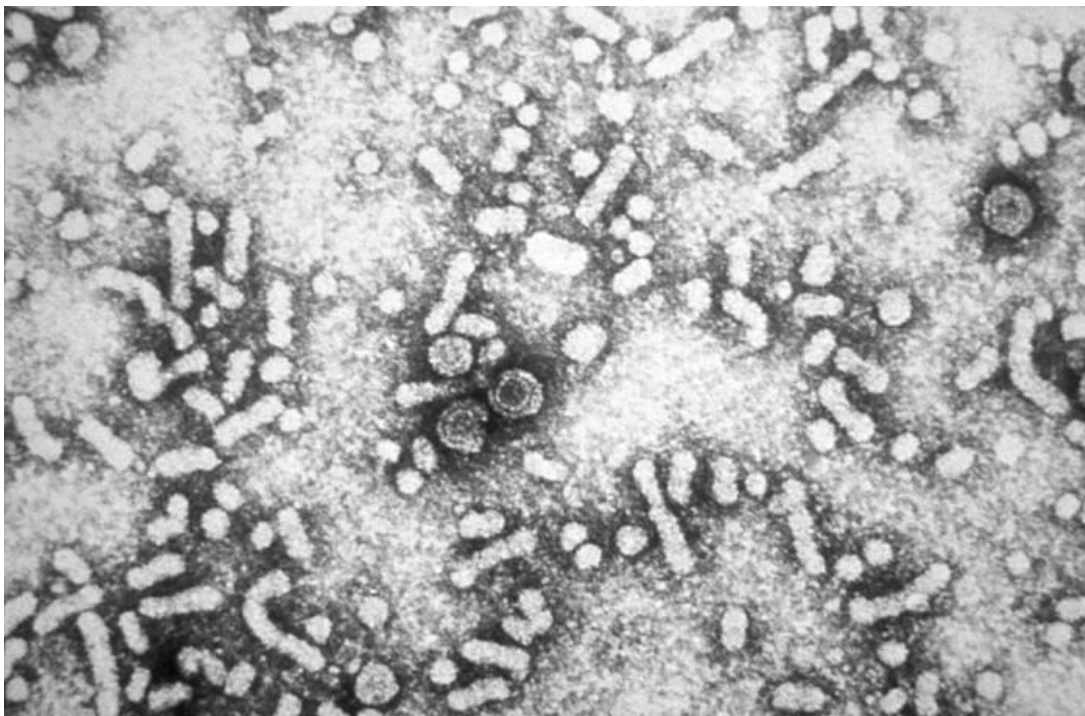


Anti-Hepatitis Agents: Pharmacologic Treatment of Hepatitis B and C

[See online here](#)

In this article, we will study the details about the various antiviral agents used to treat hepatitis, their mechanism of action, adverse effects/toxicity, contraindications, drug interactions and drugs of choice. Other important pharmacological and therapeutic aspects of individual drugs will also be studied.



Introduction

Antiviral agents are chemotherapeutic drugs that are effective against viruses. Antivirals active against **hepatitis B** are mainly used to suppress HBV DNA in cases of chronic hepatitis B, while those active against **hepatitis C** are used to eradicate the virus entirely.

Tests are performed when clinical symptoms and signs of hepatitis are present and can achieve the following:

1. Detect **current** or **previous** hepatitis infection
2. Determine **how contagious** a person with hepatitis is
3. **Monitor** a person who is being treated for hepatitis
4. Test for other conditions, such as **chronic persistent hepatitis, delta agent (hepatitis D), and nephrotic syndrome**

A **positive test result** may indicate:

1. A current hepatitis infection; may also be a new infection (**acute hepatitis**)
2. An infection that has been present for a long time (**chronic hepatitis**)
3. A hepatitis infection that is **no longer present and cannot be spread to others**

Hepatitis A test results show the following:

1. Anti-hepatitis A virus IgM (**HAV IgM**) antibodies: Recent infection with hepatitis A
2. **Total** (IgM and IgG) antibodies to hepatitis A: Previous or past infection
3. **Immunity** to hepatitis A

Hepatitis B test results show the following:

1. Hepatitis B surface antigen (**HBsAg**) positivity: Active hepatitis B infection, either recent or chronic; there is an increased likelihood of spreading the infection to others
2. Anti-hepatitis B core IgM antibodies (**HBcIgM**): Recent or past hepatitis B infection; no commercial test is available as it is not freely found in serum. Instead, **HBeAg** (hepatitis B virus excretory antigen) is used, as it is a marker of the core of the virus. This correlates with HBV replication and implies high-titer hepatitis B in serum and infectivity of serum
3. Presence of antibody to HBsAg (**HBsAb**): Resolved hepatitis B infection or means the patient has received a hepatitis B vaccine and is unlikely to become infected

Antibodies to hepatitis C can most often be detected 4–10 weeks after a patient contracts the infection. Other types of tests may be done to decide on treatment and monitor the infection.

Anti-Hepatitis Agents

Interferon α

Interferon α is a cytokine that acts through the host cell (**Janus kinases; Jaks**) that phosphorylates **STAT (signal transducers and activators of transcription)** to increase the production of antiviral proteins, resulting in the inhibition of viral translation, transcription, protein processing, maturation, and release.

Janus was the 2-faced Roman god of beginnings and endings; Jaks possess two near-identical phosphate-transferring domains. One domain exhibits the kinase activity, while the other negatively regulates the kinase activity of the first.

Interferon α increases the specific activation of a ribonuclease that degrades viral mRNA. It also increases host expression of **MHC (major histocompatibility complex) antigens**, augments the phagocytic activity of **macrophages**, promotes the formation of **natural killer cells**, and enhances proliferation and survival of **cytotoxic T cells**.

Interferon α -2a and α -2b are available for subcutaneous or intramuscular use, while interferon alfacon-1, used to combat hairy cell leukemia, malignant melanoma, and **AIDS**-related Kaposi's sarcoma, is available for subcutaneous use only. Their absorption is slow, at 2–3 administrations per week; elimination is mainly renal via **proteolytic hydrolysis**.

Pegylated (polyethylene glycol-complexed) forms can be administered once per week. **Polyethylene glycol** is readily excreted in urine; renal elimination of pegylated interferons accounts for approximately 30% of clearance; hence, a dose reduction is

required in renal insufficiency.

In **chronic hepatitis B**, interferon α therapy increases **HBeAg seroconversion** and decreases **HBV DNA load** (see image). Interferon α -2b and pegylated interferon α -2a are used in the treatment of chronic hepatitis B, while pegylated interferon α -2a and pegylated interferon α -2b are used in the treatment of chronic hepatitis C. Interferon α -2b is used in the treatment of acute hepatitis C, especially with ribavirin.

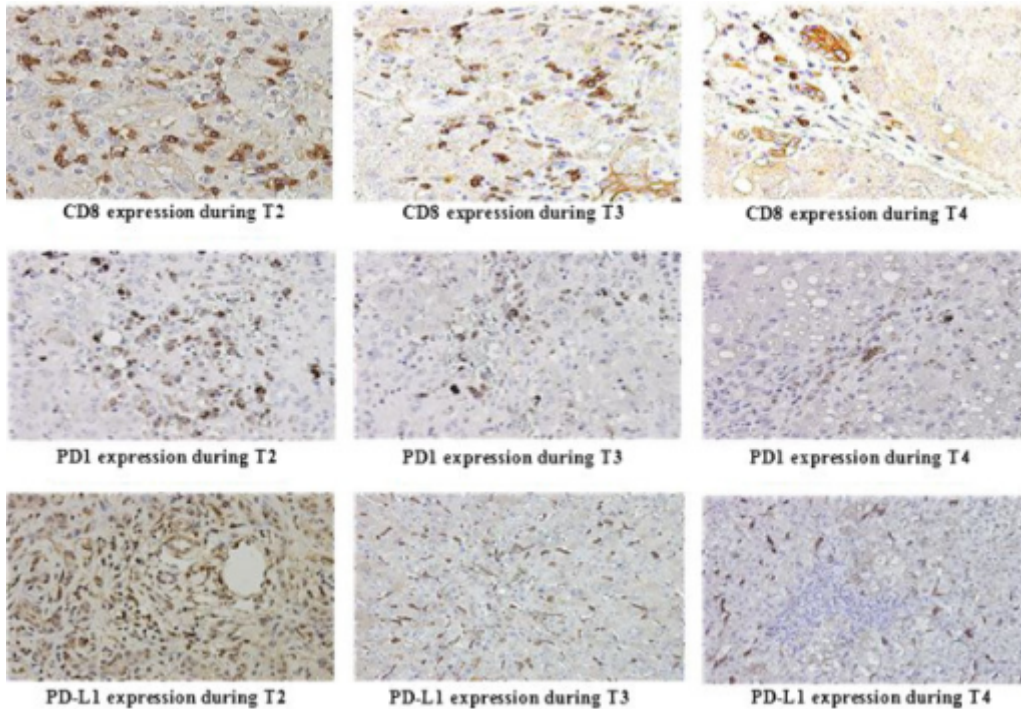


Image: Immunohistochemical staining for intrahepatic CD8-positive, PD-1-positive, and PD-L1-positive cells in patients with chronic hepatitis B. Representative figures for patients in T2, T3, and T4 sequence. N = 5, high-power field, original magnification 400 \times . During the T2 period, CD8-positive, PD-1-positive, or PD-L1-positive cells infiltrated extensively in liver tissue and they were decreased significantly in T3. In T4, the CD8-positive and PD-1-positive cells were less observed in lobular areas, while PD-L1-positive cells were also frequently observed in the liver lobular region. By: Wenjin Z, et al., *BMC Gastroenterol* (2012). License: [CC BY 2.0](https://creativecommons.org/licenses/by/2.0/)

Flu-like syndrome (fever, chills, malaise, headache, and myalgia) is the most common adverse effect (30% of patients experience this during the first week of therapy); it occurs within six hours of dosing and resolves upon continued administration. Other important adverse effects include the following:

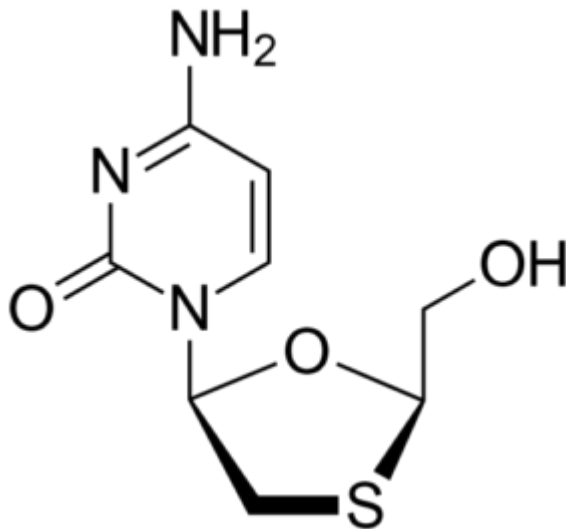
- Transient elevation of liver enzymes (during first 8–12 weeks of therapy; more common on responders)
- Neurotoxicity (confusion, somnolence, depression, mood disorders, **seizures**)
- Severe fatigue
- **Myalgia**
- Skin rash
- Hair loss
- Weight loss
- Cough
- Tinnitus
- Reversible hearing loss
- **Retinopathy**
- **Pneumonitis**
- **Myelosuppression**
- Unmasking of autoimmunity (especially **thyroiditis**)

▪ Cardiotoxicity

Autoimmune disorders, hepatic decompensation, history of **cardiac arrhythmia**, and **pregnancy** are contraindications to interferon α -therapy. Caution is required in patients with **psychiatric disease, epilepsy, cytopenias, thyroid disease, ischemic cardiac disease**, and severe **renal insufficiency**.

Important drug interactions include increased levels of theophylline and methadone, a risk of **hepatic failure** with didanosine, and a risk of cytopenias with zidovudine. Other uses of interferon alfa are in the treatment of **Kaposi's sarcoma, papillomatosis**, and **genital warts** (topical); the prevention of dissemination of **herpes zoster** in **cancer** patients; and the reduction of shedding of **cytomegalovirus** after renal transplantation.

Lamivudine



[Image](#): Lamivudine structure. By: Vaccinationist. License: [Public domain](#)

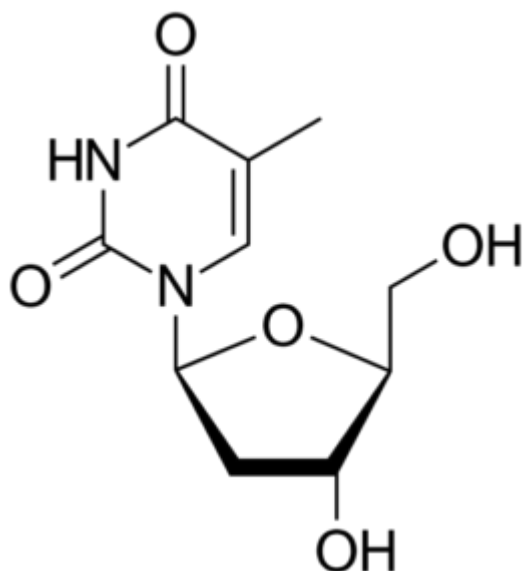
Lamivudine is a **cytosine nucleoside analog** that inhibits **hepatitis B DNA polymerase** (and HIV reverse transcriptase) by competing with **deoxycytidine triphosphate** for incorporation into viral DNA and causing **chain termination** (see image).

Its intracellular half-life is more prolonged in hepatitis B cell lines (17–19 hours) than in HIV cell lines; hence, lower doses and less frequent administration are required in chronic **hepatitis B** than in HIV infection. Its oral bioavailability is excellent (> 80%), unaffected by food, and increased by trimethoprim-sulfamethoxazole; it is eliminated almost exclusively by the kidneys.

In chronic hepatitis B, lamivudine can be used as **monotherapy** and achieves undetectable levels of **HBV DNA** in ~ 44% of patients. It produces seroconversion of HBeAg in HBeAg-positive patients; the durability of HBeAg negative status increases if the drug is continued for 4–8 months after seroconversion. HBeAg is a hepatitis B viral protein. It is an indicator of active viral replication; this means that the patient infected with hepatitis B can transmit the virus to another person. HBeAg is considered “nonparticulate” or “secretory.”

In HBeAg-negative patients, the response is initially high, but durability is low. Adverse effects are rare at doses used to treat **hepatitis B**; they include headaches, insomnia, dizziness, and nausea. Increased risk of **pancreatitis** is seen in HBV and HIV co-infection. The emergence of resistance is seen in 15%–30% of patients at one year and in 70% of patients at five years of therapy. **Cross-resistance** is seen between lamivudine and emtricitabine or entecavir, but not with adefovir.

Telbivudine



[Image](#): Telbivudine structure. By: Vaccinationist. License: [Public domain](#)

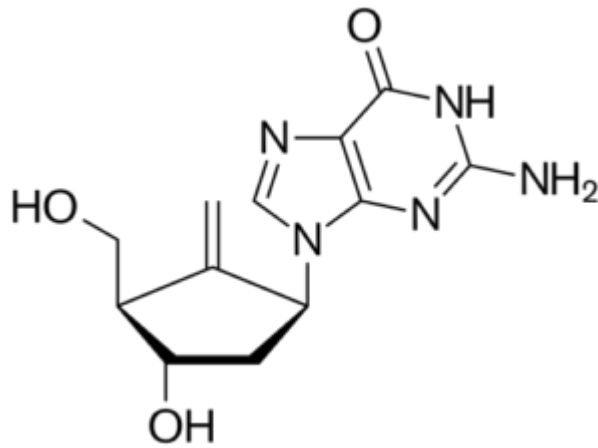
Telbivudine is a **thymidine nucleoside analog** that, after conversion into an active triphosphate form by cellular kinases, competitively inhibits **HBV DNA polymerase**, becomes incorporated into viral DNA, and **causes chain termination** (see image).

Its oral bioavailability is not affected by food, and its elimination is mainly renal. In the treatment of chronic hepatitis B, telbivudine has been shown to produce a greater reduction in HBV DNA and greater **HBeAg seroconversion**, with less scarring in the liver compared with lamivudine.

Important adverse effects include nausea, vomiting, abdominal pain, headache, fatigue, upper respiratory infection, increased creatine kinase, myalgia, myopathy, peripheral neuropathy, **lactic acidosis**, and **hepatomegaly with steatosis**. Flares of **hepatitis** may occur after discontinuation of the drug.

The emergence of resistant isolates (due to polymerase gene M204I mutation) is seen in up to 22% of patients with > one year of therapy, resulting in viral rebound.

Entecavir



[Image](#): Entecavir structure. By: Vaccinationist. License: [Public domain](#)

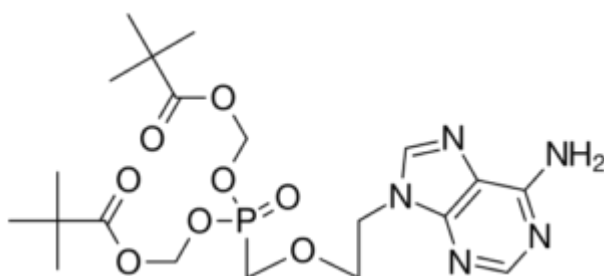
Entecavir is a guanosine nucleoside analog that competitively **inhibits HBV DNA polymerase** by inhibiting **base priming, reverse transcription** of a negative strand, and synthesis of a positive strand (see image). Its oral bioavailability is nearly 100%, which is decreased by food (should be taken on an empty stomach); it is excreted by the kidneys via **glomerular filtration** and **tubular secretion**.

In the treatment of chronic hepatitis B, compared with lamivudine, entecavir produces higher rates of **HBV DNA viral suppression**, normalization of serum ALT levels, and histologic improvement in the liver; similar rates of **HBeAg seroconversion**; and lower rates of emergence of resistance.

Important adverse effects include nausea, headache, dizziness, and fatigue. Various benign and malignant tumors in the lungs, liver, and brain, as well as vascular tumors, have been seen in animals but not in humans. HBV isolates with the S202G mutation are resistant to entecavir, but the emergence of clinical resistance is < 1% at four years.

There is cross-resistance between entecavir and lamivudine.

Adefovir Dipivoxil



[Image](#): Adefovir dipivoxil structure. By: Vaccinationist. License: [Public domain](#)

After phosphorylation by cellular kinases into active diphosphate metabolite, adefovir dipivoxil competitively inhibits **HBV DNA polymerase**, becomes incorporated into viral DNA, and causes chain termination (see image).

In addition to HBV, adefovir dipivoxil shows in vitro activity against HIV and herpes viruses.

Its oral bioavailability is ~ 60%, and is unaffected by food; it is hydrolyzed to its parent

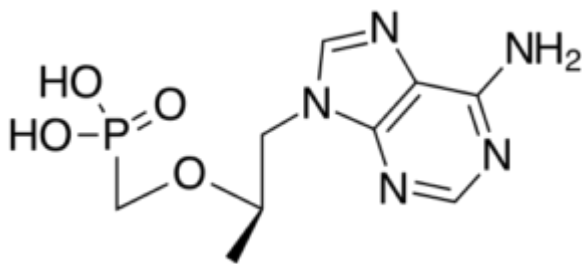
compound by blood and intestinal esterases and is excreted by glomerular filtration and active tubular secretion in urine.

Dose adjustment is required in **renal dysfunction**, but not in hepatic impairment. Among oral anti-HBV agents, it is slower to cause suppression of HBV DNA levels and is least likely to induce **HBeAg seroconversion**.

The most important adverse effect is dose-dependent **nephrotoxicity**; other possible effects include headaches, fatigue, diarrhea, abdominal pain, lactic acidosis, and **hepatic steatosis**.

Pivalic acid, a metabolic by-product of the drug, may decrease carnitine levels, although carnitine supplementation is not necessary at low doses. There is no cross-resistance between adefovir and lamivudine.

Tenofovir



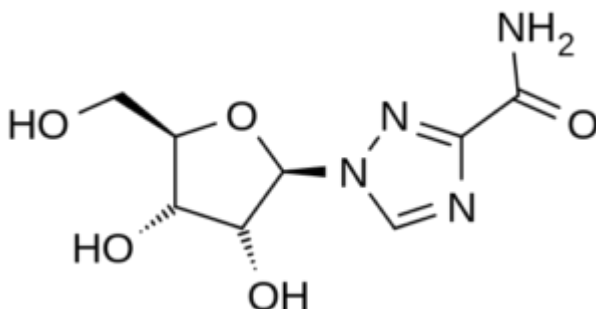
[Image](#): Tenofovir structure. By: Ed (Edgar181). License: [Public domain](#)

Tenofovir is an adenosine nucleotide analog with structural similarity to adefovir dipivoxil; it is also effective against **HIV** (see image).

Oral bioavailability is 25–40 %, intracellular half-life is > 60 hours, and elimination is mainly by the kidneys. Compared with adefovir, tenofovir has been shown to produce a higher rate of complete response, a higher rate of histologic improvement, and less frequent emergence of resistance in **chronic hepatitis B**.

Tenofovir is active against lamivudine- and entecavir-resistant hepatitis B isolates but shows reduced activity against adefovir-resistant strains. Important adverse effects include gastrointestinal upset, headache, and fatigue; **acute renal failure** and Fanconi's syndrome are rare adverse effects.

Ribavirin



[Image](#): Ribavirin skeletal. By: catclock. License: [Public domain](#)

Ribavirin is a guanosine analog that inhibits the replication of a wide range of DNA and RNA viruses such as hepatitis C, HIV, influenza A and B, parainfluenza, and **respiratory syncytial virus** (see image).

Ribavirin's chief mechanism of action is unknown, but it is known to inhibit **guanine triphosphate**, prevent capping of viral mRNA, and block RNA-dependent polymerases. Its bioavailability is increased by high-fat meals and decreased by antacids; it is mainly eliminated by the kidneys. It is used with interferon alfa in the treatment of chronic hepatitis C; monotherapy is not effective.

An important adverse effect is dose-dependent **hemolytic anemia**; others include nausea, insomnia, irritability, depression, fatigue, cough, rash, and itching. Contraindications are **anemia, ischemic vascular disease, end-stage renal disease,** and **pregnancy**.

Boceprevir and Telaprevir

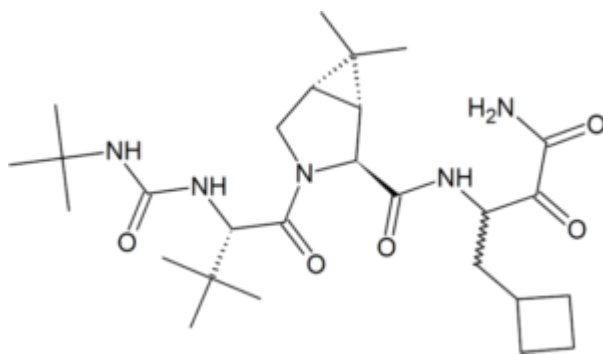


Image: Structure of boceprevir. By: LHcheM. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Boceprevir and telaprevir are HCV NS3/4A serine protease inhibitors that inhibit viral replication.

They are used in patients infected with HCV genotype 1, along with pegylated interferon alfa and ribavirin, as resistance develops quickly when used as monotherapy. Oral bioavailability is increased by food (boceprevir) and non-low-fat food (telaprevir); both undergo significant **hepatic metabolism**. Important adverse effects of boceprevir are **anemia** and **dysgeusia (distortion of the sense of taste)**, while those of telaprevir are anemia, rash, and **anorectal discomfort**.

Newer Agents

- Nucleoside analogs **emtricitabine** and **clevidine** are under clinical development for hepatitis B
- **Emtricitabine** with **tenofovir** may be especially suitable for patients co-infected with HIV and hepatitis B
- **Thymosin alpha-1** is an immunomodulator that enhances T cell response and promotes reconstitution of immune defects; used in chronic hepatitis B
- **Sofosbuvir** inhibits RNA polymerase in HCV and has been shown to achieve 95% cure rates, along with ribavirin
- HCV NS5B polymerase inhibitors are a new class of anti-HCV agents under investigation

Pharmacologic Treatment of Hepatitis B

Treatment of chronic hepatitis B is not curative, as **covalently closed circular viral DNA** persists within the cell indefinitely; hence, suppression of HBV replication is aimed at the suppression of HBV DNA to undetectable levels, **seroconversion of HBeAg** from positive to negative, and normalization of **hepatic transaminase levels**; these are considered to be adequate suppression of HBV replication.

Compared with interferon therapy, oral nucleoside/nucleotide analogs are better tolerated and produce a higher response rate, but the response is less rapid and less sustained after discontinuation; **the emergence of resistance** is also a concern.

Nucleotide analogs are effective in resistance to nucleoside analogs, and vice versa.

Pharmacologic Treatment of Hepatitis C

Unlike chronic hepatitis B, anti-hepatitis C drugs are mainly aimed at **viral eradication** rather than suppression.

In acute hepatitis C, antiviral therapy is indicated if there is persistent viremia after 12 weeks of initial seroconversion; interferon α -2b produces ~ 95% rate of clearance of HCV, compared with spontaneous clearance (15%–30%).

In chronic hepatitis C, combination therapy of **once-weekly pegylated interferon and daily oral ribavirin is the standard treatment**; monotherapy with either is less effective. In chronic hepatitis C, HCV genotypes 2 or 3, the absence of **cirrhosis of the liver**, and low pretreatment HCV RNA levels are associated with a favorable response.

Patients infected with **hepatitis C genotype 1** are treated with a protease inhibitor (telaprevir or boceprevir) in addition to interferon alfa and ribavirin.

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