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 to Anti-Hepatitis Agents

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

Important Reminder

Tests performed with clinical symptoms and signs of hepatitis are used to:

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. The test may be performed for other conditions, such as:
• Chronic persistent hepatitis
• Delta agent (hepatitis D)
• Nephrotic syndrome

A **POSITIVE test** may mean:

1. A current hepatitis infection. This may be a new infection (**acute hepatitis**).
2. It may be an infection that has been present for a long time (**chronic hepatitis**).
3. A hepatitis infection in the past, but **no longer present and cannot be spread to others**.

**Hepatitis A** test results:

1. IgM anti-hepatitis A virus (**HAVIgM**) antibodies signify a recent infection with hepatitis A.
2. **Total** (IgM and IgG) antibodies to hepatitis A, signifies a previous or past infection, or
3. **Immunity** to hepatitis A.

**Hepatitis B** tests results:

1. Hepatitis B surface antigen (**HBsAg**), positivity signifies active hepatitis B infection, either recent or chronic
2. Antibody to hepatitis B core antigen (**HBcIgM**), signifies a recent or past hepatitis B infection, but no commercial test available because it is not freely found in serum. Instead, **HbeAg** (Hepatitis B e antigen) is used, a marker of the core of the virus. Correlates with HBV replication and implies high titer HBV in serum and infectivity of serum.
3. A positive **Antibody to HBsAg (**HBsAb**) means a past hepatitis B infection or
4. Having received the hepatitis B vaccine and unlikely to become infected
5. As mentioned above, the Hepatitis B type e antigen (**HBeAg**), means having a chronic hepatitis B infection and the increased likeliness to spread the infection to others through sexual contact or by sharing needles

Antibodies to hepatitis C can most often be detected 4—10 weeks after you get the infection. Other types of tests may be done to decide on treatment and monitor the hepatitis C infection.

**Anti-Hepatitis Agents**

**Interferon α**

Interferon α is a cytokine acting through host cell **Janus kinases (Jaks)** that phosphorylate **STAT (Signal Transducers and Activators of Transcription)** to increase production of antiviral proteins, resulting in the inhibition of viral translation, transcription, protein processing, maturation, and release.

The name of the Janus is taken from the two-faced Roman god of beginnings and endings, Janus because the 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 also increases 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 interferon 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; allowing for 2 or 3 administrations per week; elimination is mainly renal via proteolytic hydrolysis.

Pegylated (polyethylene glycol-complexed) forms can be administered once a week. Polyethylene glycol is readily excreted in urine; renal elimination of pegylated interferons accounts for ~ 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. 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 are used in the treatment of acute hepatitis C, especially with ribavirin.

Flu-like syndrome (fever, chills, malaise, headache, and myalgia) is the most common side effect (30% during the 1st week of therapy) that occurs within 6 hours of dosing and resolves upon continued administration. Other important adverse effects are 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 are 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 sarcoma, papillomatis, genital warts (topical), prevention of dissemination of herpes zoster in cancer patients, and the reduction of shedding of CMV after renal transplantation.

Lamivudine

A cytosine nucleoside analog that inhibits HBV DNA polymerase (and HIV reverse transcriptase) by competing with deoxycytidine triphosphate for incorporation into viral DNA and causes chain termination.

Its intracellular half-life is more prolonged in HBV 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%), is unaffected by food and increased by trimethoprim-sulfamethoxazole; it is eliminated almost exclusively by the kidneys.
In chronic hepatitis B, it 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 still increases if the drug is continued for 4-8 months after seroconversion. As a reminder, HBeAg is a hepatitis B viral protein. It is an indicator of active viral replication; this means the person infected with Hepatitis B can likely transmit the virus on 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 in **hepatitis B**; these 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 1 year and in 70 % of patients at 5 years of therapy. **Cross-resistance** is seen between lamivudine and entecitabine or entecavir, but not with adefovir.

**Telbivudine**

![Telbivudine structure](image-url)

A **thymidine nucleoside analog** that, after conversion into active triphosphate form by cellular kinases, competitively inhibits **HBV DNA polymerase**, gets incorporated into viral DNA and **causes chain termination**.

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

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

The emergence of resistant isolates (due to polymerase gene M204I mutation) is seen in up to 22 % of patients with > 1 year of therapy resulting in viral rebound.
Entecavir

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. Its oral bioavailability is nearly 100 %, decreased by food (taken on an empty stomach); it is excreted by the kidneys by glomerular filtration and tubular secretion.

In the treatment of chronic hepatitis B, as compared to lamivudine, it 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 are 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 4 years.

There is cross-resistance between entecavir and lamivudine.

Adefovir Dipivoxil

Diester prodrug of adefovir, that after phosphorylation by cellular kinases into active diphosphate metabolite competitively inhibits HBV DNA polymerase, gets incorporated into viral DNA and causes chain termination.

In addition to HBV, it shows in vitro activity against HIV and herpes viruses.
Its oral bioavailability is ~ 60 %, unaffected by food; 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 side effects are headaches, fatigue, diarrhea, abdominal pain, lactic acidosis, hepatic steatosis, etc.

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**

![Tenofovir structure](https://example.com/tenofovir_structure.png)

An adenosine nucleotide analog with structural similarity to adefovir dipivoxil; also effective against HIV.

Oral bioavailability is 25—40 %, the intracellular half-life is > 60 h, and elimination is mainly by the kidneys. As compared to adefovir, it has shown to produce a higher rate of complete response, a higher rate of histologic improvement, and the less frequent emergence of resistance in chronic hepatitis B.

Active against lamivudine- and entecavir-resistant HBV isolates but shows reduced activity against adefovir-resistant strains. Important adverse effects are gastrointestinal upset, headache, fatigue; rarely acute renal failure and Fanconi's syndrome.

**Ribavirin**

![Ribavirin-skeletal](https://example.com/ribavirin_skeletal.png)

A guanosine analog that inhibits the replication of a wide range of DNA and RNA viruses like hepatitis C, HIF, influenza A and B, parainfluenza and respiratory syncytial virus. Its chief mechanism of action is unknown, but it is known to inhibit guanine triphosphate, to prevent capping of viral mRNA, and to block RNA-dependent polymerases. Its bioavailability is increased by high-fat meals and is 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

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 clevudine are under clinical development for hepatitis B.
- Emtricitabine with tenofovir may be especially suitable for patients co-infected with HIV and HBV.
- 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 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 because covalently closed circular (ccc) viral DNA persists within the cell indefinitely; hence, suppression of HBV replication is aimed at suppression of HBV DNA to undetectable levels, seroconversion of HBeAg from positive to negative, and normalization of hepatic transaminase levels are considered as adequate suppression of HBV replication.

As compared to 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, as compared to spontaneous clearance (15—30 %).

In chronic hepatitis C, a combination therapy of once weekly pegylated interferon and daily oral ribavirin is the standard treatment; monotherapy with either of the two is less effective. In chronic hepatitis C, HCV genotypes 2 or 3, the absence of cirrhosis of the liver and low pre-treatment 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.

Review Questions

The right answers can be found below the references.

1. Which of the following anti-hepatitis B drug has been associated with Fanconi’s syndrome as an adverse effect?
   A. Interferon α
   B. Lamivudine
   C. Telbivudine
   D. Entecavir
   E. Tenofovir

2. Which of the following drug is not used in the treatment of hepatitis?
   A. Lamivudine
   B. Ribavirin
   C. Tenofovir
   D. Boceprevir
   E. Zanamivir

3. Which of the following statements are true?
A. Lamivudine has poor bioavailability (less than 10 %) on oral therapy
B. Adefovir dipivoxil act by inhibiting the binding of aminoacyl-t RNA with ribosome
C. Anti-hepatitis C drugs are aimed at viral suppression
D. Anti-hepatitis C drugs are aimed at viral eradication

References


Correct answers: 1E; 2E; 3D

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