

# **University of Karbala**

## **College of veterinary medicine**

### **Pharmacology lect # 3**

#### **Antiviral Drugs**

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Most antiviral agents currently available in the market have been developed in the last two decades. This burst of activity was a result of the successes in development of the anti-herpes virus nucleoside analog acyclovir, whose discovery and development resulted in the awarding of a Nobel Prize to Gertrude Elion and George Hitchings in 1988. Since viruses depend on the host cells for biosynthetic machinery to reproduce, there were doubts the possibility of developing antiviral drugs with selective toxicity. However, these doubts were erased with development of antiviral drugs that have selective toxicity oriented toward the virus itself.

Viruses are small microorganisms that consist of either double- or single-stranded DNA or RNA located inside a protein coat. There several stages involved in the replication of this virus thus there are classes of antiviral agents that able to attack the virus at each stage (Table 1). Additionally, host cell molecules that are essential to viral replication also offer targets for involvement. Figure 1 provides information on the replicative cycle of typical DNA and RNA viruses. **Smallpox, chickenpox, Shingles, oral and genital herpes, conjunctivitis, hepatitis B, and papilloma (warts)** are examples for DNA viruses. Most DNA viruses enter the host cell nucleus, where the viral DNA is transcribed into mRNA by host cell polymerase; mRNA is translated in the usual host cell fashion into virus-specific proteins (Figure 1A).

For RNA viruses, the replication relies either on enzymes in the virion to synthesize mRNA or had the viral RNA serving as its own mRNA. The mRNA is translated into various viral proteins, including RNA polymerase, which directs the synthesis of more viral mRNA and genomic RNA (Figure 1B). Examples of RNA viruses include:

**German measles, rabies, meningitis, colds, hepatitis A, west Nile meningeoncephalitis, yellow fever, hepatitis C, influenza, measles, mumps, and sever acute respiratory syndrome (SARS).** *Retroviruses are a special group of RNA viruses that include human immunodeficiency virus (HIV).*

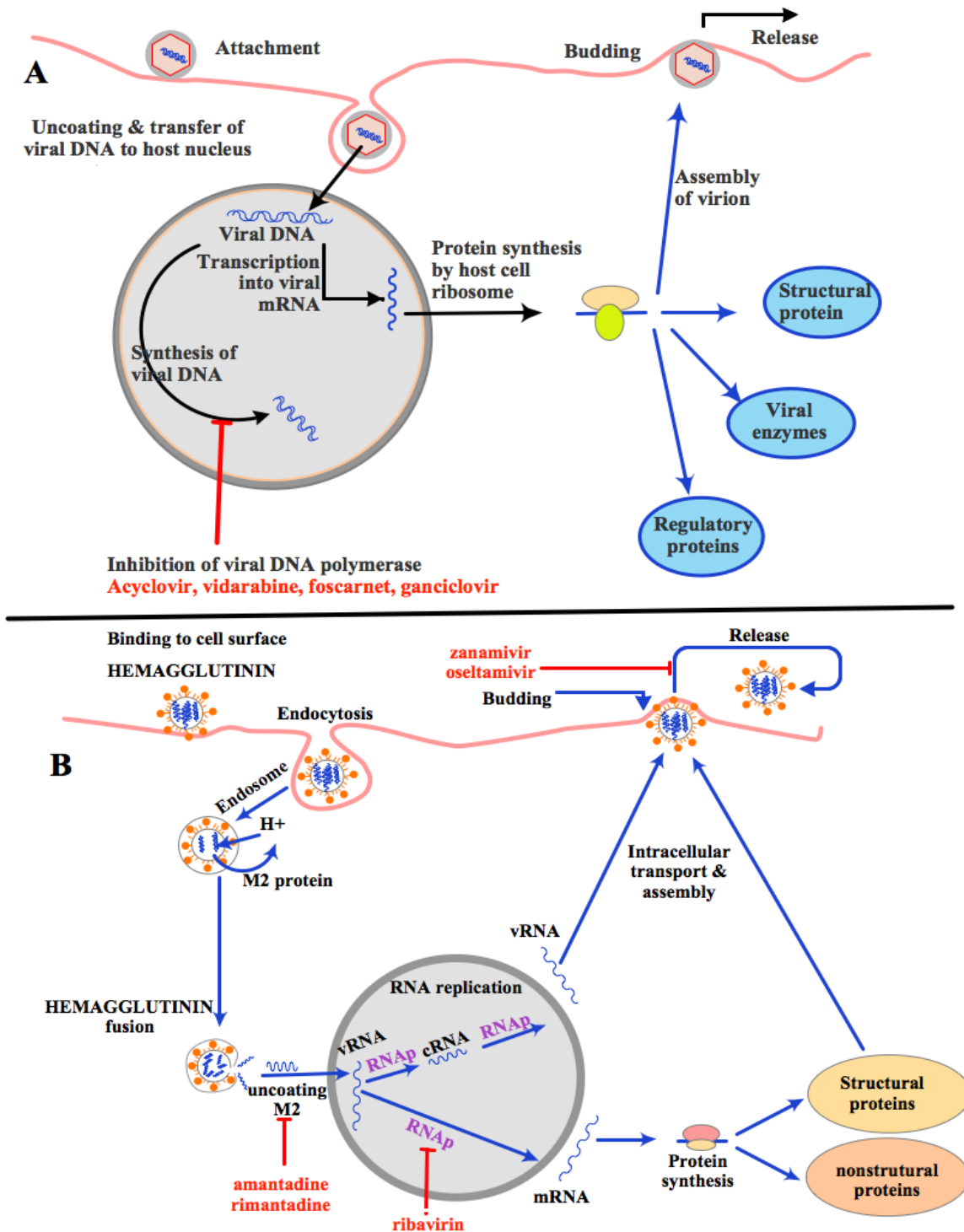


Figure 1. Replicative cycles of DNA (A) and RNA (B)

**Table 1. Stages of virus replication and possible targets of action of antiviral agents**

Stage of replication	Classes of selective inhibitors
<b>Cell entry</b> Attachment Penetration	Soluble receptor decoys, antireceptor antibodies, fusion protein inhibitors
<b>Uncoating</b> Release of viral genome	Ion channel blockers, capsid stabilizers
<b>Transcription of viral genome</b> Transcription of viral messenger RNA Replication of viral genome	Inhibitors of viral DNA polymerase, RNA polymerase, reverse transcriptase, helicase, primase, or integrase
<b>Translation of viral proteins</b> Regulatory proteins Structural proteins	Interferons, antisense oligonucleotides, ribozymes Inhibitors of regulatory proteins
<b>Post-translation modifications</b> Photolytic cleavage Myristoylation, glycosylation	Protease inhibitors
<b>Assembly of virion components</b>	Interferons, assembly protein inhibitors
<b>Release</b> Budding, cell lysis	Neuraminidase inhibitors, antiviral antibodies, cytotoxic lymphocytes

### Antiviral Agents:

1. **Amantadine:** It is 1-adamantanamine hydrochloride. Amantadine is an anti-influenza agent.

**Mechanism of action:** When influenza viruses replicate within the host cell, a viral membrane protein known as M2 (an integral membrane protein that functions as an ion channel) forms an ion-channel for H<sup>+</sup> influx from the endosome into the virion prior to fusion of the viral membrane with the endosomal membrane. Amantadine binds to M2 protein and blocks its ion channel activity and thus inhibits viral uncoating and replication (Figure 1B).

**Therapeutic uses:** The primary use of amantadine in veterinary medicine is an adjunct to NSAIDs for the treatment of chronic pain in dogs and cats. It is effective; for treating some, but not all, influenza viruses.

**Pharmacokinetic:** Orally, about 50% of the dose is absorbed in horses and high levels are attained in secretions. It is excreted unchanged by the kidneys.

**Administration:** It is administered once daily in dogs and cats as an adjunct to treat chronic pain.

**Resistance:** Develops rapidly.

**Adverse effects:** agitation, loose stools, flatulence, or diarrhea, particularly early in therapy.

2. **Acyclovir:** Is a guanosine derivative with selectivity for particular herpes viruses.

**Mechanism of action:** It is metabolized in the host cell to the monophosphate by thymidine kinase, which is more active in the virus than in the host cell. The host cell then converts the monophosphate to the acyclovir triphosphate that inhibits the viral DNA polymerase, ending the nucleotide chain prematurely (Figure 1A).

**Therapeutic uses:** It is used to treat ocular and respiratory infections of herpes 1 of cats. Although acyclovir is active against equine herpes, oral absorption is poor in horses and therapeutic levels are not attainable.

**Pharmacokinetics:** Acyclovir is poorly absorbed after oral administration. It is widely distributed throughout the body tissues and fluids, including the brain and CSF.

**Administration:** Acyclovir is administered orally twice a day to cats.

**Adverse effect:** Leucopenia and anemia may occur and they are reversible if treatment is discontinued.

3. **Zidovudine (AZT):** It is a synthetic thymidine analog with potent activity against a broad spectrum of retroviruses including HIV-1, HIV-2, and human T-cell lymphotropic viruses (HTLV) I and II.

**Mechanism of action:** Zidovudine is phosphorylated by host cell enzymes to AZT 5'-triphosphate, which competes with host 5'-thymidine, which is essential for proviral DNA formation by reverse transcriptase of the virus. The incorporation of the 5'-triphosphate zidovudine into the viral DNA chain produces the termination of viral DNA synthesis. Mammalian DNA polymerase does not incorporate the zidovudine (Figure 1).

**Therapeutic uses:** Zidovudine is FDA-approved for the treatment of adults and children with HIV infection and for preventing mother-to-child transmission of HIV infection; it is still recommended for post-exposure prophylaxis in HIV-exposed

healthcare workers. It has limited use in veterinary medicine. It can be used in cats to treat Feline Leukemia Virus (FLV) infection where it produces temporary alleviation of the clinical signs and increase quality of life and survival time in most cats, particularly when clinical signs of immunodeficiency are evident. It is not effective against feline leukemia virus at nontoxic doses.

**Pharmacokinetics:** Zidovudine is well absorbed orally with half-life about 2 hours in cats. It is metabolized in the liver by glucuronide conjugation and excreted in urine.

**Administration:** Zidovudine is administered orally 2-3 times a day for a minimum of 4 weeks.

**Resistance:** Mutation of virus target sites may result rapidly and resistance to zidovudine is expected with long-term use.

**Adverse effects:** Anemia and reduction in hemoglobin are the most common side effects. Diarrhea and weakness may also occur.

4. **Interferons (IFNs):** They are potent cytokines that possess antiviral, immunomodulatory, and antiproliferative activities. These proteins are synthesized by host cells in response to various inducers and, in turn, cause biochemical changes leading to an antiviral state in cells. In humans, there are three major classes of interferons with significant antiviral activity that are currently recognized as:  $\alpha$ ,  $\beta$ , and  $\gamma$ . IFN- $\alpha$  and IFN- $\beta$  may be produced by nearly all cells in response to viral infection and a variety of other stimuli, including double-stranded RNA and certain cytokines. IFN- $\gamma$  production is restricted to T-lymphocytes and natural killer cells responding to antigenic stimuli, mitogens, and specific cytokines. IFN- $\alpha$  and IFN- $\beta$  exhibit antiviral and antiproliferative actions; stimulate the cytotoxic activity of lymphocytes, natural killer cells, and macrophages; and upregulate class I major histocompatibility (MHC) antigens and other surface markers. IFN- $\gamma$  has less antiviral activity but more potent immunoregulatory effects, particularly macrophage activation, expression of class II MHC antigens, and mediation of local inflammatory responses. Most animal viruses are inhibited by IFNs, although many DNA viruses are relatively insensitive.

**Mechanism of action:** Following binding to specific cellular receptor, IFNs activate the JAK-STAT [(signaling pathway transmits information from chemical signals

outside the cell, through the cell membrane, and into gene promoters on the DNA in the cell nucleus, which causes DNA transcription and activity in the cell. The JAK-STAT system is a major signaling alternative to the second messenger system. The JAK-STAT system consists of three main components: (1) a receptor (2) Janus kinase (JAK) and (3) Signal Transducer and Activator of Transcription (STAT)] signal-transduction pathway and lead to the nuclear translocation of a cellular protein complex that binds to genes containing an IFN-specific response element. This in turn, leads to synthesis of over two dozen proteins that contribute to viral resistance mediated at different stages of viral penetration.

5. **Cat omega interferons:** proteins produced by host cells when they are attacked by viruses. Cat omega interferon is produced by genetic engineering and is a type I interferon closely related to alpha interferon.

**Mechanism of action:** it is not a direct attack on the virus but by altering host cell metabolism to induce proteins that protect against viral invasion by several methods including destruction of mRNA and blockade of translational proteins resulting in the inhibition of viral replication.

**Therapeutic uses:** Feline omega interferon can be used to treat cat viral infections as well as canine parvovirus.

**Administration:** Interferons may be given SC or other parenteral routes depending on the virus to be treated once a day.