

South African Hepatitis C Management Guidelines 2010

Introduction

The hepatitis C virus (HCV) is a global public health problem and a leading cause of chronic liver disease¹ and the past decade has seen several significant advances in the management of persons infected with the virus.

The prevalence of HCV infection in South Africa is not known but has been estimated to be between 0.1² and 1.7 %.³

Phylogenetic analysis of the HCV has revealed 6 main genotypes and most published data relate to genotypes 1, 2 and 3. Genotypes 4, 5 and 6 however represent > 20 % of HCV infections worldwide. Genotype 5 is found predominantly in South Africa^{4,5} where it represents up to 40 % of all HCV genotypes.

Chronic hepatitis C is an important cause of end stage liver disease and individuals with HCV-related cirrhosis have a 30 % risk of developing hepatic decompensation in 10 years and a 1 – 3 % per annum risk of developing hepatocellular carcinoma (HCC).⁶

Male gender, infection at an advanced age, obesity⁷, consumption of > 50 g alcohol per day⁸ and co-infection with the human immunodeficiency virus (HIV)⁹ are predictive of more rapid progression to fibrosis.

This document is based largely on the American Association for the Study of Liver Diseases (AASLD) 2009 Practice Guidelines and aims to provide clinicians with evidence based approaches to the management of HCV infection. It is recognized that reasonable physicians may deviate from the strategy and remain within acceptable standards of treatment.

Diagnosis

The 2 classes of assays used in the diagnosis and management of HCV infection are

- Serologic assays that detect specific antibodies to the HCV (anti-HCV)
- Molecular assays that detect viral nucleic acid (HCV RNA).

All persons suspected of having acute or chronic hepatitis C or are at increased risk of HCV infection should be tested for anti-HCV.

HCV RNA testing should be performed in

- Individuals who are anti-HCV positive.
- Patients in whom antiviral treatment is being considered.
- Patients with unexplained liver disease whose anti-HCV is negative and are suspected of having acute hepatitis C or are immunocompromised.

Historically qualitative molecular assays have been more sensitive than quantitative molecular assays but, with the increasing sensitivity of the latter, this is no longer the case. For monitoring purposes it is important to use the same

laboratory test before and during therapy.

HCV genotyping should be performed in all HCV-infected persons prior to Interferon based treatment in order to plan for the dosage and duration of therapy and to estimate the likelihood of a response.

A liver biopsy should be considered if the treating physician requires information on the fibrosis stage for prognostic purposes or to make a therapeutic decision. It is furthermore useful in identifying that subset of patients with significant fibrosis but normal transaminases and to exclude co-existing liver disease.

Iron overload¹⁰ and steatosis^{11,12} reduce the likelihood of achieving a sustained virologic response (SVR) and should be treated prior to embarking on treatment with Pegylated Interferon (Peg-IFN) and Ribavirin. An SVR can now be achieved in almost 90 % of patients with genotypes 2 and 3 and, in this subset, a liver biopsy need only be done if there is clinical evidence of cirrhosis.

Currently available non-invasive tests may be useful in defining the presence or absence of advanced fibrosis in persons with chronic HCV infection but should not replace the liver biopsy in routine clinical practice.¹³

Treatment of chronic hepatitis C

The goal of therapy is to prevent complications and death from HCV infection.

The currently recommended therapy of chronic hepatitis C infection is the combination of a Peg-IFN and Ribavirin.¹⁴⁻¹⁶

Treatment should be considered in all adults with confirmed chronic hepatitis C and particularly in those who are at increased risk of developing cirrhosis. For patients in whom liver histology is available, treatment is indicated if advanced fibrosis (F₂ or F₃ according to the METAVIR scoring system) is present. As with all decisions in medicine, a balance must be struck between the benefit and risk of therapy and fibrosis is not a prerequisite for treatment.

Symptomatic cryoglobulinaemia is an indication for anti-viral therapy regardless of the stage of liver disease.

Additional factors that may influence the decision to treat are age, occupations in which there is a risk of transmission to others, quality of life, co-morbidities, the potential for serious side effects and the likelihood of treatment success.

Treatment may worsen psychiatric disorders and, in such patients, a pre-treatment psychiatric evaluation and close follow-up are mandatory.

Treatment is currently contraindicated in

- Age less than 2 years.
- Untreated thyroid disease.
- Autoimmune hepatitis or other autoimmune condition known to be exacerbated by Peg-IFN or Ribavirin.

- Decompensated liver disease.
- Severe concurrent medical disease such as severe hypertension, significant coronary artery disease, heart failure, chronic obstructive pulmonary disease, poorly controlled diabetes mellitus.
- Pregnancy or an unwillingness to use adequate contraception.
- Major uncontrolled depressive illness.
- Known hypersensitivity to drugs used to treat HCV infection.
- Solid organ transplantation (heart, lung or kidney).

Obesity is believed to play a role in the progression of fibrosis in HCV-infected individuals and may adversely affect treatment outcome. Patients with a BMI > 25.0 kg/m² should therefore be advised to lose weight.

Excessive alcohol consumption results in rapid progression of fibrosis, enhances viral replication and may interfere with treatment. Although no consensus exists, it seems reasonable to recommend either the complete cessation of alcohol intake or restricting its use whilst on treatment. Alcoholics should be abstinent for at least 1 year before commencing anti-viral treatment.

All patients with chronic hepatitis C should be screened for hepatitis A and B and, if not immune, offered vaccination.

Venesection is recommended in patients in whom a liver biopsy reveals significant iron overload.

There is no evidence that herbal products have a role in the treatment of patients with acute or chronic hepatitis C.

Because of the slow evolution of chronic hepatitis C, treatment responses are defined by surrogate virologic parameters rather than clinical endpoints.

The major predictors of a SVR are viral genotype and pre-treatment viral load.¹⁴⁻¹⁶ SVR rates are higher in genotype non-1 infections (predominantly genotypes 2 and 3) and in those with a viral load of < 600,000 IU/mL. Other less consistently reported baseline characteristics associated with a favourable response are female gender, age < 40 years, lower body weight (< 75 kg), the absence of insulin resistance, ALT levels > 3 times the upper limit of normal and the absence of bridging fibrosis or cirrhosis.

Patients with HCV-related cirrhosis, who achieve an SVR regardless of genotype, should continue to be monitored at 6 to 12 month intervals for the development of HCC.¹⁷

A RVR is highly predictive of achieving a SVR independent of genotype and regardless of treatment regimen.^{18,19}

Failure to achieve at least a pEVR is the most robust means of identifying non-responders in patients with genotype 1 infection.^{15,20-22} As less than 3 % of such individuals achieve an SVR, this is an indication to stop treatment. The clinical utility of an EVR is less helpful in patients with genotypes 2 and 3 infection since a majority of such individuals clear the virus by 12 weeks and respond to therapy.

Treatment of HCV genotypes 1¹⁶ and 4 infection²³

Duration of treatment: 48 weeks.

Therapeutic options

Peginterferon α -2a 180 μ g per week subcutaneously + Ribavirin according to body mass (\leq 75 kg: 1,000 mg per day; > 75 kg but \leq 90 kg: 1,200 mg per day; > 90 kg: 1,400 mg per day).¹⁵

or

Peginterferon α -2b 1.5 μ g/kg per week subcutaneously + Ribavirin according to body mass (< 65 kg: 800 mg per day; \geq 65 kg but \leq 85 kg: 1,000 mg per day; > 85 kg but \leq 105 kg: 1,200 mg per day; > 105 kg: 1,400 mg per day).^{14,24}

Treatment may be discontinued

- In patients who do not achieve at least a pEVR
- In patients who achieve a pEVR but are still HCV RNA positive at week 24.

In patients in whom viral clearance is delayed (HCV RNA becomes negative between weeks 12 and 24), consideration should be given to extending therapy to 72 weeks.^{25,26}

Patients in whom treatment is continued through 48 to 72 weeks and whose HCV RNA is negative at end of treatment should be retested for HCV RNA 24 weeks later to establish whether an SVR has been achieved.

Treatment of HCV genotypes 2 and 3 infection¹⁶

Duration of treatment: 24 weeks.

Therapeutic options

Peginterferon α -2a 180 μ g per week subcutaneously + Ribavirin 800 mg per day.

or

Peginterferon α -2b 1.5 g/kg per week subcutaneously + Ribavirin 800 mg per day.

Virologic response	Definition
Rapid virologic response (RVR)	HCV RNA negative at treatment week 4 by a sensitive PCR-based quantitative assay
Complete early virologic response (cEVR)	HCV RNA negative at treatment week 12
Partial early virologic response (pEVR)	\geq 2 log ₁₀ reduction in HCV RNA compared to baseline HCV RNA at treatment week 12
End-of-treatment response (ETR)	HCV RNA negative at the end of treatment week 24 or 48
Sustained virologic response (SVR)	HCV RNA negative 24 weeks after cessation of treatment
Breakthrough	Reappearance of HCV RNA in serum whilst still on therapy
Relapse	Reappearance of HCV RNA in serum after therapy is discontinued
Non-responder	Failure to clear HCV RNA from serum 24 weeks of treatment
Null responder	Failure to decrease HCV RNA by > 2 log ₁₀ after 24 weeks of therapy
Partial responder	> 2 log ₁₀ decrease in HCV RNA but still HCV RNA positive at week 24

Treatment may be discontinued in patients who do not achieve at least a pEVR.

In patients in whom viral clearance is delayed (HCV RNA becomes negative between weeks 12 and 24), consideration should be given to extending therapy to 48 weeks.

Patients in whom treatment is continued through 24 to 48 weeks and whose

HCV RNA is negative at end of treatment should be retested for HCV RNA 24 weeks later to establish whether a SVR has been achieved.

Treatment of HCV genotypes 5 and 6 infection

Patients with genotypes 5 and 6 are underrepresented in trials of Peg IFN and Ribavirin and, despite the lack of data, these individuals are generally treated for 48 weeks.²⁷

A recent viral kinetic study in non-cirrhotic patients with genotype 5 revealed first and second phase declines similar to those seen in genotypes 2 and 3.²⁸

These findings suggest that a shorter duration of therapy may be feasible but, in view of the geographic variations in treatment outcomes, more data are required.²⁹

Adverse events

Almost all patients treated with Peg IFN and Ribavirin experience 1 or more adverse events during the course of therapy.

The most common adverse events of Peg IFN are

- Influenza-like symptoms.
- Neuropsychiatric side effects. Depression-specific symptoms respond well to serotonergic antidepressants whereas neurovegetative symptoms do not and the assistance of a psychiatrist may be required.
- Haematologic abnormalities (anaemia, neutropaenia and thrombocytopaenia) are the most common reasons for dose modification. Growth factors are occasionally required.
- The induction of autoimmune disorders.

The most common side effect of Ribavirin is haemolytic anaemia. The drug is cleared by the kidneys and should therefore be used with extreme caution in patients with renal disease or renal failure. It is furthermore teratogenic and embryocidal in animals and it is therefore essential that female patients and female partners of male patients do not fall pregnant during the treatment period or in the 6 months thereafter. Two reliable forms of contraception should be used and a pregnancy test done 6 months after completion of therapy.

Monitoring during therapy

A full physical examination is mandatory and should include an examination of the eyes and urinalysis. An ECG should be done if clinically relevant and X-rays of the chest if there is a history of pre-existing pulmonary disease or current respiratory symptoms.

The following investigations should be performed in the 2 weeks before starting treatment

- Haematology (full blood count, INR and PTT).
- Chemistry (electrolytes, urea, creatinine, glucose, liver

function tests, cholesterol and uric acid).

- Thyroid function tests (TSH and FT₄).
- A pregnancy test should be done 1 day prior to starting treatment in female patients and in female partners of male patients who are of childbearing potential.
- HCV RNA (viral load and genotype).

Emotional status should be carefully monitored as depression is not uncommon and suicides have been reported.

A reasonable schedule would be monthly visits during the first 12 weeks of treatment followed by visits every 8 to 12 weeks thereafter until the end of therapy.

In clinical studies monitoring tests were done according to the following schedule

- Haematology and chemistry at weeks 1, 2, 4, 6 and 8 and then every 4 weeks. The frequency is however dependent on the degree of bone marrow suppression and the need for growth factor support.
- TSH and FT₄ every 12 weeks.
- Pregnancy test every 4 weeks.

A pregnancy test should be done if menstruation is delayed by more than 1 week.

Patients receiving Peg IFN and Ribavirin should have a quantitative HCV RNA test at week 12. Individuals who fail to achieve at least a pEVR are unlikely to achieve a SVR response and the treatment should therefore be stopped. Patients who achieve a pEVR should be retested at week 24 and, if HCV RNA is still detectable, treatment should be stopped.

The following investigations should be done 8 weeks after completion of treatment

- Haematology (full blood count).
- Chemistry (ALT).

The following investigations should be done 24 weeks after completion of treatment

- Haematology (full blood count).
- Chemistry (ALT).
- Qualitative HCV RNA.

Failure to detect HCV RNA at this point is indicative of a SVR.

Patients in whom therapy was stopped prematurely should be followed for at least 12 weeks after discontinuation of medication.

Treatment of persons with acute hepatitis C

All patients with acute hepatitis C should be considered for IFN-based therapy. Treatment may be delayed for 8 – 12 weeks to allow for spontaneous resolution. Excellent results have been achieved with standard IFN monotherapy³⁰ but, because of ease of administration, Peg IFN is preferred. No definite recommendation can be made about the optimal duration of treatment but it is reasonable to treat for 12 weeks and, in certain situations, 24 weeks. No recommendation can be made for or against the addition of Ribavirin and the decision will therefore need to be made on an individual basis.

Special populations

Persons with normal serum aminotransferases

Persons with persistently normal ALT levels usually have significantly less fibrosis than those with abnormal ALT levels. There are however reports of marked fibrosis in 5 – 30 % and cirrhosis in 1 % of those with persistently normal ALT levels.³¹⁻³³

Several studies have shown that standard-of-care treatment achieves the same SVR rate in this subset of patients.³⁴⁻³⁶

Patients with compensated and decompensated cirrhosis

Patients with HCV-related compensated cirrhosis can be treated with the standard regimen of Peg IFN + Ribavirin. They require close monitoring for adverse events and a lower SVR should be anticipated.¹⁴⁻¹⁶

Patients with HCV-related decompensated cirrhosis should be considered for liver transplantation.

The allograft is almost invariably re-infected with HCV and progressive post-transplant disease is common.^{37,38}

Since eradication of HCV pre-transplantation is associated with a lower likelihood of post-transplantation infection, there is a strong incentive to treat the HCV infection before transplantation, provided the risks of treatment are acceptable.

Retreatment of patients who failed to respond to previous treatment

Retreatment with Peg IFN + Ribavirin can be considered in non-responders or relapsers who were treated with non-pegylated IFN ± Ribavirin or with Peg IFN monotherapy.

Retreatment with Peg IFN + Ribavirin in patients who did not achieve an SVR after a prior full course of Peg IFN + Ribavirin is not recommended.

Maintenance therapy is not recommended for patients with bridging fibrosis or cirrhosis who have failed a prior course of Peg IFN + Ribavirin.

HCV-infected children

Children infected with HCV are more likely than adults to spontaneously clear the virus and have been shown to have minimal progression of their disease over 5 – 20 years.³⁹

Recent data indicate that combination therapy with Peg IFN + Ribavirin is safe in children. Children aged 2 – 17 years who are infected with HCV may be appropriate candidates for treatment and should receive Peg IFN α -2b 60 μ g/m² weekly subcutaneously + Ribavirin 15 mg/kg daily for 48 weeks.

Chronic kidney disease (CKD)

The kidney plays a central role in the clearance of both IFN and Ribavirin. The severity of the CKD therefore dictates the treatment regimen and, because of the high incidence of adverse events, such patients need to be closely monitored and often require growth factors.

Patients with chronic HCV infection and mild kidney disease (GFR > 60 mL/minute) can be treated with the same combination antiviral therapy as that used in persons without kidney disease.

Persons with chronic HCV infection and severe kidney

disease not undergoing haemodialysis can be treated with reduced doses of both Peg IFN (Peg IFN α -2a 135 μ g/week subcutaneously or Peg IFN α -2b 1 μ g/kg/week subcutaneously) and Ribavirin (200 – 800 mg/day) with careful monitoring for adverse effects.

HCV-infected haemodialysis patients have a higher mortality rate than non-infected haemodialysis patients due to more rapid progression to cirrhosis and/or hepatocellular carcinoma.⁴⁰⁻⁴² Treatment of HCV infection in patients on dialysis is fraught with difficulties and requires meticulous attention to side effect management. Standard IFN (IFN 2a or IFN 2b 3 MU tiw subcutaneously), which may be just as effective as Peg IFN or Peg IFN in reduced dosage (Peg IFN α -2a 135 μ g/week or Peg IFN α -2b 1 μ g/kg/week subcutaneously) may be considered. Ribavirin can be used in combination with IFN in markedly reduced daily dosage.

Furthermore, HCV-infected patients who undergo kidney transplantation have reduced graft survival and survival rates.⁴³⁻⁴⁵ It is therefore generally accepted that persons with chronic kidney disease who are infected with HCV should be treated before they require kidney transplantation.⁴⁶

Treatment is not recommended for patients with chronic HCV infection who have undergone kidney transplantation, unless they develop fibrosing cholestatic hepatitis.⁴⁷

Patients with cryoglobulinaemia and mild to moderate proteinuria and slowly progressive kidney disease can be treated with either standard IFN or reduced doses of Peg-IFN α and Ribavirin.⁴⁸

Patients with cryoglobulinaemia and marked proteinuria with evidence of progressive kidney disease or an acute flare of cryoglobulinaemia can be treated with Rituximab, Cyclophosphamide and Methylprednisolone or plasma exchange followed by IFN based treatment once the acute process has subsided.

Haematologic disorders

Patients with haemophilia do not require a liver biopsy and their treatment need not be modified.

Patients with thalassaemia minor infected with the HCV should receive Peg-IFN monotherapy. Combination therapy may be offered to non-responders and close monitoring as well as the assistance of a haematologist are strongly recommended.

HCV/HBV co-infection

Liver histology, HBV and HCV viral loads and HCV genotype are important in selecting appropriate treatment. The HCV genotype determines the duration of combination treatment with Peg-IFN and Ribavirin. Should treatment of the HBV infection be deemed necessary, Peg-IFN should be continued for a total of 48 weeks.

HCV/HIV co-infection

Although HCV/HIV co-infection is uncommon in South Africa, all patients with HCV infection should be screened for HIV.

The progression of liver disease is more rapid in HCV/HIV co-infected individuals and the risk of cirrhosis is double that in HCV mono-infected individuals.^{49,50}

Hepatitis C should be treated in the HCV/HIV co-infected patient in whom the likelihood of serious liver disease and a treatment response are judged to outweigh the risk of

morbidity from the adverse effects of therapy.

The likelihood of achieving an SVR is lower in HCV/HIV co-infected persons than in those with HCV mono-infection.⁵¹⁻⁵⁵

In patients with a CD4⁺ count < 200/μL, HIV treatment should be optimised before providing HCV treatment. Most authorities wait several months before initiating therapy so that the adverse effects of anti-retroviral therapy are not confused with those caused by Peg-IFN and Ribavirin. In patients with a CD4⁺ count > 200/μL, the HCV infection should be treated first.

Until more definitive data become available, initial treatment of hepatitis C in HIV-infected patients should be Peg IFN + Ribavirin for 48 weeks.⁵³⁻⁵⁶

HIV-infected patients with decompensated liver disease (CTP Class B or C) should not be treated with Peg INF and Ribavirin.

Patients receiving Zidovudine⁵⁷ and/or Didanosine⁵⁸⁻⁶⁰ should be switched to an equivalent anti-retroviral agent before beginning therapy with Ribavirin.

Treatment of patients after solid organ transplantation

IFN-based treatment should not be used in recipients of heart, lung or kidney grafts except for patients who develop fibrosing cholestatic hepatitis.

Treatment of HCV-related disease following liver transplantation should be initiated in appropriate candidates after demonstration of recurrent histologic disease and under the supervision of a physician experienced in transplantation.

Recreational drug use

Recreational drug use is often associated with behavioural disorders, psychiatric disorders, alcohol abuse and infections with HBV and/or HIV. The likelihood of successfully treating HCV infection in this setting is enhanced by participation in a rehabilitation program as well as psychological and psychiatric input.

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