M, Garcia-Samaniego J, Munoz-Sanchez M, Moreno-Otero R; TeraVIC-4 Study Group Peginterferon-alfa2a plus ribavirin for 48 versus 72 weeks in patients with detectable hepatitis C virus RNA at week 4 of treatment. *Gastroenterology* 2006;131:451-60
27. Zeuzem S, Hultcrantz R, Bourliere M, Goeser T, Marcellin P, Sanchez-Tapias J, Sarrazin C, Harvey J, Brass C, Albrecht J. Peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with HCV genotypes 2 or 3. *J Hepatol* 2004;40:993-9
28. Shiffman M, Pappas S, Bacon B, et al. Utility of virologic response at weeks 4 and 12 in the prediction of SVR rates in genotype 2/3 patients treated with peginterferon alfa 2A plus ribavirin: findings from ACCELERATE. *Hepatology* 2006;44:316A
29. von Wagner M, Huber M, Berg T, Hinrichsen H, Rasenack J, Heintges T, Bergk A, Bernsmeier C, Haussinger D, Herrmann E, Zeuzem S. Peginterferon-alpha-2a (40KD) and ribavirin for 16 or 24 weeks in patients with genotype 2 or 3 chronic hepatitis C. *Gastroenterology* 2005;129:522-7
30. Mangia A, Santoro R, Minerva N, Ricci GL, Carretta V, Persico M, Vinelli F, Scotto G, Bacca D, Annese M, Romano M, Zechini F, Sogari F, Spirito F, Andriulli A. Peginterferon alfa-2b and ribavirin for 12 vs. 24 weeks in HCV genotype 2 or 3. *N Engl J Med*. 2005 Jun 23;352(25):2609-17.
31. Dalgard O, Bjoro K, Hellum KB, Myrvang B, Ritland S, Skaug K, Raknerud N, Bell H. Treatment with pegylated interferon and ribavirin in HCV infection with genotype 2 or 3 for 14 weeks: a pilot study. *Hepatology*. 2004 Dec;40(6):1260-5.
32. Shiffman M, Pappas S, Nyberg L, et al. Peginterferon alfa 2A plus ribavirin for 16 or 24 weeks in patients with HCV genotype 2 or 3: final results of the accelerate trial. In: EASL. Vienna, Austria, 2006
33. Shiffman M, Pappas S, Greenbloom S, et al. Effect of drug exposure on sustained virologic response (SVR) in patients with chronic hepatitis C virus genotype 2 or 3 treated with peginterferon alfa 2A (40KD) plus ribavirin for 16 or 24 weeks. *Hepatology* 2006;44:317A (abstract 342)
34. Derbala M, Amer A, Bener A, Lopez AC, Omar M and El Ghannam M. Pegylated interferon-alpha 2b-ribavirin combination in Egyptian patients with genotype 4 chronic hepatitis. *J Viral Hepat* 2005;12:380-5
35. Diago M, Hassanein T, Rodes J, Ackrill AM and Sedarati F. Optimized virologic response in hepatitis C virus genotype 4 with peginterferon-alpha2a and ribavirin. *Ann Intern Med* 2004;140:72-3

36. Kamal SM, El Tawil AA, Nakano T, et al. Peginterferon [alpha]-2b and ribavirin therapy in chronic hepatitis C genotype 4: impact of treatment duration and viral kinetics on sustained virological response. *Gut* 2005;54:858-66
37. Jacobson IM, Gonzalez SA, Ahmed F, Lebovics E, Min AD, Bodenheimer HC Jr, Esposito SP, Brown RS Jr, Brau N, Klion FM, Tobias H, Bini EJ, Brodsky N, Cerulli MA, Aytaman A, Gardner PW, Geders JM, Spivack JE, Rahmin MG, Berman DH, Ehrlich J, Russo MW, Chait M, Rovner D, Edlin BR. A randomized trial of pegylated interferon alpha-2b plus ribavirin in the retreatment of chronic hepatitis C. *Am J Gastroenterol.* 2005 Nov;100(11):2453-62
38. Mathew A, Peiffer LP, Rhoades K, McGarrity T. Sustained viral response to pegylated interferon α -2b and ribavirin in chronic hepatitis C refractory to prior treatment. *Dig Dis Sci* 2006; 51: 1965-61.
39. Krawitt EL, Ashikaga T, Gordon SR, Ferrentino N, Ray MA, Lidofsky SD; New York New England Study Team. Peginterferon alfa-2b and ribavirin for treatment-refractory chronic hepatitis C. *J Hepatol.* 2005 Aug;43(2):243-9.
40. Parise E, Cheinquer H, Crespo D et al. Peginterferon alfa-2a (40KD) (PEGASYS) plus ribavirin (COPEGUS) in retreatment of chronic hepatitis C patients, nonresponders and relapsers to previous conventional interferon plus ribavirin therapy. *Brz J Infect Dis* 2006; 10: 11-16.
41. Taliani G, Gemignani G, Ferrari C, Aceti A, Bartolozzi D, Blanc PL, Capanni M, Esperti F, Forte P, Guadagnino V, Mari T, Marino N, Milani S, Pasquazzi C, Rosina F, Tacconi D, Toti M, Zignego AL, Messerini L, Stroffolini T; Nonresponder Retreatment Group. Pegylated interferon alfa-2b plus ribavirin in the retreatment of interferon-ribavirin nonresponder patients. *Gastroenterology.* 2006 Apr;130(4):1098-106
42. Sherman M, Yoshida EM, Deschenes M, Kraiden M, Bain VG, Peltekian K, Anderson F, Kaita K, Simonyi S, Balshaw R, Lee SS; Canadian Pegasys Study Group. Peginterferon alfa-2a (40KD) plus ribavirin in chronic hepatitis C patients who failed previous interferon therapy. *Gut.* 2006 Nov;55(11):1631-8.
43. Everson GT, Hoefs JC, Seeff LB, Bonkovsky HL, Naishadham D, Shiffman ML, Kahn JA, Lok AS, Di Bisceglie AM, Lee WM, Dienstag JL, Ghany MG, Morishima C; HALT-C Trial Group. Impact of disease severity on outcome of antiviral therapy for chronic hepatitis C: Lessons from the HALT-C trial. *Hepatology.* 2006 Dec;44(6):1675-84
44. Poynard T, Schiff E, Terg R et al. Sustained virologic response (SVR) in the EPIC 3 Trial : week twelve virology predicts SVR in previous interferon/ribavirin treatment failures receiving peg-Intron/Rebetol (PR) weight based dosing (WBD). *J Virol Hepatol* 2005; 42 (suppl 2): 40-41.
- 45.
46. Cornberg M, Hadem J, Herrmann E, Schuppert F, Schmidt HH, Reiser M, Marschal O, Steffen M, Manns MP, Wedemeyer H. Treatment with daily consensus interferon (CIFN) plus ribavirin in non-responder patients with chronic hepatitis C: a randomized open-label pilot study. *J Hepatol.* 2006 Feb;44(2):291-301.
47. Russo MW, Goldsweig CD, Jacobson IM, Brown RS Jr. Interferon monotherapy for dialysis patients with chronic hepatitis C: an analysis of the literature on efficacy and safety. *Am J Gastroenterol.* 2003 Jul;98(7):1610-5.
48. Seeff LB, Hoofnagle JH National Institutes of Health Consensus Development Conference: management of hepatitis C: 2002. *Hepatology.* 2002 Nov;36(5 Suppl 1):S1-2
49. Gonzalez-Roncero F, Gentil MA, Valdivia MA, Algarra G, Pereira P, Toro J, Sayago M, Mateos J. Outcome of kidney transplant in chronic hepatitis C virus patients: effect of pretransplantation interferon-alpha2b monotherapy. *Transplant Proc.* 2003 Aug;35(5):1745-7.
50. Russo MW, Ghalib R, Sigal S, Joshi V. Randomized trial of pegylated interferon alpha 2b monotherapy in patients with chronic hepatitis C. *Nephrol Dial Transplant* 2006; 21: 437-43.
51. Kokoglu OF, Ucmak H, Hosoglu S et al. Efficacy and tolerability of pegylated-interferon alpha-2a in hemodialysis patients with chronic hepatitis C. *J Gastroenterol Hepatol* 2006; 575-80;
52. Sporea I, Sirlu R, Golea O et al. Peg-interferon alfa 2a (40 kDa) in patients on chronic haemodialysis with chronic hepatitis C. Preliminary results. *Rom J Gastroenterol* 2004; 13: 99-102
53. Bruchfeld A, Lindahl K, Reichard O et al. Pegylated interferon and ribavirin treatment for hepatitis C in haemodialysis patients. *J Viral Hepat* 2006; 13: 315-21

54. Iacobellis A, Siciliano M, Perri F, Annicchiarico BE, Leandro G, Caruso N, Accadia , Bombardieri G, Andriulli A. Peginterferon alfa-2b and ribavirin in patients with hepatitis C virus and decompensated cirrhosis: A controlled study. *J Hepatol.* 2007 Feb; 46(2): 206-212.
55. Everson GT, Trotter J, Forman L, Kugelmas M, Halprin A, Fey B, Ray C. Treatment of advanced hepatitis C with a low accelerating dosage regimen of antiviral therapy. *Hepatology.* 2005 Aug;42(2):255-62
56. Everson GT. Treatment of chronic hepatitis C in patients with decompensated cirrhosis. *Rev Gastroenterol Disord* 2004; 4 suppl 1: S31-28
57. Mazzaro C, Zorat F, Caizzi M, Donada C, Di Gennaro G, Maso LD, Carniello G, Virgolini L, Tirelli U, Pozzato G. Treatment with peg-interferon alfa-2b and ribavirin of hepatitis C virus-associated mixed cryoglobulinemia: a pilot study. *J Hepatol.* 2005 May;42(5):632-8.
58. Cacoub P, Saadoun D, Limal N, Sene D, Lidove O, Piette JC. PEGylated interferon alfa-2b and ribavirin treatment in patients with hepatitis C virus-related systemic vasculitis. *Arthritis Rheum.* 2005 Mar;52(3):911-5
59. Alric L, Plaisier E, Thebault S Peron JM, Rostaing L, Pourrat J, Ronco P, Piette JC, Cacoub P. . Influence of antiviral therapy in hepatitis C virus-associated cryoglobulinemic MPGN. *Am J Kidney Dis* 2004; 43: 617-23
60. Levine JW, Gota C, Fessler BJ Fessler BJ, Calabrese LH, Cooper SM. Persistent cryoglobulinemic vasculitis following successful treatment of hepatitis C virus. *J Rheumatol* 2005; 32: 1164-67;
61. Inati A, Taher A, Ghorra S Koussa S, Taha M, Aoun E, Sharara AI. . Efficacy and tolerability of peginterferon alpha 2a with or without ribavirin in thalassaemia major patients with chronic hepatitis C virus infection. *Br J Haematol* 2005; 130: 644-46
62. Matsuo K, Kusano A, Sugumar A, Nakamura S, Tajima K, Mueller NE. Effect of hepatitis C virus infection on the risk of non-Hodgkin's lymphoma: a meta-analysis of epidemiological studies. *Cancer Sci.* 2004 Sep;95(9):745-52
63. Engels EA, Chatterjee N, Cerhan JR, Davis S, Cozen W, Severson RK, Whitby D, Colt JS, Hartge P. Hepatitis C virus infection and non-Hodgkin lymphoma: results of the NCI-SEER multi-center case-control study. *Int J Cancer.* 2004 Aug 10;111(1):76-80
64. Gisbert JP, Garcia-Buey L, Arranz R, Blas C, Pinilla I, Khorrami S, Acevedo A, Borque MJ, Pajares JM, Fernandez-Ranada JM, Moreno-Otero R. The prevalence of hepatitis C virus infection in patients with non-Hodgkin's lymphoma. *Eur J Gastroenterol Hepatol.* 2004 Feb;16(2):135-8.
65. Gisbert JP, Garcia-Buey L, Pajares JM, Moreno-Otero R. Systematic review: regression of lymphoproliferative disorders after treatment for chronic hepatitis C infection. *Aliment Pharmacol Ther* 2005; 21: 653-62
66. Vallisa D, Bernuzzi P, Arcaini L, Sacchi S, Callea V, Marasca R, Lazzaro A, Trabacchi E, Anselmi E, Arcari AL, Moroni C, Berte R, Lazzarino M, Cavanna L. Role of anti-hepatitis C virus (HCV) treatment in HCV-related, low-grade, B-cell, non-Hodgkin's lymphoma: a multicenter Italian experience. *J Clin Oncol.* 2005 Jan 20;23(3):468-73.
67. Amin J, Kaye M, Skidmore S, Pillay D, Cooper DA, Dore GJ. HIV and hepatitis C coinfection within the CAESAR study *HIV Med.* 2004 May;5(3):174-9
68. Bica I, McGovern B, Dhar R, Stone D, McGowan K, Scheib R, Snyderman DR. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. *Clin Infect Dis.* 2001 Feb 1;32(3):492-7
69. Benhamou Y, Di Martino V, Bochet M, Colombet G, Thibault V, Liou A, Katlama C, Poynard T; MultivirC Group. Factors affecting liver fibrosis in human immunodeficiency virus-and hepatitis C virus-coinfected patients: impact of protease inhibitor therapy. *Hepatology.* 2001 Aug;34(2):283-7
70. Perez-Olmeda M, Nunez M, Romero M, Gonzalez J, Castro A, Arribas JR, Pedreira J, Barreiro P, Garcia-Samaniego J, Martin-Carbonero L, Jimenez-Nacher I, Soriano V. Pegylated IFN-alpha2b plus ribavirin as therapy for chronic hepatitis C in HIV-infected patients. *AIDS.* 2003 May 2;17(7):1023-8
71. Voigt E, Schulz C, Klausen G, Goelz J, Mauss S, Schmutz G, Jessen H, Weitner L, Mutz A, Schranz D, Rockstroh JK, Kaad Study Group. Pegylated interferon alpha-2b plus ribavirin for the treatment of chronic hepatitis C in HIV-coinfected patients. *J Infect.* 2006 Jul;53(1):36-42.
72. Hopkins S, Lambourne J, Farrell G, McCullagh L, Hennessy M, Clarke S, Mulcahy F, Bergin C. Role of individualization of hepatitis C virus (HCV) therapy duration in HIV/HCV-coinfected individuals. *HIV Med.* 2006 May;7(4):248-54

73. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, Lissen E, Gonzalez-Garcia J, Lazzarin A, Carosi G, Sasadeusz J, Katlama C, Montaner J, Sette H Jr, Passe S, De Pamphilis J, Duff F, Schrenk UM, Dieterich DT; APRICOT Study Group. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med*. 2004 Jul 29;351(5):438-50
74. Chung RT, Andersen J, Volberding P, Robbins GK, Liu T, Sherman KE, Peters MG, Koziel MJ, Bhan AK, Alston B, Colquhoun D, Nevin T, Harb G, van der Horst C; AIDS Clinical Trials Group A5071 Study Team. Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. *N Engl J Med*. 2004 Jul 29;351(5):451-9.
75. Carrat F, Bani-Sadr F, Pol S, Rosenthal E, Lunel-Fabiani F, Benzekri A, Morand P, Goujard C, Pialoux G, Piroth L, Salmon-Ceron D, Degott C, Cacoub P, Perronne C; ANRS HCO2 RIBAVIC Study Team. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. *JAMA*. 2004 Dec 15;292(23):2839-48
76. Laguno M, Murillas J, Blanco JL, Martinez E, Miquel R, Sanchez-Tapias JM, Bargallo X, Garcia-Criado A, de Lazzari E, Larrousse M, Leon A, Lonca M, Milinkovic A, Gatell JM, Mallolas J. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients. *AIDS*. 2004 Sep 3;18(13):F27-36
77. Alvarez D, Dieterich DT, Brau N, Moorehead L, Ball L, Sulkowski MS. Zidovudine use but not weight-based ribavirin dosing impacts anaemia during HCV treatment in HIV-infected persons *J Viral Hepat*. 2006 Oct;13(10):683-9.
78. Casiraghi MA, De Paschale M, Romano L, Biffi R, Assi A, Binelli G, Zanetti AR. Long-term outcome (35 years) of hepatitis C after acquisition of infection through mini transfusions of blood given at birth. *Hepatology*. 2004 Jan;39(1):90-6
79. Guido M, Bortolotti F, Leandro G, Jara P, Hierro L, Larrauri J, Barbera C, Giacchino R, Zancan L, Balli F, Crivellaro C, Cristina E, Pucci A, Rugge M. Fibrosis in chronic hepatitis C acquired in infancy: is it only a matter of time? *Am J Gastroenterol*. 2003 Mar;98(3):660-3
80. Gonzalez-Peralta RP, Kelly DA, Haber B, Molleston J, Murray KF, Jonas MM, Shelton M, Mieli-Vergani G, Lurie Y, Martin S, Lang T, Baczkowski A, Geffner M, Gupta S, Laughlin M; International Pediatric Hepatitis C Therapy Group. Interferon alfa-2b in combination with ribavirin for the treatment of chronic hepatitis C in children: efficacy, safety, and pharmacokinetics. *Hepatology*. 2005 Nov;42(5):1010-8.
81. Schwarz KB, Mohan P, Narkewicz MR, Molleston JP, Nash SR, Hu S, Wang K, Gries JM. Safety, efficacy and pharmacokinetics of peginterferon alpha2a (40 kd) in children with chronic hepatitis C. *J Pediatr Gastroenterol Nutr*. 2006 Oct;43(4):499-505.
82. Wirth S, Pieper-Boustani H, Lang T, Ballauff A, Kullmer U, Gerner P, Wintermeyer P, Jenke A. Peginterferon alfa-2b plus ribavirin treatment in children and adolescents with chronic hepatitis C. *Hepatology*. 2005 May;41(5):1013-8.
83. Fischer RP, Haley RW. Biases in surveillance of hepatitis C infection systematically underestimate the etiologic role of tattooing. *J Gastroenterol Hepatol*. 2004 Oct;19(10):1222-3.
84. Fischer B, Haydon E, Rehm J, Krajden M, Reimer J. Injection drug use and the hepatitis C virus: considerations for a targeted treatment approach--the case study of Canada. *J Urban Health*. 2004 Sep;81(3):428-47
85. Muga R, Sanvisens A, Bolao F, Tor J, Santesmases J, Pujol R, Tural C, Langohr K, Rey-Joly C, Munoz A. Significant reductions of HIV prevalence but not of hepatitis C virus infections in injection drug users from metropolitan Barcelona: 1987-2001. *Drug Alcohol Depend*. 2006 Apr;82 Suppl 1:S29-33.
86. Lumbreras B, Jarrin I, del Amo J, Perez-Hoyos S, Muga R, Garcia-de la Hera M, Ferreros I, Sanvisens A, Hurtado I, Hernandez-Aguado I. Impact of hepatitis C infection on long-term mortality of injecting drug users from 1990 to 2002: differences before and after HAART. *AIDS*. 2006 Jan 2;20(1):111-6
87. Reynolds GL, Fisher DG, Jaffe A, Edwards J. Follow-up for medical care among drug users with hepatitis C. *Eval Health Prof*. 2006 Dec;29(4):355-66
88. Hagan H, Latka MH, Campbell JV, Golub ET, Garfein RS, Thomas DA, Kapadia F, Strathdee SA; Study to Reduce Intravenous Exposures Project Team. Eligibility for treatment of hepatitis C virus infection among young injection drug users in 3 US cities. *Clin Infect Dis*. 2006 Mar 1;42(5):669-72

89. Nunes D, Saitz R, Libman H, Cheng DM, Vidaver J, Samet JH. Barriers to treatment of hepatitis C in HIV/HCV-coinfected adults with alcohol problems. *Alcohol Clin Exp Res*. 2006 Sep;30(9):1520-6.
90. Strathdee SA, Latka M, Campbell J, O'Driscoll PT, Golub ET, Kapadia F, Pollini RA, Garfein RS, Thomas DL, Hagan H; Study to Reduce Intravenous Exposures Project. Factors associated with interest in initiating treatment for hepatitis C Virus (HCV) infection among young HCV-infected injection drug users. *Clin Infect Dis*. 2005 Apr 15;40 Suppl 5:S304-12
91. Doab A, Treloar C, Dore GJ. Knowledge and attitudes about treatment for hepatitis C virus infection and barriers to treatment among current injection drug users in Australia *Clin Infect Dis*. 2005 Apr 15;40 Suppl 5:S313-20.
92. Pockros PJ, Shiffman ML, Schiff ER, Sulkowski MS, Younossi Z, Dieterich DT, Wright TL, Mody SH, Tang KL, Goon BL, Bowers PJ, Leitz G, Afdhal NH; PROACTIVE Study Group. Epoetin alfa improves quality of life in anemic HCV-infected patients receiving combination therapy. *Hepatology*. 2004 Dec;40(6):1450-8.
93. Afdhal NH, Dieterich DT, Pockros PJ, Schiff ER, Shiffman ML, Sulkowski MS, Wright T, Younossi Z, Goon BL, Tang KL, Bowers PJ; Proactive Study Group. Epoetin alfa maintains ribavirin dose in HCV-infected patients: a prospective, double-blind, randomized controlled study. *Gastroenterology*. 2004 May;126(5):1302-11
94. Dieterich DT, Wasserman R, Brau N, Hassanein TI, Bini EJ, Bowers PJ, Sulkowski MS. Once-weekly epoetin alfa improves anemia and facilitates maintenance of ribavirin dosing in hepatitis C virus-infected patients receiving ribavirin plus interferon alfa. *Am J Gastroenterol*. 2003 Nov;98(11):2491-9.
95. Shiffman ML, Price A, Hubbard S, Wilson M, Salvatori J, Sterling RK, Stravitz RT, Luketic VA, Sanyal AJ, Treatment of chronic hepatitis C virus (HCV) genotype 1 with peginterferon alfa-2B (PEGIFN), high weight based dose ribavirin (RVN) and epoetin alfa (EPO) enhances sustained virologic response (SVR). *Hepatology*, Vol. 42, No. 4, Suppl. 1, 2005; 217A
96. Cooper CL, Al-Bedwawi S. Infection rates in HIV-HCV patients treated with interferon are similar to those in HCV mono-infection and not related to neutropenia. *HIV Clin Trials*. 2006 Sep-Oct;7(5):251-4.
97. Lebray P, Nalpas B, Vallet-Pichard A, Broissand C, Sobesky R, Serpaggi J, Fontaine H, Pol S. The impact of haematopoietic growth factors on the management and efficacy of antiviral treatment in patients with hepatitis C virus. *Antivir Ther*. 2005;10(6):769-76
98. American Gastroenterological Association Medical Position Statement: guidelines for the use of enteral nutrition" *Gastroenterology* 1995 pp. 1280-1281