



TREATMENTS FOR HEPATITIS C

- Standard therapy for the treatment of hepatitis C is pegylated interferon in combination with ribavirin. In people unable to take ribavirin, interferon monotherapy is used but outcomes are less satisfactory.
- The lack of detectable HCV RNA by PCR 6 months after completion of treatment gives a strong indication that therapy has been successful and is known as a sustained viral response (SVR). Studies show that over 99% people who achieve SVR remain clear of the virus.
- Treatment outcomes have improved markedly and an 80–90% SVR is expected for people with genotype 2 or 3. People with a genotype 1 or 4 infection should achieve a 40–45% SVR with current treatment schedules.
- New treatment schedules (shorter courses for rapid responders and longer courses for some genotype 1 infections) are being developed as research identifies optimal management pathways.
- For some people the side effects of treatment can be severe and they may require specialist management skills.



SUMMARY OF IMPORTANT POINTS



WHAT IS THE AIM OF TREATMENT?

- To stop viral replication and eliminate the virus.
- To prevent or delay the development of cirrhosis, liver failure and liver cancer.

WHO SHOULD BE TREATED?

Treatment is available for the majority of people with hepatitis C infection. It is recommended for people most at risk of developing cirrhosis and for those requesting treatment after a full discussion of the disease, its natural history and treatment outcomes. People with cirrhosis have a lower response rate to treatment, but it is thought that treatment will slow down the progression of liver disease.

ELIGIBILITY FOR TREATMENT UNDER MEDICARE

People who reside in Australia (excluding Norfolk Island) are eligible for treatment under Medicare if they hold Australian citizenship; have been issued with a permanent visa; or hold New Zealand citizenship. For persons who have applied for a permanent visa (excluding an application for a parent visa) – other requirements apply and they should be advised to contact Medicare on 132 011 for further information.

CONSIDERATIONS PRIOR TO TREATMENT

The side effects of pharmaceutical treatment can be unpleasant, difficult to manage and at times quite debilitating. Consequently, it is very important that people considering treatment are fully informed about possible outcomes and side effects and that they receive appropriate medical and psychological assessment prior to treatment.

In addition, issues such as the timing of pregnancy and the need for contraception during and after treatment, the contraindications for treatment during breastfeeding and personal commitments such as employment and domestic

responsibilities should be considered. Available psychosocial support options should be explored. This will enable each person to make a fully informed choice about whether to proceed with treatment.



TREATMENTS: PEGYLATED INTERFERON AND RIBAVIRIN

In Australia, records show that 2,847 people with chronic hepatitis C infection were prescribed pegylated interferon and ribavirin combination therapy or pegylated interferon alone in 2006.

INTERFERON

Interferons are proteins produced by the human body in response to any viral infection. The interferons used in the treatment of hepatitis C are synthetically manufactured and taken in higher doses than those which occur naturally in the body. Interferon therapy can boost a person's immune response and inhibit viral growth. The sustained viral response (SVR) with interferon alone is between 15% and 20%. Modifying the interferon molecule by attaching polyethylene glycol extends the duration of the therapeutic effect of the drug so that dosing only needs to occur once a week instead of three times weekly. This form of interferon is known as pegylated interferon. Interferon is injected under the skin (subcutaneously) using a very fine needle.

RIBAVIRIN

Ribavirin is a drug taken orally that alters the body's immune response to viruses. In the treatment of hepatitis C, it has been shown to be very effective in combination with interferon rather than as a treatment on its own.

COMBINATION THERAPY

Combination therapy is the standard form of treatment for hepatitis C. It consists of pegylated interferon and ribavirin. Treatment consists of a 24 or 48 week course of pegylated interferon injections, self-administered once a week, plus ribavirin capsules taken twice daily.

HOW EFFECTIVE IS COMBINATION THERAPY?

A person's response to treatment is related to several factors:

- genotype – people with genotypes 2 and 3 have been shown to have a higher response rate and in general need a shorter course of treatment than people with genotypes 1 and 4;
- degree of liver scarring (**fibrosis**) – people with advanced liver disease respond less well to therapy and may require longer treatment courses;
- amount of virus present in blood (viral load) – the lower the amount of virus, the more likely it is that therapy will clear the virus;
- age – younger people are more likely to respond to treatment; and
- sex – women are more likely than men to respond to treatment.

Expected outcomes for treatment with pegylated interferon and ribavirin are:

Genotypes 1 and 4: 48 week course of treatment	40–45% SVR
Genotypes 2 and 3: 24 week course of treatment	80–90% SVR

Long-term follow-up studies (over 7–8 years) of people with a sustained response show that almost all continue to be HCV RNA negative by PCR.

If ribavirin cannot be taken, pegylated interferon can be used as monotherapy and it provides the following outcomes for people with long term infection:

Genotype 1	11–14% SVR
Genotype 2 and 3	36–49% SVR
(No data is available for genotype 4.)	

HOW LONG SHOULD COMBINATION THERAPY CONTINUE?

Combination therapy can be demanding and it is important to monitor the overall health of the person undergoing treatment. Clinically, if a person with genotype 1 or 4 still has detectable levels of virus in their blood after 24 weeks of their 48 weeks of treatment, they only have a 2% chance of achieving a sustained viral response and their treatment should be stopped.

WHAT ARE THE SIDE EFFECTS OF COMBINATION THERAPY?

Combination therapy can cause a range of side effects, which vary in intensity from person to person. Side effects can also be dose-related; higher doses are often accompanied by more severe side effects. During the first few weeks of therapy many people develop a 'flu-like' illness (particularly pronounced after the first injection), together with fatigue, malaise, muscle aches and low-grade fever. This tends to subside as treatment continues.

ADVERSE EFFECTS OF INTERFERON AND RIBAVIRIN

Interferon and ribavirin each have specific side effects.

Interferon

Systemic

- malaise, nausea, fever, weight loss, diarrhoea, temporary hair loss
- exacerbation of diabetes

Neurological

- loss of concentration, sleep disturbance, paraesthesiae (loss of sensation), exacerbation of epilepsy, visual loss (rare), deafness (rare)

Psychological

- depression, irritability, psychosis

Myelosuppression

- low white blood cell count, thrombocytopenia

Induction of autoimmunity

- autoimmune thyroid disease, haemolytic anaemia, thrombocytopenic purpura (bleeding disorder), psoriasis, worsening of psoriasis, worsening of autoimmune hepatitis

Cardiac

- arrhythmia, congestive failure

Ribavirin

Haematological

- haemolytic anaemia

Respiratory tract

- cough, dyspnoea, pharyngitis, sinusitis

Embryonic development

- possible birth defect

NEW THERAPIES FOR HEPATITIS C

The current gold standard for treatment of hepatitis C infection is combination therapy. However, several recent studies show that by more closely monitoring the viral load while on therapy, predictions can be made about the likelihood of a long-term response or SVR. For example, at present a viral load measurement at week 12 of therapy for persons with genotype 1 infection that is at least two \log_{10} lower than the baseline measurement predicts the person is likely to respond. In the future we are likely to see predictions made about long term response based on viral load measurements as early as week 4. The diagnosis of acute hepatitis C infection has also been highlighted because new studies show that using early monotherapy with pegylated interferon for 24 weeks prevents the infection becoming chronic in nearly all cases.

A number of people, particularly those infected with genotype 1, do not respond to combination therapy and others poorly tolerate the treatment because of

adverse side effects. This emphasises the need for other therapies which are better tolerated and give an enhanced response rate. Several pharmaceutical companies have developed so-called first generation small molecule inhibitors directed against some of the virus-specific enzymes involved in virus multiplication, such as the protease and polymerase. Preliminary results show that they can inhibit hepatitis C virus replication but as monotherapy, resistance soon develops. Clinical trials are underway examining these agents in various combinations, including with pegylated interferon and ribavirin, to determine if they can improve response rates.

VACCINATIONS

Note that vaccination against hepatitis A and B is recommended for people with hepatitis C, or with hepatitis C/HIV co-infection, who are not immune to hepatitis A or hepatitis B. See *Chapter 3: Reducing Hepatitis C Transmission in the Community*.

HEPATITIS C TREATMENT FOR PEOPLE WITH HEPATITIS C AND HIV CO-INFECTION

- Co-infection with HIV leads to a more aggressive form of liver disease in hepatitis C infected patients. Response to treatment is also reduced in persons with a HIV co-infection compared to those with hepatitis C infection only.
- People with low CD4 counts are those in greatest need of hepatitis C therapy. The aims of therapy in advanced HIV should be to delay progression of liver disease rather than to achieve eradication of both viruses.
- The potential interaction between the drugs used to treat HIV infection and the drugs used to treat hepatitis C can lead to hepatotoxicity and this should be monitored closely
- The timing and sequence of treatment for hepatitis C and HIV co-infection remains a complex issue and specialist advice from an infectious diseases physician is required.

QUALITY OF LIFE ISSUES DURING TREATMENT

For some people, the physical and psychological side effects of combination therapy can be overwhelming. Given that treatment can last for up to twelve months, some people find it hard to continue to work and many people experience difficulties in their personal and professional lives. Health care workers need to be aware of the social and psychological pressures that can result from a course of combination therapy and, where appropriate and available, refer people to treatment support groups.



In some people, treatment can have a considerable impact on their mental health, causing mood swings, anxiety and depression or exacerbating existing conditions. Mental health status should be closely monitored throughout treatment.

To help people minimise the negative side effects that can be associated with treatment, appropriate support mechanisms should be an essential feature in the clinical setting. Additionally, hepatitis councils offer confidential telephone information lines (national telephone number 1300 437 222) and support groups that people on treatment may find useful. *See Chapter 5: Living with Hepatitis C; and Contacts Section in Resources.*

ACCESS TO TREATMENT FOR ABORIGINAL AND TORRES STRAIT ISLANDER PEOPLE

It appears from the limited data available that Aboriginal and Torres Strait Islander people are accessing and successfully completing treatment at a much lower rate than non-Aboriginal people. This is due to a number of factors:

- a limited number of prescribers in Aboriginal Health Services;
- lack of support;
- lack of knowledge about hepatitis C; and
- remote and rural locations make access to treatment difficult.

ACCESS TO TREATMENT FOR PEOPLE IN RURAL OR REMOTE AREAS

Access to treatment for hepatitis C is currently restricted to specialist services linked to major regional hospitals. Many people live too far away from a regional-based treatment centre to have easy access to treatments under Section 100 of the Pharmaceutical Benefits Scheme (a government subsidised treatment schedule). Shared Care and Enhanced Primary Care (EPC) initiatives are gradually expanding through rural Australia, allowing more people with hepatitis C to access treatment and have their care managed in a partnership arrangement between specialists, GPs and other health care services. The expansion of these programs nationwide will ensure greater access to specialised care and treatment services. However, under current regulations, initial prescriptions for treatment can only be issued by a specialist centre.



ACCESS TO TREATMENT FOR PEOPLE WHO INJECT DRUGS

People who inject drugs, including those who are using drug substitution therapy, have been able to access hepatitis C treatment under Section 100 of the Pharmaceutical Benefits Scheme since 1999. All people seeking treatment should be assessed using the Section 100 PBS criteria.

Many health care workers have not been trained or supported to work with people who inject drugs. As a result, prejudices and past experience may lead health care workers to treat people who inject drugs less favourably. The ability to comply with treatment, the cost of treatment, support while on treatment, and access to treatment are issues identified by all people with hepatitis C. Drug and alcohol services are increasingly addressing hepatitis C-related issues with their clients by offering education, testing, counselling and referral to hepatitis C treatment services. *See Chapter 7: Preventing Discrimination and Reducing Stigma and Isolation.*

S100 – PHARMACEUTICAL BENEFITS SCHEME

(Section 100 items: Schedule of Pharmaceutical Benefits available online: www.pbs.gov.au)

Combination therapies Pegasys RBV[®] and Pegatron[®] and monotherapies PEG-Intron Redipen[®] and Pegasys[®] are listed as highly specialised drugs under Section 100 of the National Health Act. These drugs can only be prescribed by specialist hospital units and dispensed through pharmacies within hospitals that participate in the Highly Specialised Drug Program. Medical practitioners must be formally associated with specialist hospitals to prescribe these drugs as pharmaceutical benefit items. Generally, prescriptions for highly specialised drugs are not covered by the Pharmaceutical Benefits Scheme when dispensed by community pharmacies. See *Chapter 4: Hepatitis C Testing for information about PCR and other tests associated with treatment.*

S100 CRITERIA FOR TREATMENTS FOR HEPATITIS C – AUGUST 2007

Ribavirin and peginterferon alfa-2a (Pegasys RBV[®]) and Ribavirin and peginterferon alfa-2b (Pegatron[®])

CAUTION: Treatment with peg interferon alfa has been associated with depression and suicide in some patients. Patients with a history of suicidal ideation or depressive illness should be warned of the risks. Psychiatric status during therapy should be monitored.

CAUTION: Ribavirin is a category X drug and must not be given to pregnant women. Pregnancy in female patients or in the partners of male patients must be avoided during treatment and during the 6-month period after cessation of treatment.

Authority Required (Refer to section on S100 Pharmaceutical Benefits Scheme above).

Treatment, managed by an accredited treatment centre, of chronic hepatitis C in patients 18 years or older who have compensated liver disease and who have received no prior interferon alfa or peg interferon alfa treatment for hepatitis C and who satisfy all of the following criteria:

1. Documented chronic hepatitis C infection (repeatedly anti-HCV positive and HCV RNA positive).
2. Contraception:
 - Female patients of child-bearing age are not pregnant, not breast-feeding, and both patient and their partner are using effective forms of contraception (one for each partner).
 - Male patients and their partners are using effective forms of contraception (one for each partner). Female partners of male patients are not pregnant.

For patients with genotype 2 or 3 hepatitis C without hepatic cirrhosis or bridging fibrosis, the treatment course is limited to 24 weeks. For hepatitis C patients with genotype 1, 4, 5 or 6 and those genotype 2 or 3 patients with hepatic cirrhosis or bridging fibrosis, the treatment course is limited to 48 weeks.

Patients with genotype 1, 4, 5 or 6 who are eligible for 48 weeks of treatment may only continue treatment after the first 12 weeks if the result of an HCV RNA quantitative assay (performed at the same laboratory using the same test) shows that the plasma HCV RNA has become undetectable or the viral load has decreased by at least a 2 log drop. (An HCV RNA assay at week 12 is unnecessary for genotype 2 and 3 patients because of the high likelihood of early viral response by week 12).

Patients with genotype 1, 4, 5 or 6 who are viral positive at week 12 but have attained at least a 2 log drop in viral load may only continue treatment after the first 24 weeks of treatment if plasma HCV RNA is not detectable by an HCV RNA qualitative assay at week 24. Similarly, genotype 2 or 3 patients with hepatic cirrhosis or bridging fibrosis may only continue treatment after the first 24 weeks if plasma HCV RNA is not detectable by an HCV RNA qualitative assay at week 24. An HCV RNA qualitative assay at week 24 is unnecessary for those patients with genotype 1, 4, 5 or 6 who became viral negative at week 12.

NOTE: Treatment centres are required to have access to the following appropriate specialist facilities for the provision of clinical support services for hepatitis C:

- a nurse educator/counsellor for patients; and
- 24 hour access by patients to medical advice; and
- an established liver clinic; and
- facilities for safe liver biopsy.

NOTE: A liver biopsy is no longer a specific requirement to access treatment.

MONOTHERAPY OPTIONS

Further information on the S100 criteria for pegylated interferon for patients who have chronic hepatitis C and have a contraindication to ribavirin can be found at *Section 100 items: Schedule of Pharmaceutical Benefits* available online: www.pbs.gov.au

COMMONLY ASKED QUESTIONS

ANTIVIRAL THERAPY SOUNDS LIKE IT IS A VERY DIFFICULT EXPERIENCE. WHY WOULD I CONSIDER IT?

You may choose to consider treatment to improve your health and sense of well-being. The aim of antiviral therapy is to stop viral multiplication in the short term, achieve viral clearance and thus limit damage to the liver in the long term. Both conventional and complementary therapies also aim to reduce other consequences of chronic hepatitis C that can reduce quality of life, such as fatigue and nausea.

IF I EXPERIENCE SIDE EFFECTS WHILE UNDERGOING COMBINATION THERAPY, WILL MY TREATMENT BE STOPPED?

Some people experience severe side effects while on treatment. It is a personal decision whether to continue with therapy. Certainly, some people decide that the side effects are too difficult to manage and they discontinue therapy. If treatment is stopped for any length of time, you may be ineligible to resume treatment under the s100 guidelines. It is important that you discuss these and all other treatment-related decisions with your liver specialist and if you wish to, with a counsellor. Most specialists will try and arrange for a temporary dose reduction to alleviate side effects rather than a complete discontinuation of therapy. Recent reports indicate that a dose reduction has little impact on the chances of a long term response.

AM I ELIGIBLE FOR SUBSIDISED TREATMENT IF I AM A CURRENT INJECTING DRUG USER OR ON A PHARMACOTHERAPY PROGRAM (EG METHADONE MAINTENANCE)?

The current s100 criteria for treatment for hepatitis C do not exclude treatment of current injecting drug users or people on a pharmacotherapy program. Your liver specialist will discuss whether current drug use is likely to have a negative impact on the efficacy of treatment, the risk of reinfection, side effects and contraception requirements. Note: that only one course of treatment is available under the PBS.

HOW IS THE TOTAL TIME OF THERAPY DETERMINED?

Therapy involves either a 24 or 48-week course of peginterferon and ribavirin, and the length of treatment is determined by genotype. Each person should discuss all treatment options with their liver specialist.

HOW DO I LEARN TO GIVE MYSELF THE PEGINTERFERON INJECTION?

Pre-filled, dose-measured, easy-to-use syringes are available from the pharmaceutical companies who supply peginterferon. Experienced service providers at your treatment centre will help you to develop confidence in your ability to self-inject.

WHAT IS THE MOST UP-TO-DATE TREATMENT AVAILABLE FOR HEPATITIS C, FOR PEOPLE WHO ARE CO-INFECTED WITH HIV?

Having HIV does not exclude you from treatment for hepatitis C. Consult with an infectious diseases specialist and a liver specialist, and refer to the protocol for combination therapy.

I LIVE IN THE COUNTRY. MY NEAREST LIVER CLINIC IS IN THE CITY. IF I START TREATMENT, HOW OFTEN WOULD I NEED TO VISIT THE LIVER CLINIC?

The need to travel to specialist clinics will vary and depends on the relationship your GP has with the specialist. It is important to find a GP who will develop a shared care arrangement with the specialist clinic. Shared care is a system that operates between GPs/physicians in rural or remote areas and liver specialists in major regional centres. In some states and territories, shared care is also practised in metropolitan and outer suburban areas. The aim of shared care is to provide optimum input for people who live in rural or remote areas by reducing their travel time and expenses, whilst still having access to medical interventions. Visits to the major centre may be needed as infrequently as 3 monthly after the first month.

WHAT HAPPENS IF I CHOOSE NOT TO HAVE TREATMENT?

You can still be treated later if your decision or circumstances change. The effects of the virus on the liver may advance without treatment, but these changes occur very slowly over several years. Some people will never require treatment. Your specialist will advise if there are immediate risks from deferring treatment. This will usually occur if your disease has been active and there is evidence of liver scarring.

CAN IT EVER BE TOO LATE FOR TREATMENT?

No, it is never too late to seek treatment. However, older patients generally experience more adverse side effects from treatment and have a tendency to a lower success rate. Nevertheless, in Australia, people 65 years and older have been successfully treated. People with more advanced liver disease can also have a lower success rate from treatment and need to consult with their liver specialist.