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Antiviral drugs

Pharmacology 3

Dr. Heba Khader

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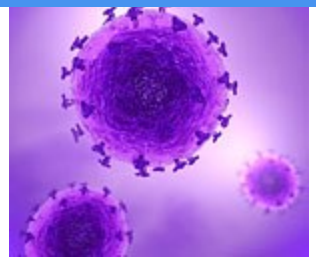
OVERVIEW



- Viruses are obligate intracellular parasites.
- they lack both cell wall and cell membrane.
- They don't carry out metabolic processes.
- viral reproduction uses much of the host's metabolic machinery .
- viruses are not affected by antimicrobial agent.
- Certain viruses multiply in the cytoplasm but others do in the nucleus.

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Structure of viruses

- Nucleic acid core: DNA or RNA
- Often contain crucial virus-specific enzymes
- Surrounded by protein: "capsid"
- Sometimes an outer lipid "envelope"
- Complete viral particle: "virion"

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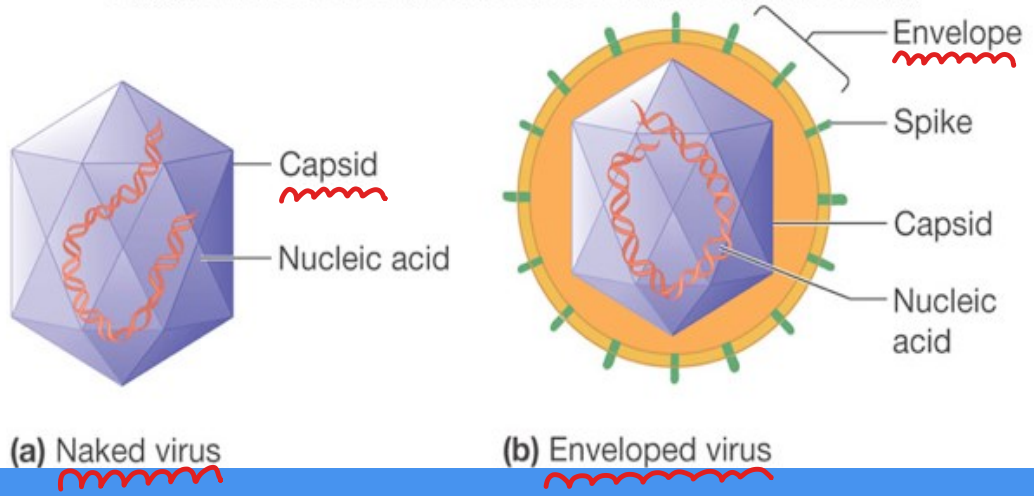

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❖ Some examples of viruses & the diseases they cause are as follows:

DNA viruses :

- Pox viruses (smallpox جَدَرِيّ... the WHO certified the global eradication of smallpox in 1979).
- Herpes viruses
  - Varicella-zoster viruse (VZV) :chicken pox جدري الماء and shingles
  - HSV-1 cause oral herpes (which can include symptoms known as "cold sores").
  - HSV-2 is a sexually transmitted infection that causes genital herpes.
  - Cytomegalovirus (CMV)
- Adenoviruses (sore throat, conjunctives)
- Hepadnaoviruses (hepatitis B virus(HBV))
- Papillomaviruses (warts)

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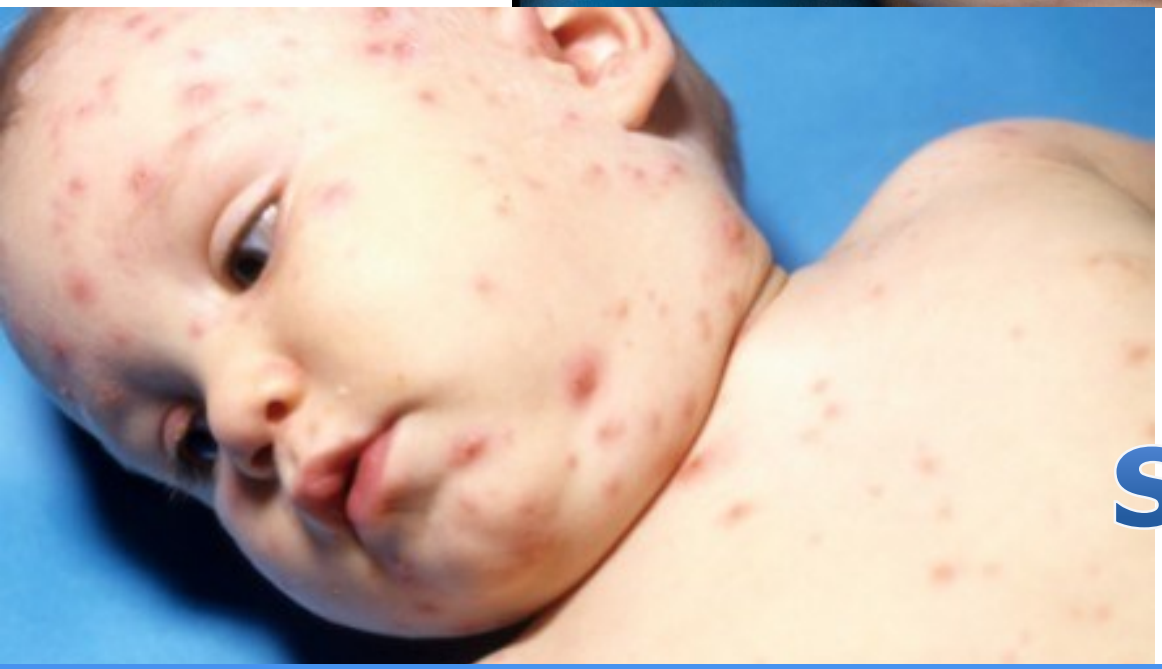
chicken-pox



smallpox

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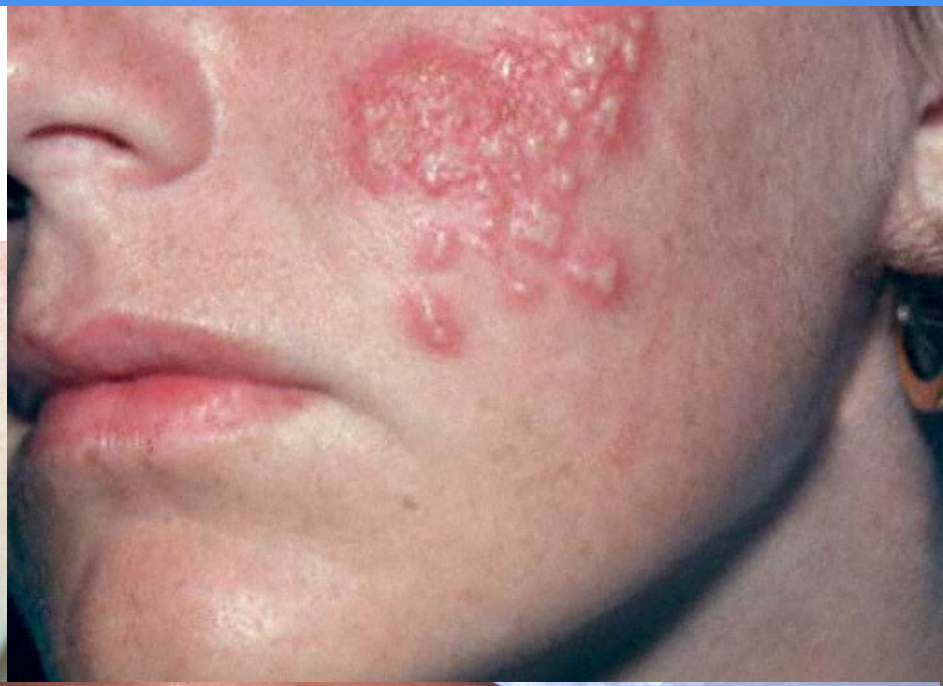
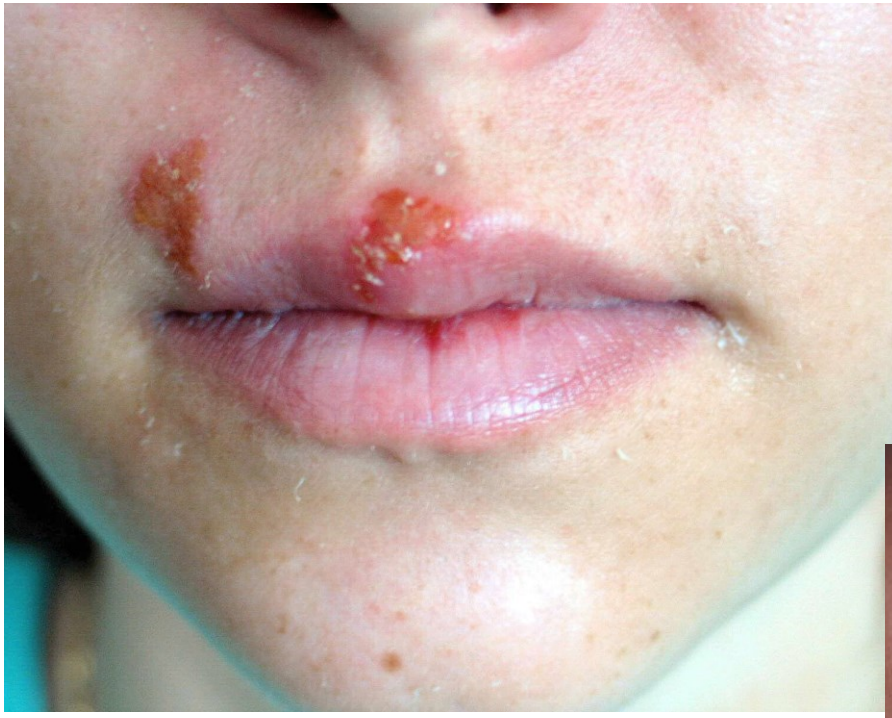
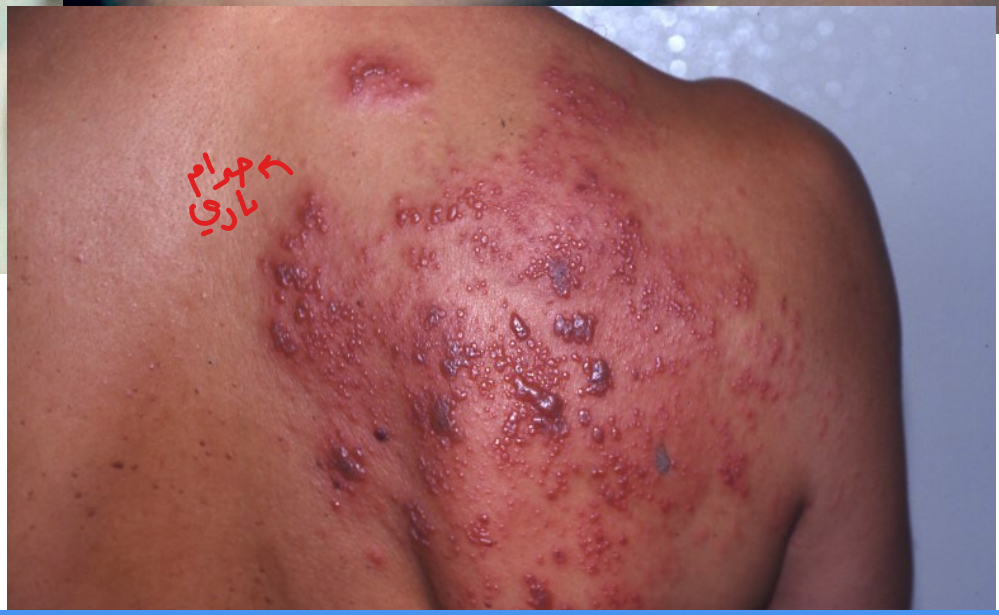
Herpes







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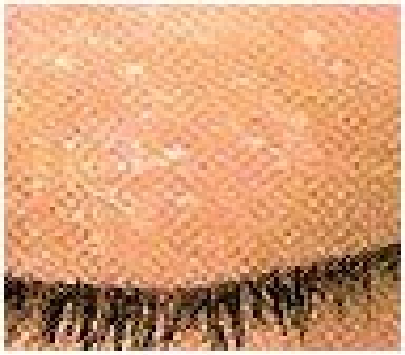
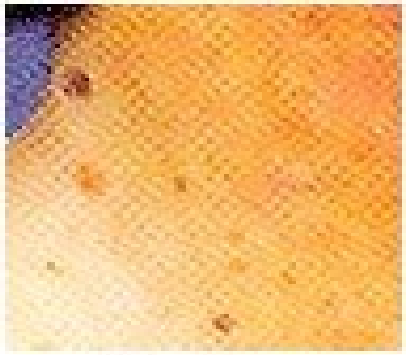
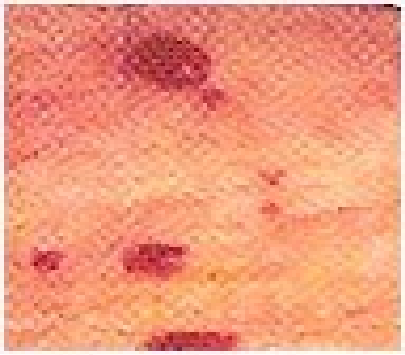
Warts



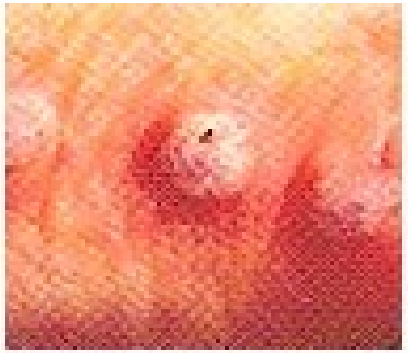
Milia



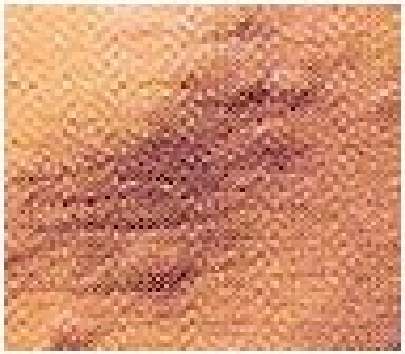
Skin Tags



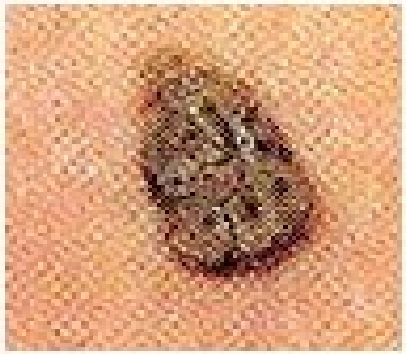
Blood Spots



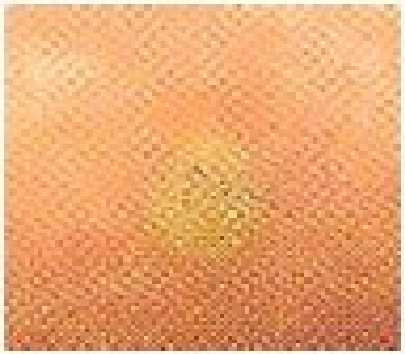
Common Wart



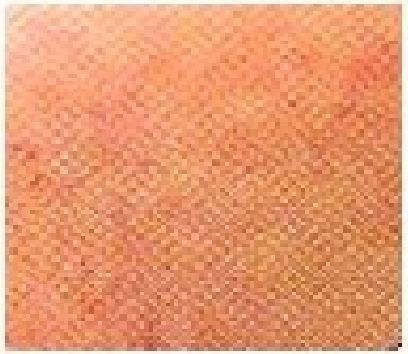
Plane Wart



Seborrhoeic Wart



Planter Wart



Thread Veins

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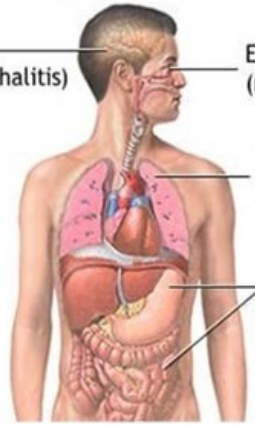
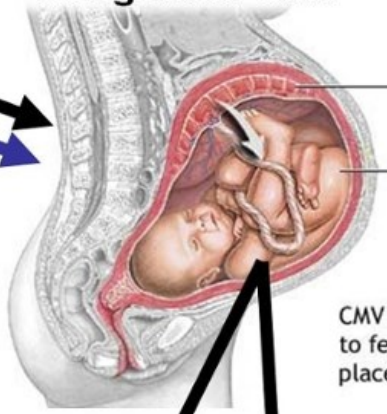
CMV & Disease

Immune suppressed end organ CMV disease

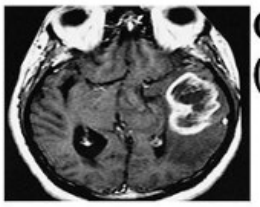


Congenital CMV

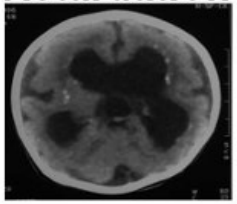


CMV is passed to fetus through placenta

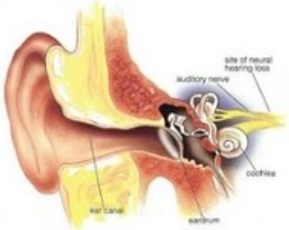
Cancer (glioblastoma)



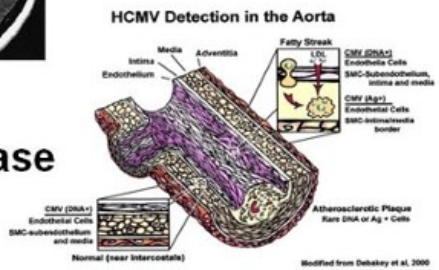
Mental Retardation



Deafness



Vascular disease (atherosclerosis)



→ Primary Infection

→ Reactivation/re-infection

⇢ Contributing factor

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RNA viruses:

- Orthomyxoviruses (influenza)
- Paramyxoviruses (measles الحصبة, mumps النكاف)
- Rubella virus (German measles الحصبة الألمانية)
- Rhabdovirus (rabies داء الكلَب)
- Picornavirus (colds, meningitis, HAV, poliomyelitis شلل الأطفال)
- Hepacivirus (Hepatitis C virus (HCV))
- Retroviruses (AIDS, T-cell lukemia)
- Arenaviruses (lassa fever)
- Arbovirus (yellow fever)

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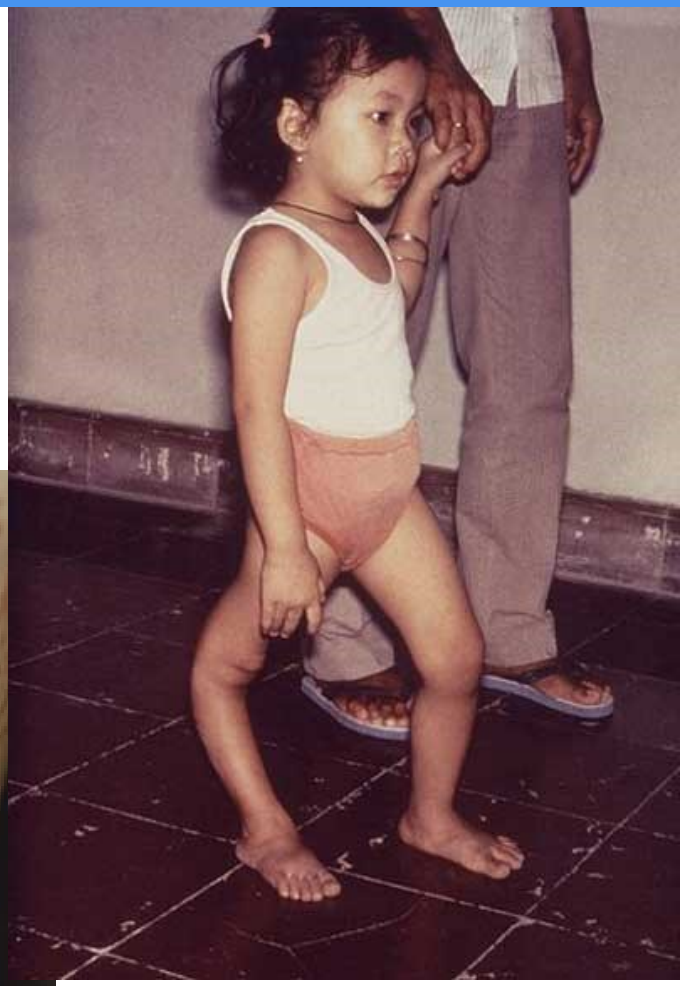
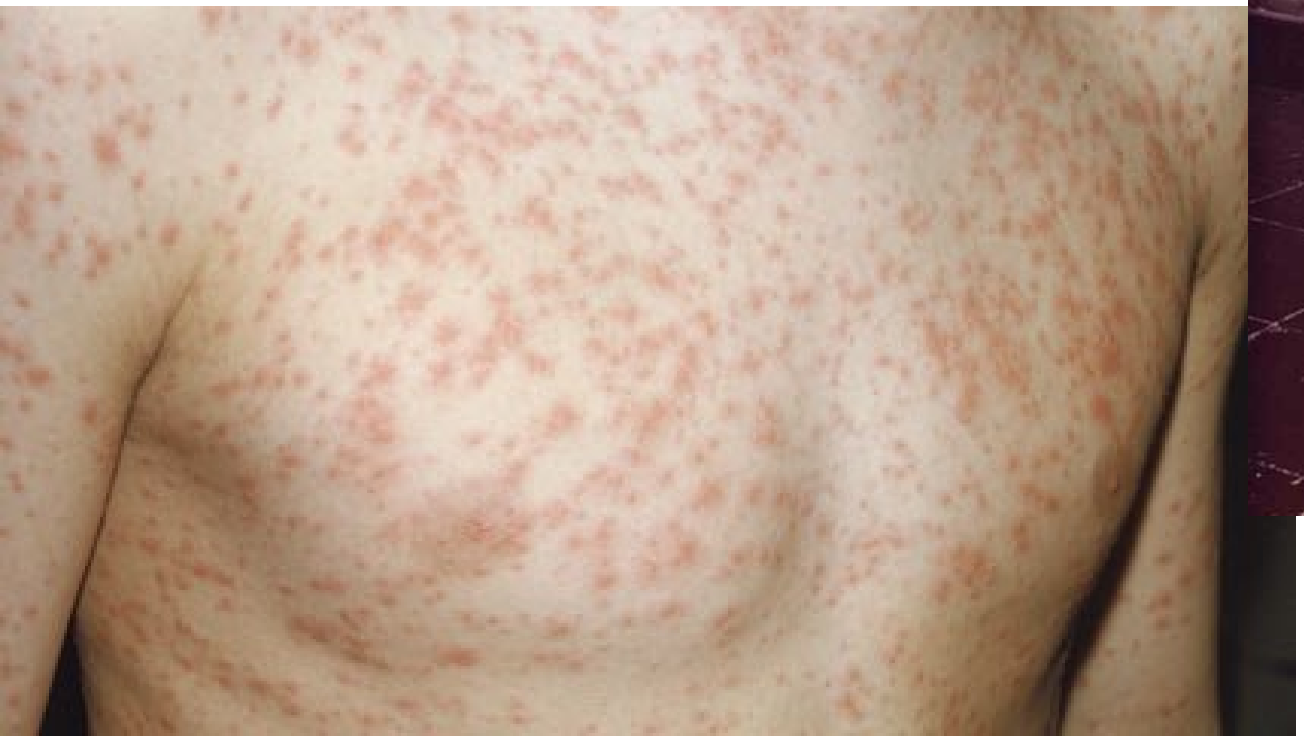
Poliomyelitis-





rubella-german-measles

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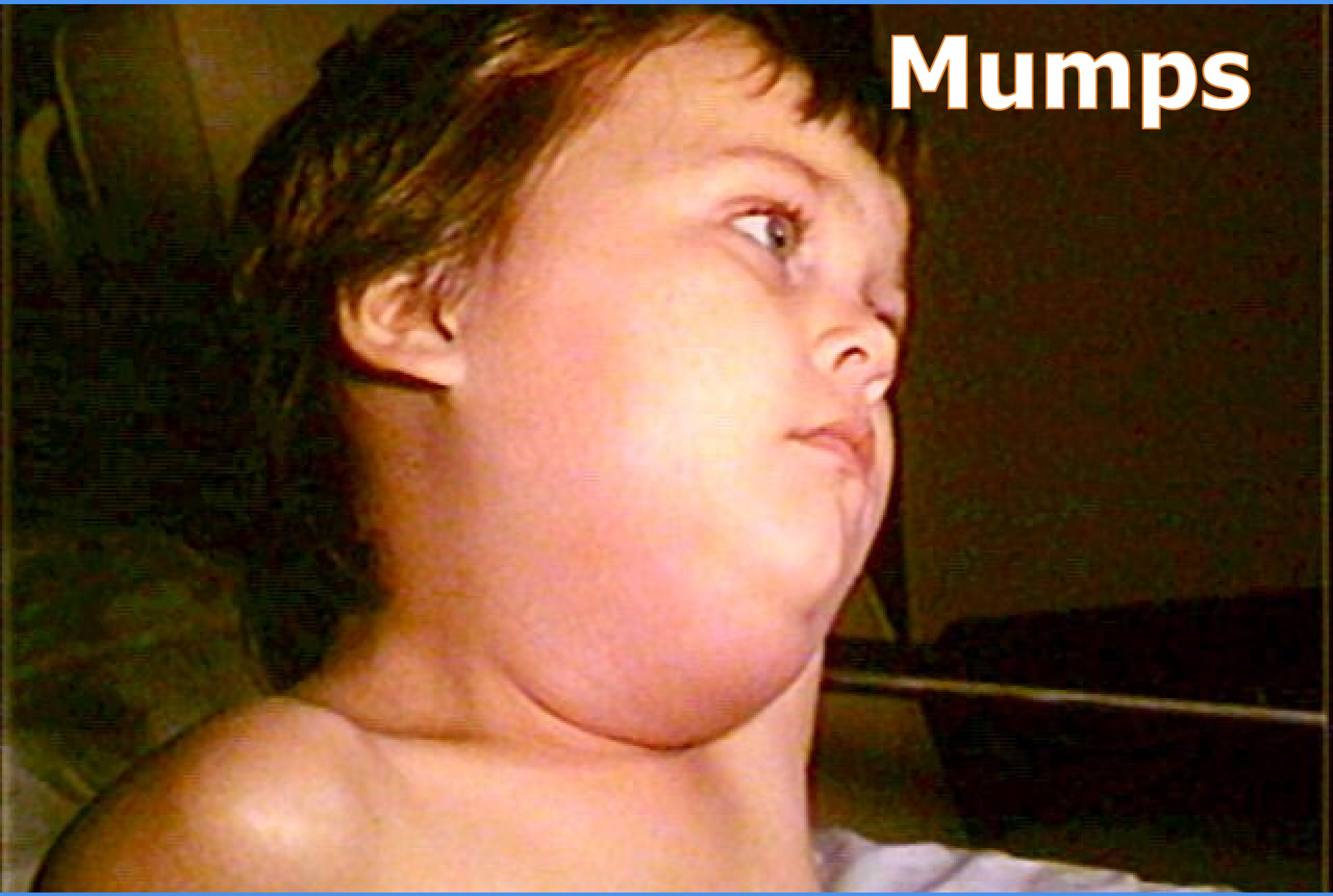

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Stages of viral replication

(1) Attachment of the virus to receptors on the host cell surface;

(2) Entry of the virus through the host cell membrane;

(3) uncoating of viral nucleic acid;

(4) synthesis of early regulatory proteins, eg, nucleic acid polymerases;

(5) synthesis of new viral RNA or DNA;

(6) integration into the nuclear genome;

(7) synthesis of late, structural proteins;

(8) assembly (maturation) of viral particles;

(9) release from the cell.

- Antiviral agents can potentially target any of these steps.

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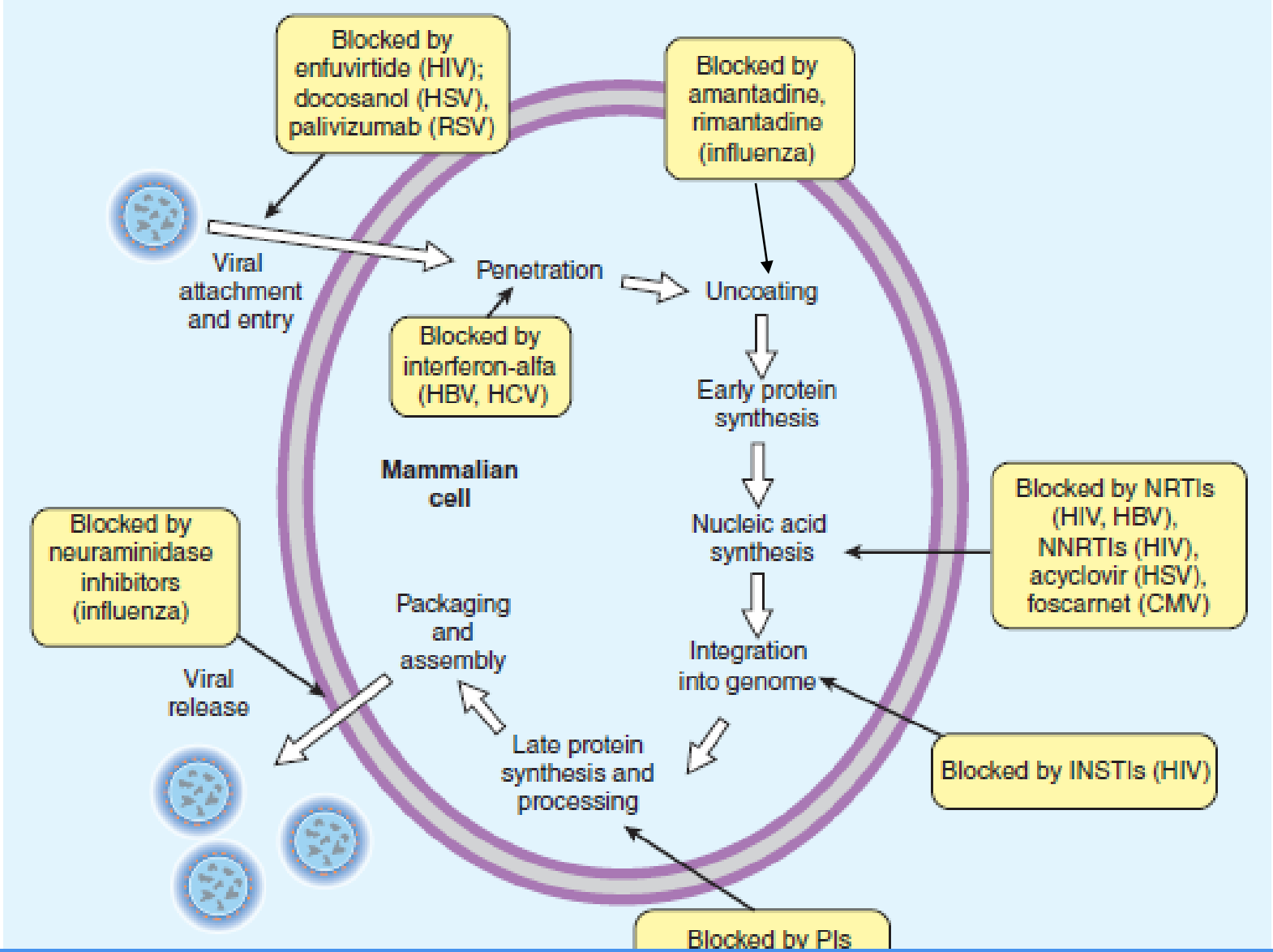

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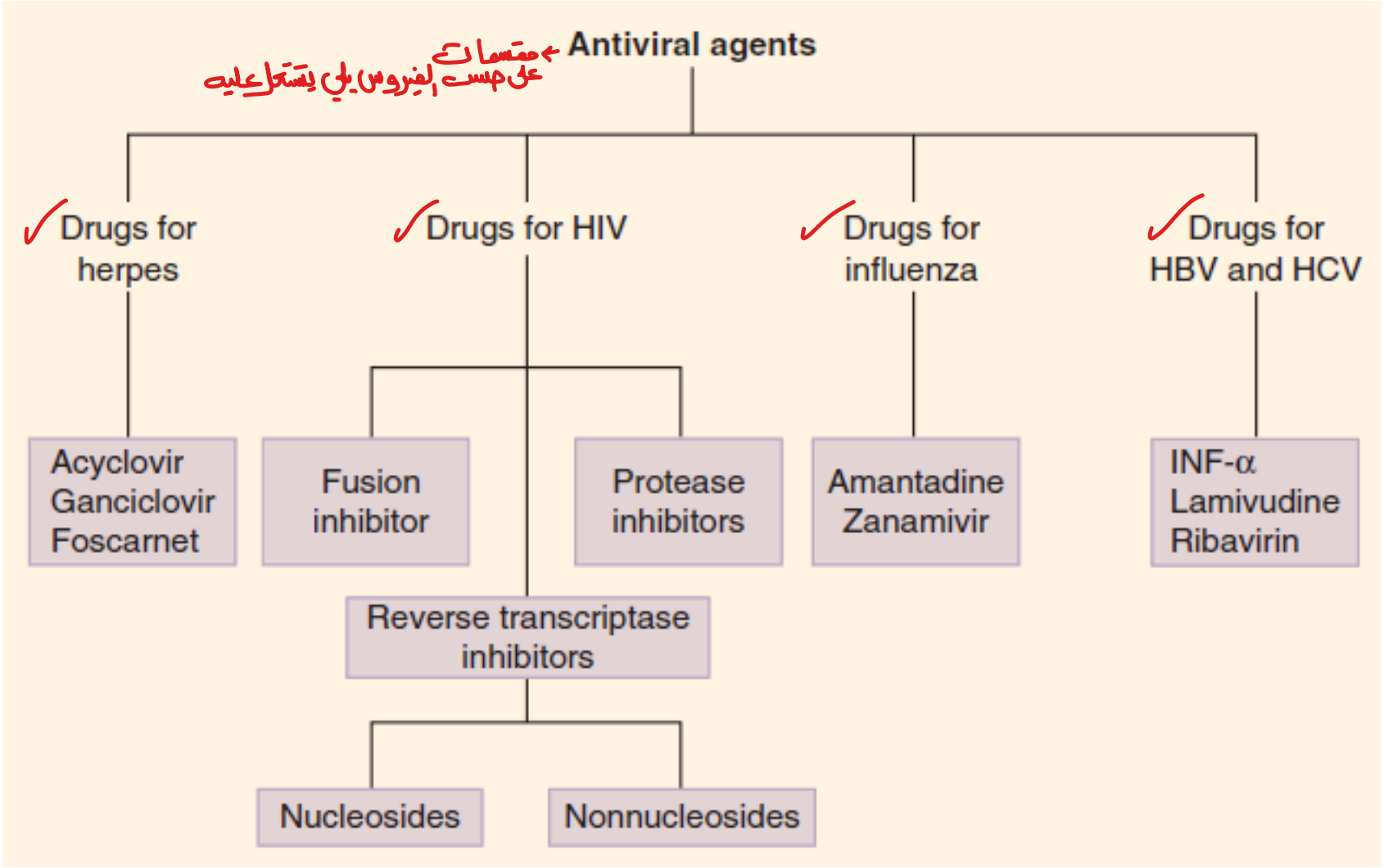

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Agents To Treat Herpes Simplex Virus (HSV),Varicella-zoster Virus (VZV) & Cytomegalovirus (CMV) Infections

- **Acyclovir**
- **Valacyclovir**
- **Famciclovir**

  Oral guanosine analogues
- **Penciclover**... topical guanosine analogue
- **Cidofovir**
- **Foscarent**
- **Ganciclovir**

  Anti-CMV infections
- **Vidarabine**... topical adenosine analogue
- **Trifluridine**... topical pyrimidine analogue
- **Docosanol**... topical for orolabial herpes (cold sores)

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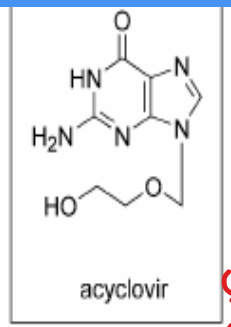
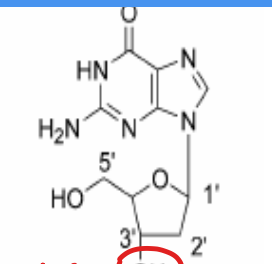
Acyclovir (acycloguanosine)

- Acyclic guanosine analoge
- Active against HSV1 HSV2 & VZV.



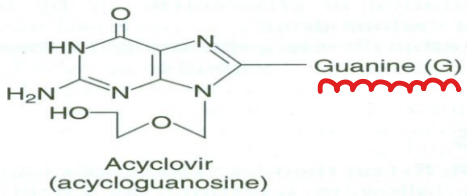


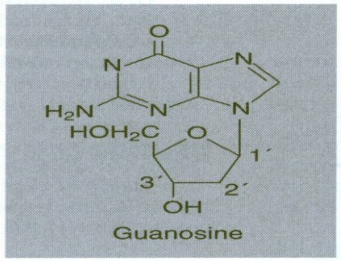
نساعدي إنحال بناء سلسلة د DNA

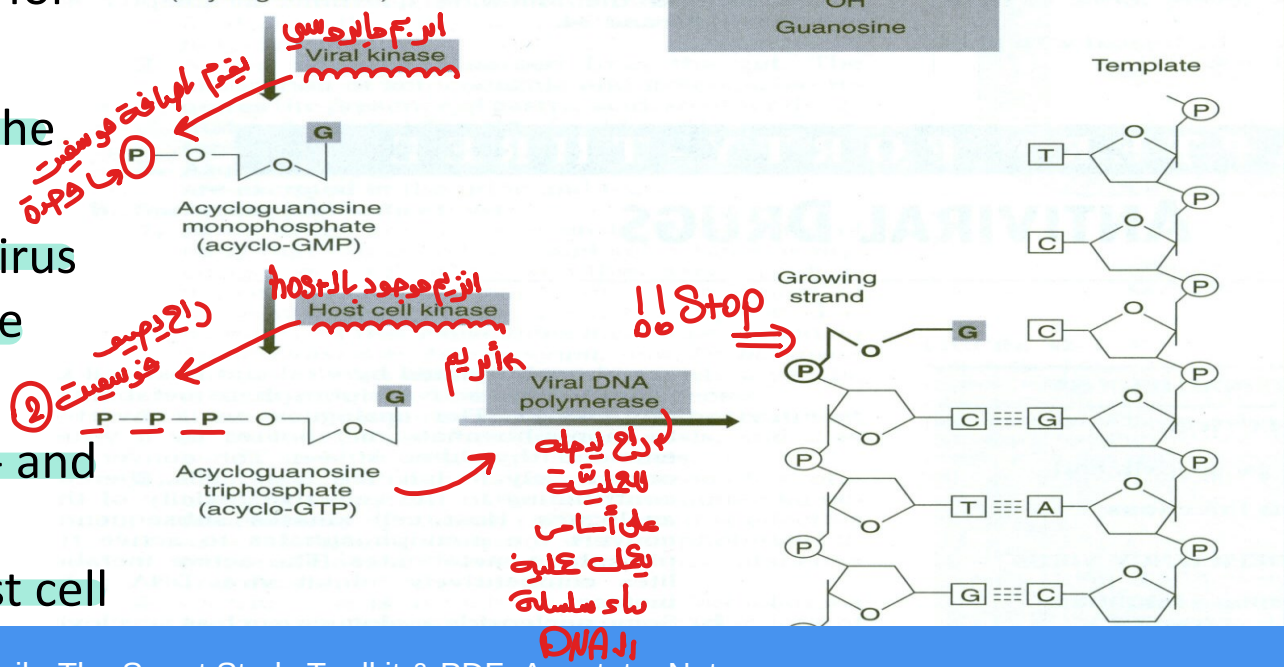
- Administration: topical ointment, intravenous, oral

Mechanism of action:

- Acyclovir requires three phosphorylation steps for activation
  - converted first to the monophosphate derivative by the virus specified thymidine kinase
  - and then to the di- and triphosphate compounds by host cell







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Acyclovir (acycloguanosine)

- The active metabolite of acyclovir inhibits DNA replication in two ways:
  1. Acyclovir triphosphate acts as a competitive inhibitor for the incorporation of deoxyguanosine triphosphate (dGTP) into the viral DNA.
  2. In addition, acyclovir that is incorporated into viral DNA acts as a chain terminator because it lacks the 3-hydroxy group necessary for further chain elongation.
- Because acyclovir requires the viral kinase for initial phosphorylation, acyclovir is selectively activated—and the active metabolite accumulates— only in infected cells.

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Acyclovir (acycloguanosine)

PKs:

- IV, oral (poor 15-20%), topical .
- Well distributed throughout the body including CSF.
- Excreted by the kidney.

Adverse effect:

- topical administration :local irritation .
- oral: headache, diarrhea, nausea.
- IV : transient renal dysfunction at high doses.

Resistance:

- can develop in HSV or VZV through alteration in either the viral thymidine kinase or the DNA polymerase

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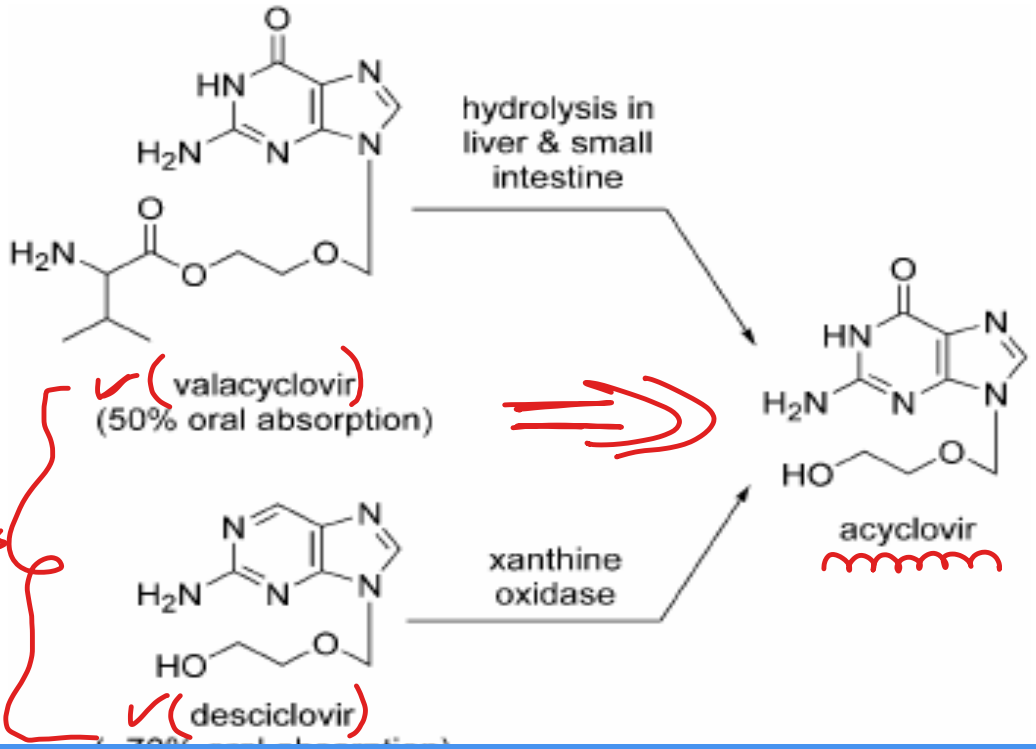
Valacyclovir

- Valacyclovir is the l-valyl ester of acyclovir.

Acyclovir: Pharmacokinetics

- Fairly poor oral absorption (15-30%)
- Improved by design of suitable prodrugs:



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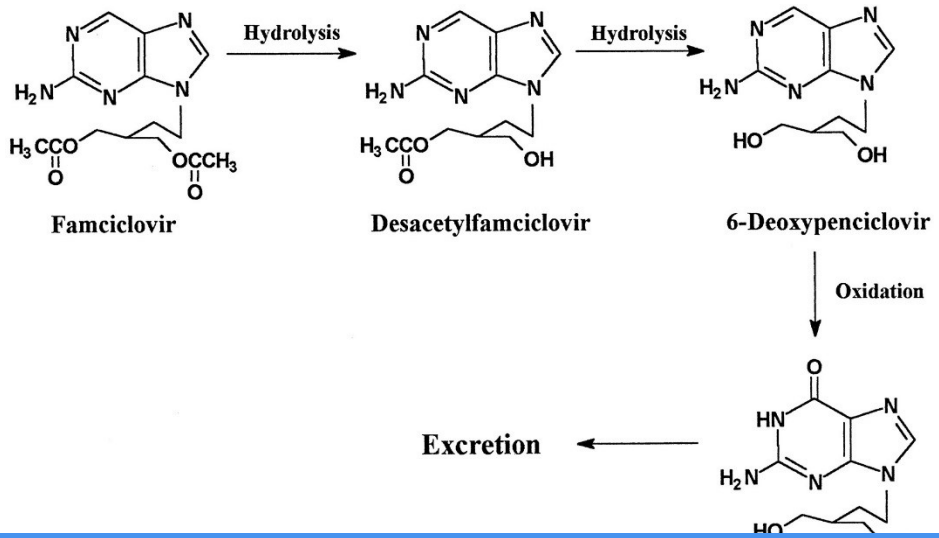
Famciclovir (prodrug)

- Prodrug of penciclovir
- After oral administration, famciclovir is rapidly deacetylated and oxidized by first-pass metabolism to penciclovir.
- As with acyclovir, activation by phosphorylation is catalyzed by the virus-specified thymidine kinase in infected cells, followed by competitive inhibition of the viral DNA polymerase to block DNA synthesis.



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Agents To Treat Cytomegalovirus (CMV) Infections

- **Valganciclovir…** an l-valyl ester prodrug of ganciclovir
- **Ganciclovir…** an acyclic guanosine analog (an analog of acyclovir that has greater activity against CMV)
- **Cidofovir**…a cytosine nucleotide analog…does not require phosphorylation
- **Foscarent**…an inorganic pyrophosphate analog that inhibits herpesvirus DNA polymerase, RNA polymerase, and HIV reverse transcriptase directly without requiring activation by phosphorylation.

TABLE 49–2 Agents to treat cytomegalovirus (CMV) infection.

Agent	Route of Administration	Use	Recommended Adult Dosage[1]
Valganciclovir	Oral	CMV retinitis treatment	Induction: 900 mg bid × 21 days Maintenance: 900 mg daily
	Oral	CMV prophylaxis (transplant patients)	900 mg daily
Ganciclovir	Intravenous	CMV retinitis treatment	Induction: 5 mg/kg q12h × 14–21 days Maintenance: 5 mg/kg/d or 6 mg/kg five times per week
Foscarnet	Intravenous	CMV retinitis treatment	Induction: 60 mg/kg q8h or 90 mg/kg q12h × 14–21 days Maintenance: 90–120 mg/kg/d
Cidofovir	Intravenous	CMV retinitis treatment	Induction: 5 mg/kg/wk × 2 weeks Maintenance: 5 mg/kg every week

[1] …

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Antihepatitis agents

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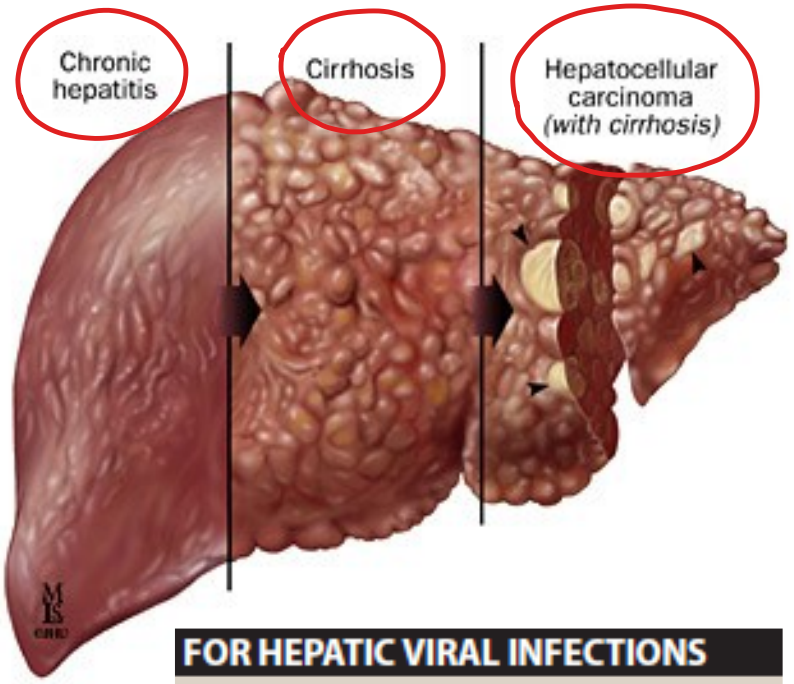
Viral Hepatitis

- The hepatitis viruses thus far identified (A, B, C, D, and E) each have a pathogenesis specifically involving replication in and destruction of hepatocytes.
- Of this group, hepatitis B (a DNA virus) and hepatitis C (an RNA virus) are the most common causes of chronic hepatitis cirrhosis, and hepatocellular carcinoma and are the only hepatic viral infections for which therapy is currently available.



FOR HEPATIC VIRAL INFECTIONS

Adefovir HEPSERA
Boceprevir VICTRELIS
Entecavir BARACLUDE
Interferon INTRON, AVONEX
Lamivudine EPIVIR-HBV
Pegylated interferon PEGASYS, PEG-INTRON
Telaprevir INCIVEK
Telbivudine TYZEKA

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Anti-Hepatitis Agents

١

- **Interferons**
- Interferons are a family of naturally occurring, inducible glycoproteins that interfere with the ability of viruses to infect cells. The interferons are synthesized by recombinant DNA technology.
- At least three types of interferons exist—α, β, and γ.
- One of the 15 interferon-α glycoproteins, *interferon-α-2b* has been approved for treatment of hepatitis B and C.

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Anti-Hepatitis Agents

- **Interferons**
- In "**pegylated**" formulations, bis-monomethoxy polyethylene glycol has been covalently attached to either *interferon-α-2a* or *-α-2b* to increase the size of the molecule.
- The larger molecular size delays absorption from the injection site, lengthens the duration of action of the drug, and also decreases its clearance.

- Injectable preparations of interferon alfa are available for treatment of both HBV and HCV infections (either subcutaneously or intramuscularly)

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TABLE 49–6 Drugs used to treat viral hepatitis.

Agent	Indication	Recommended Adult Dosage	Route of Administration
Nucleoside/nucleotide analogs			
Adefovir dipivoxil[1]	Chronic hepatitis B	10 mg qd	Oral
Entecavir[1]	Chronic hepatitis B	500 mg qd	Oral
Lamivudine[1]	Chronic hepatitis B	100 mg qd (150 mg qd if co-infection with HIV is present)	Oral
Tenofovir[1]	Chronic hepatitis B	300 mg qd	Oral
Telbivudine[1]	Chronic hepatitis B	600 mg qd	Oral
Interferons			
Interferon alfa-2b	Chronic hepatitis B	5 million units qd or 10 million units three times weekly	Subcutaneous or intramuscular
Interferon alfa-2b[1]	Acute hepatitis C	5 million units qd for 3–4 weeks, then 5 million units three times weekly	Subcutaneous or intramuscular
Pegylated interferon alfa-2a[1]	Chronic hepatitis B	180 mcg once weekly	Subcutaneous
Pegylated interferon alfa-2a[1]	Chronic hepatitis C	180 mcg once weekly plus ribavirin (800–1200 mg/d)	Subcutaneous
Pegylated interferon alfa-2b[1]	Chronic hepatitis C	1.5 mcg/kg once weekly with ribavirin (800–1200 mg/d)	Subcutaneous
Protease inhibitors			
Boceprevir	Chronic hepatitis C	800 mg tid × 24–44 weeks with peg-interferon alfa-2a or peg-interferon alfa-2b	Oral
Telaprevir	Chronic hepatitis C	750 mg tid × 12 weeks with peg-interferon alfa-2a or peg-interferon alfa-2b	Oral
Polymerase inhibitor			
Sofosbuvir	Chronic hepatitis C	400 mg qd (see text)	Oral

[1]Dose must be reduced in patients with renal insufficiency.

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Anti-Hepatitis Agents

- **Mechanism of action:** Interferon alfa appears to function by induction of intracellular signals following binding to specific cell membrane receptors, resulting in inhibition of viral penetration, translation, transcription, protein processing, maturation, and release.
- as well as increased host expression of major histocompatibility complex antigens, enhanced phagocytic activity of macrophages, and augmentation of the proliferation and survival of cytotoxic T cells.

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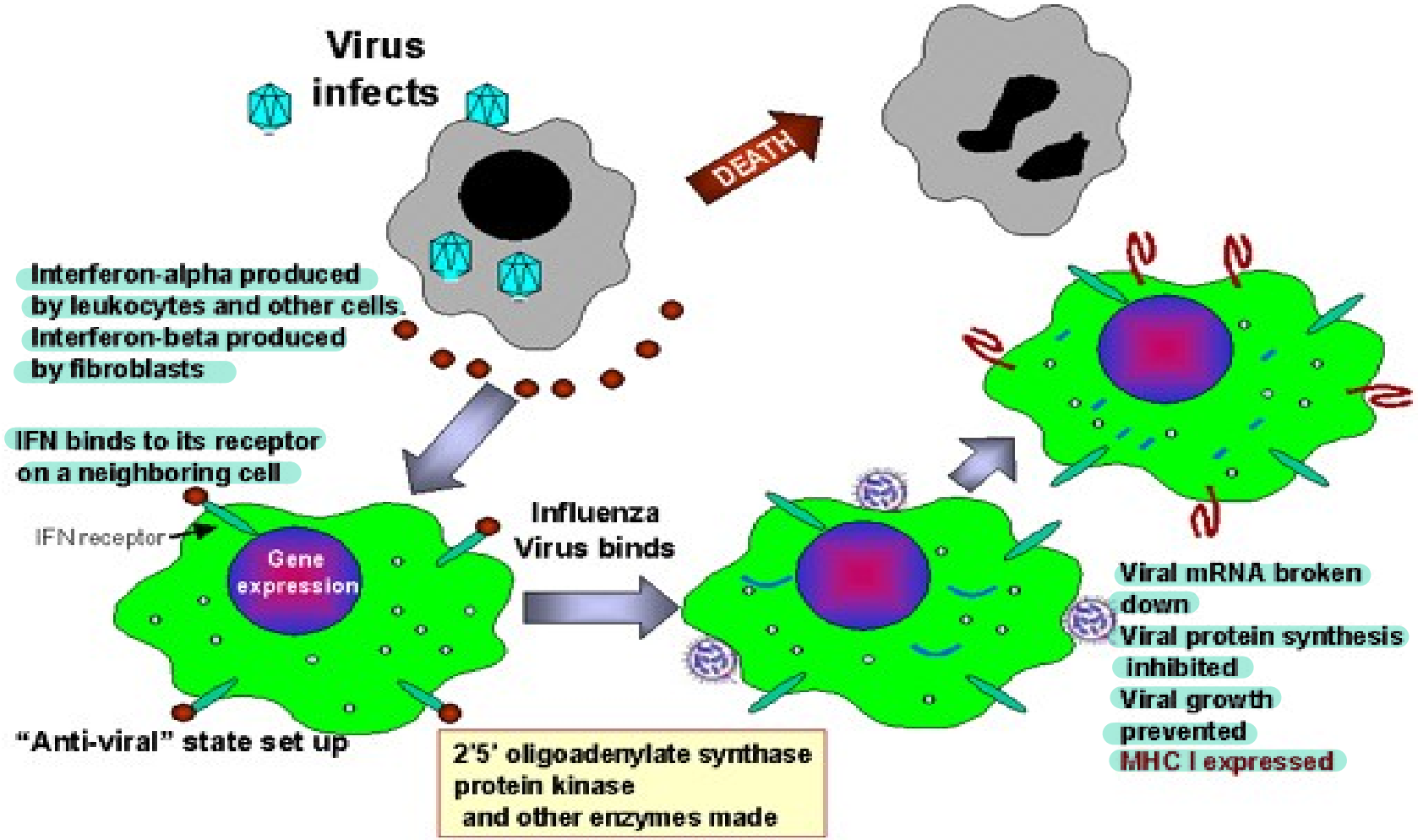
Anti-Hepatitis Agents



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Anti-Hepatitis Agents

- **Adverse effects:**
- flu-like syndrome (ie, headache, fevers, chills, myalgias, and malaise) that typically occurs within 6 hours after dosing in more than 30% of patients during the first week of therapy and tends to resolve upon continued administration.

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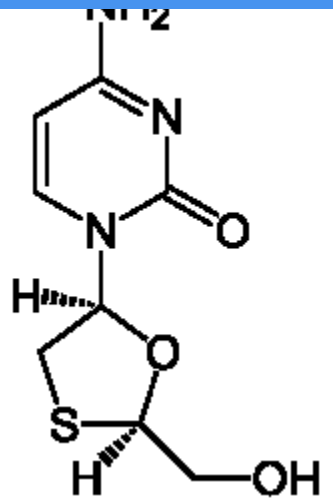
Anti-Hepatitis Agents



– **Lamivudine**

- Cytosine analog first developed for HIV
- Lower dose used for HBV (100 mg/day)

MOA:

- It is phosphorylated to the triphosphate which competes with dCTP for incorporation into growing DNA chains, causing chain termination.
- This compound competitively inhibits HBV DNA polymerase at concentrations that have negligible effects on host DNA polymerase.

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Anti-Hepatitis Agents

- **Boceprevir and telaprevir**
- Boceprevir and telaprevir are oral antiviral agents for the adjunctive treatment of chronic HCV.
- They are **protease inhibitors**, thus inhibiting viral replication in host cells.
- They have a low barrier to resistance and, when used as monotherapy, resistance quickly develops. Therefore, boceprevir or telaprevir should be used in combination with peginterferon alfa and ribavirin in order to improve response rates and reduce the emergence of viral resistance.
- Metabolized by the CYP3A4/5 pathways and are inhibitors of CYP3A4/5 and P-glycoprotein transporter.
- Co-administration with numerous drugs is contraindicated, including rifampin, ergot derivatives, cisapride, lovastatin, simvastatin, alfuzosin, sildenafil or tadalafil when used for pulmonary hypertension, pimozide, St. John's wort, triazolam, and midazolam.

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Anti-Influenza drugs

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Anti-Influenza drugs

A. Amantadine/ Rimantadine (Inhibitors of viral uncoating)

- Rimantadine is an α-methyl derivative of amantadine
- MOA : block the M2 proton ion channel of the virus particle and inhibit uncoating of the viral RNA within infected host cells, thus preventing its replication.

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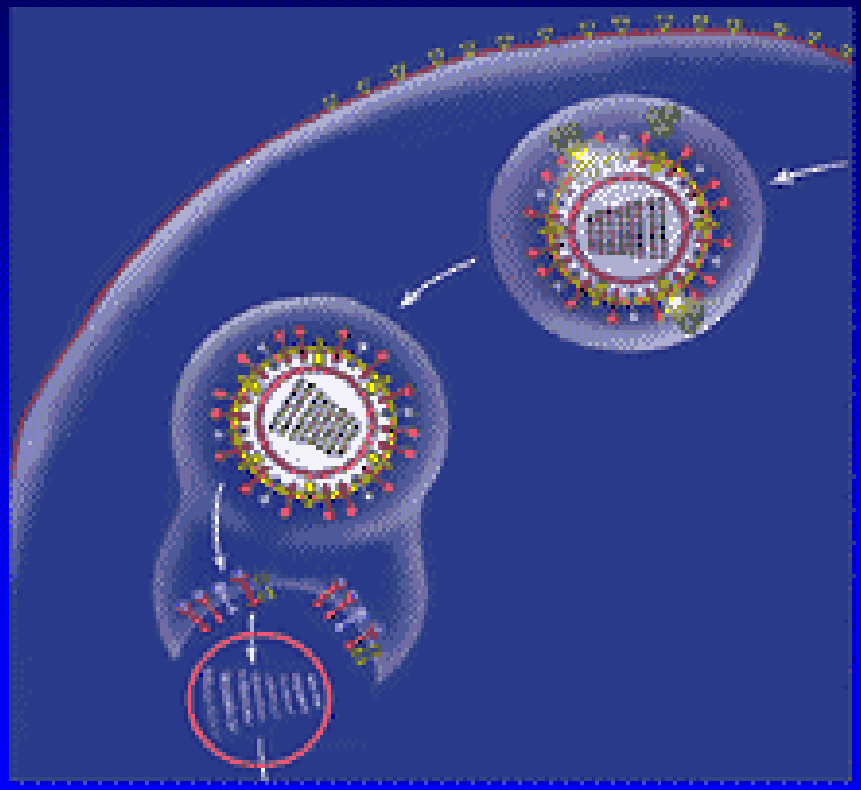
Amantadine and Rimantadine: Mechanism of Action



- Blocks M2 protein channel (type A only)
- Disrupts hydrogen transport, viral uncoating in host cell and therefore viral RNA transcription

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Pharmacokinetics:

	absorption	*Crossing BBB*	*metabolism*	*excretion*
Amantadine	Well absorbed orally	can	Not extensively metabolized	By kidney
Rimantadine	Well absorbed orally	Can't	Extensively by liver	By kidney

Dose reductions are required for both agents in the elderly and in patients with renal insufficiency, and for rimantadine in patients with marked hepatic insufficiency.

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Amantadine/ Rimantadine

Adverse effects:

- CNS effect (insomnia, dizziness, ataxia, hallucinations, and seizure).
- Both agents are teratogenic in rodents, and birth defects have been reported after exposure during pregnancy.
- GI effect (anorexia , nausea)

Resistance: Change in amino acid of the M2 matrix protein

- due to high rates of resistance in both H1N1 and H3N2 viruses, these agents are no longer recommended for the prevention or treatment of influenza.

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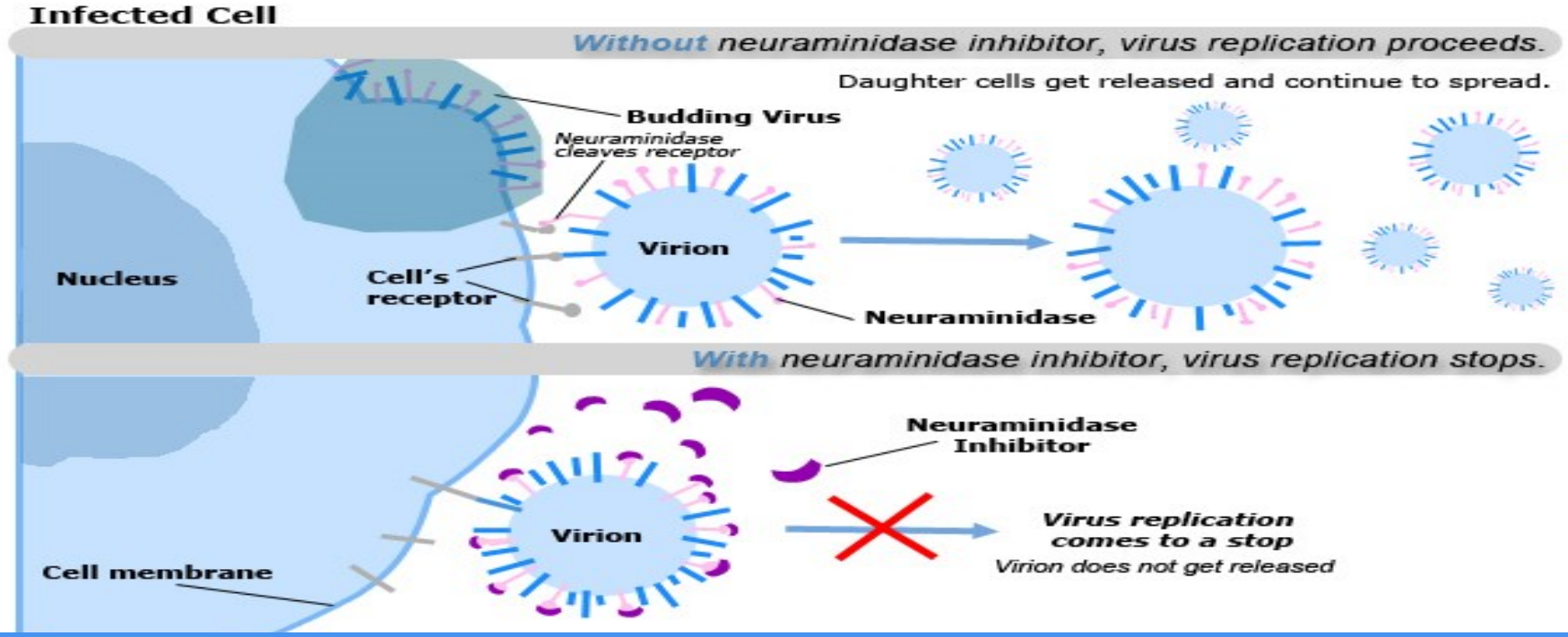
B. Oseltamivir (Tamiflu) / Zanamavir (Neuraminidase inhibitors)

- Influenza A & B
- MOA : Neuraminidase inhibitors so these drugs prevent the release of new virions and their spread from cell.



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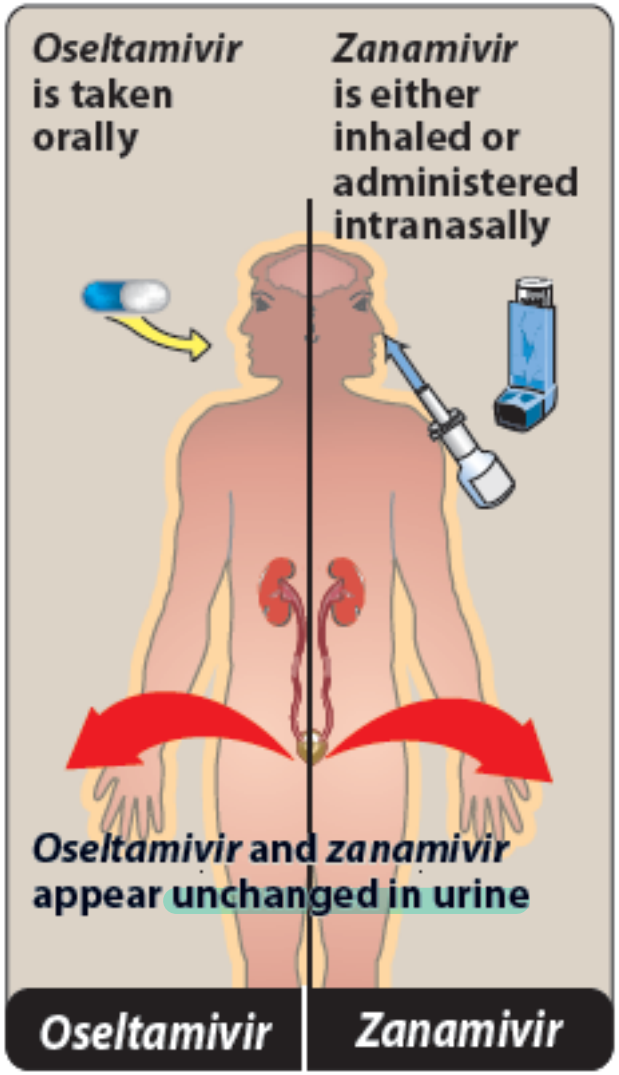
❖ PK

- **Oseltamivir:**
- orally administered prodrug.
- The dosage is 75 mg twice daily for 5 days for treatment and 75 mg once daily for prevention.
- **Zanamavir** is administered via oral inhalation.



❖Side effect:

- **Oseltamivir**: GI symptoms…Taking oseltamivir with food does not interfere with absorption and may decrease nausea and vomiting.
- **Zanamavir:** cough, throat discomfort , bronchospasm…not recommended for patients with underlying airway disease.

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ANTIRETROVIRAL AGENTS

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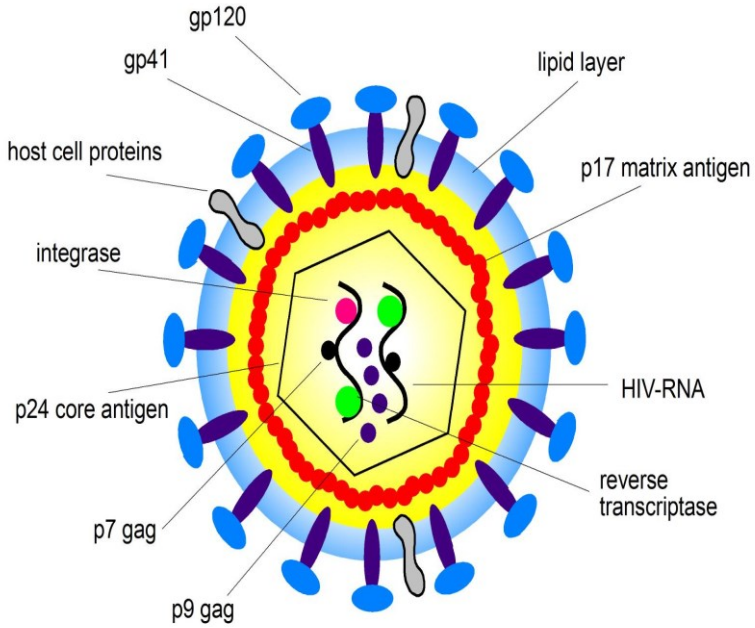
ANTIRETROVIRAL AGENTS

*HIV – the **H**uman **I**mmunodeficiency **V**irus is the retrovirus that causes AIDS.

*HIV attaches to CD4 receptors to enter cells($CD4^+$ cells).



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Overview of HIV treatment

- Prior to approval of *zidovudine* in 1987, treatment of HIV infections focused on decreasing the occurrence of opportunistic infections that caused a high degree of morbidity and mortality in AIDS patients.
- Today, the viral life cycle is understood, and a combination of drugs is used to suppress replication of HIV and restore the number of CD4 cells and immunocompetence to the host. This multidrug regimen is commonly referred to as "highly active antiretroviral therapy," or HAART.

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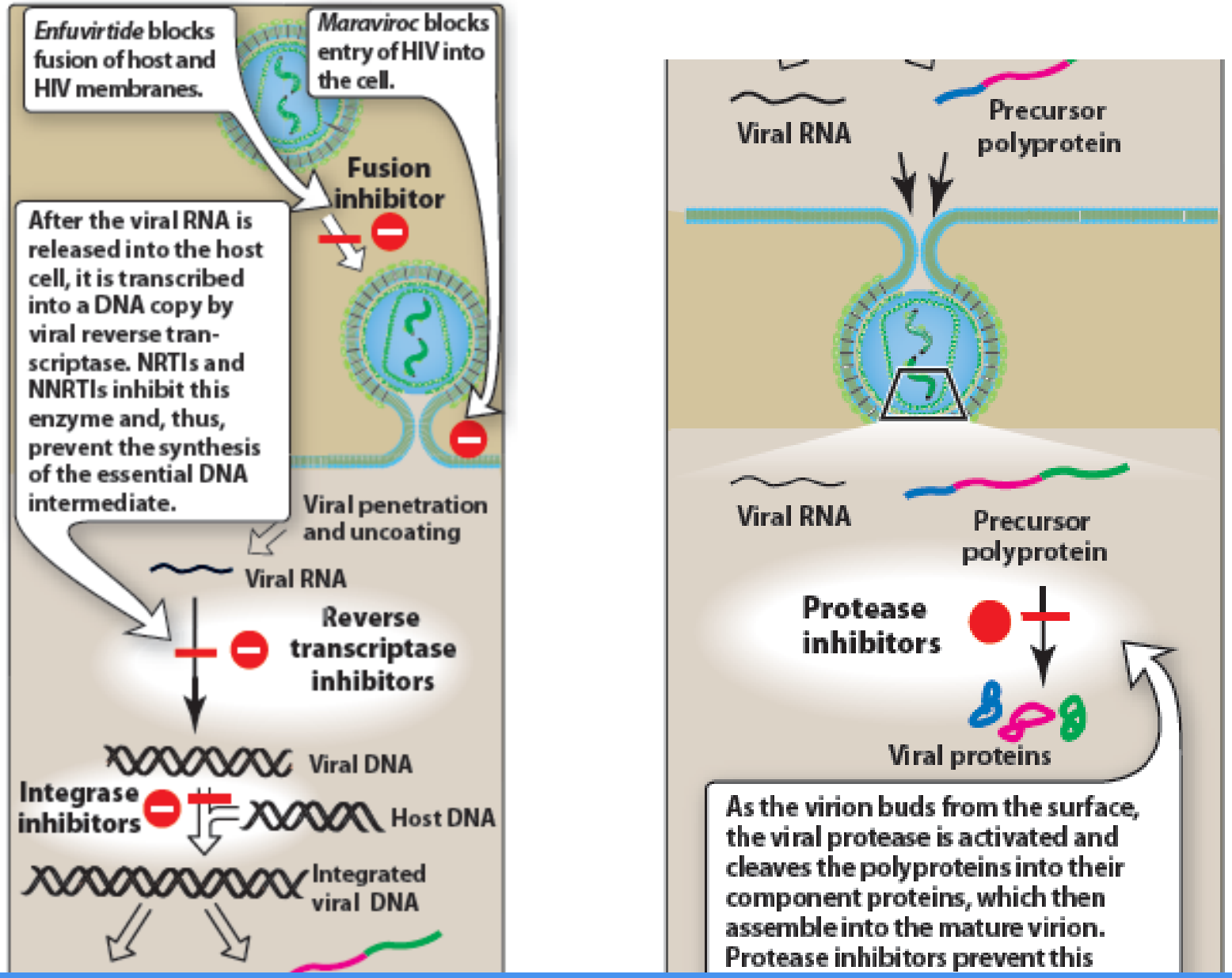
ANTIRETROVIRAL AGENTS



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ANTIRETROVIRAL AGENTS

1. **Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)**
2. **Nonnucleoside reverse transcriptase inhibitors (NNRTIs)**
3. **Protease inhibitors (PIs)**
4. **CCR5 receptor antagonists**
5. **Fusion inhibitors**
6. **Integrase inhibitors:** raltegravir.

TABLE 49–2 Major antiretroviral drugs.

Subclass	Prototype (مثال للمجموعة)	Other Significant Agents
Nucleoside reverse transcriptase inhibitors	Zidovudine	Abacavir, didanosine, emtricitabine, lamivudine, stavudine, zalcitabine, zidovudine
Nonnucleoside reverse transcriptase inhibitors	Delavirdine	Efavirenz, etravirine, nevirapine, tenofovir
Protease inhibitors	Indinavir	Amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
CCR-5 antagonist	Maraviroc	
Fusion inhibitor	Enfuvirtide	

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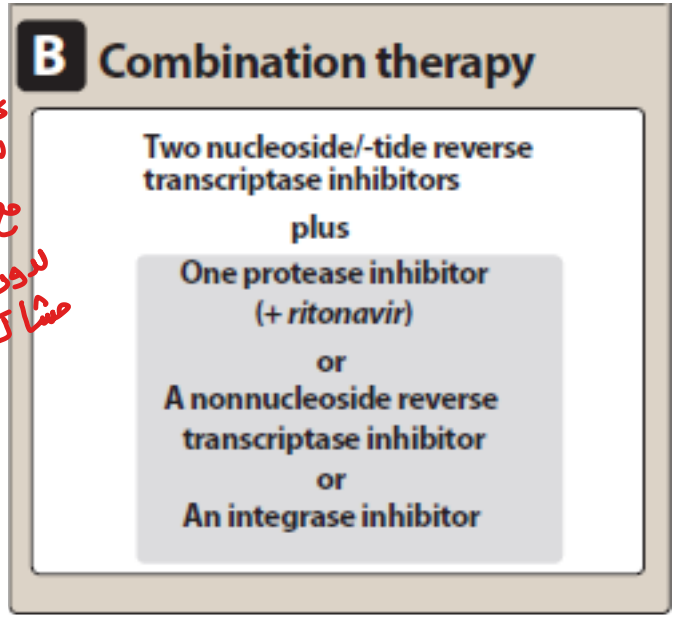
ANTIRETROVIRAL AGENTS

Administration of combination antiretroviral therapy, typically including at least three antiretroviral agents has become the standard of care (based on potency, susceptibility and tolerability).



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NRTIs

- NRTIs are considered the "backbone" of antiretroviral therapy and are generally used in combination with other classes of agents, such as an NNRTI, PI, or integrase inhibitor.

- NRTIs are usually given in pairs, and many are available as coformulations in order to decrease pill burden and improve adherence.
- However, certain NRTI combinations should be avoided, due to either:

1. Drug-drug interactions (eg, didanosine plus tenofovir),
2. Similar resistance patterns (eg, lamivudine plus emtricitabine) or
3. Overlapping toxicities (eg, stavudine plus didanosine).

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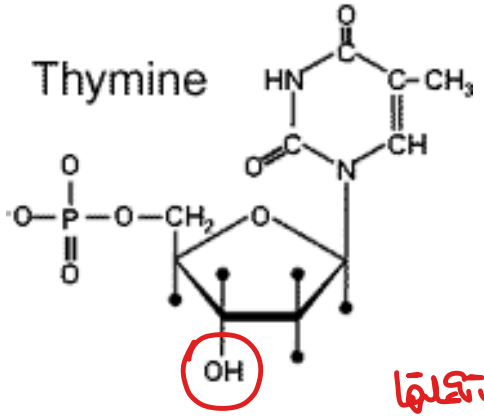
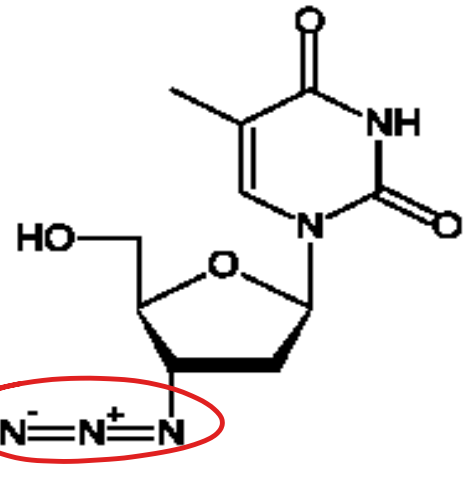
NRTIs

- NRTIs are analogs of native ribosides, which <u>all lack a 3'-hydroxyl group</u>.





Zidovudine (3'-Azido-3'Deoxythymidine ,AZT)
Approved in 1987, the first agent available for treatment of HIV infection

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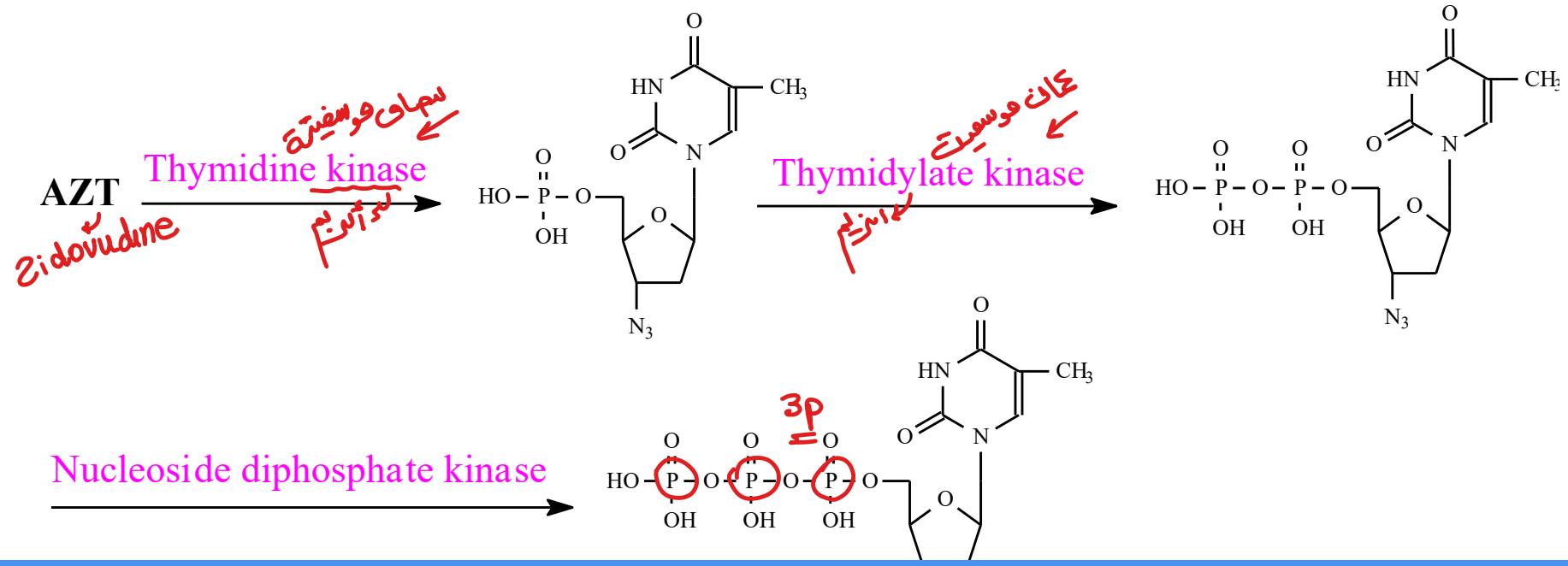
NRTIs

- **MOA:**
- Once they enter cells, they are phosphorylated by a variety of cellular enzymes to the corresponding triphosphate analog, which is preferentially incorporated into the viral DNA by virus reverse transcriptase.



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NRTIs

- **MOA:**
- The NRTIs act by competitive inhibition of HIV-1 reverse transcriptase and incorporation into the growing viral DNA chain causes premature chain termination due to inhibition of binding with the incoming nucleotide (because the 3'-hydroxyl group is not present, a 3'-5'-phosphodiester bond between an incoming nucleoside triphosphate and the growing DNA chain cannot be formed)

- **Resistance:**
- Mutation in the viral reverse transcriptase.

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NRTIs

- **Pharmacokinetics:**
- The NRTIs are primarily renally excreted, and all require dosage adjustment in renal insufficiency except *abacavir,* which is metabolized by alcohol dehydrogenase and glucuronyl transferase.

- **Drug interactions:**
- Due to the renal excretion of the NRTIs, there are not many drug interactions encountered with these agents (compared to NNRTIs)

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NRTIs

- **Adverse effects**:
- due to inhibition of the mitochondrial DNA polymerase in certain tissues.
- The dideoxynucleosides, such as zalcitabine, didanosine, and stavudine, have a greater affinity for the mitochondrial DNA polymerase, leading to such toxicities as **peripheral neuropathy, pancreatitis, and lipoatrophy**. (When more than one NRTI is given, care is taken not to have overlapping toxicities).
- All of the NRTIs have been associated with a potentially fatal liver toxicity characterized by lactic acidosis and hepatomegaly with steatosis.

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NNRTIs

Nonnucleoside reverse transcriptase inhibitors:

- *Delavirdine*
- *Efavirenz*
- *Etravirine*
- *Nevirapine*

- **MOA:**
- The NNRTIs bind directly to HIV-1 reverse transcriptase and inhibit its activity.
- The binding site of NNRTIs is near to but distinct from that of NRTIs. Unlike the NRTI agents, NNRTIs neither compete with nucleoside triphosphates nor require phosphorylation to be active.

- **Resistance:**
- Mutation in reverse transcriptase.
- However, there is no cross-resistance between the NNRTIs and the NRTIs; in fact, some nucleoside-resistant viruses display hypersusceptibility to NNRTIs.

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NNRTIs

Nonnucleoside reverse transcriptase inhibitors:

- *Delavirdine*
- *Efavirenz*
- *Etravirine*
- *Nevirapine*

- **Adverse Effects:**
- gastrointestinal intolerance and skin rash.

- **Drug interactions:**
- A limitation to use of NNRTI agents as a component of antiretroviral therapy is their metabolism by the CYP450 system, leading to innumerable potential drug-drug interactions.
- All NNRTI agents are substrates for CYP3A4 and can act as:
- inducers (nevirapine)
- inhibitors (delavirdine)
- or
- mixed inducers and inhibitors (efavirenz, etravirine).

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Protease inhibitors

- Amprenavir
- Atazanavir
- Darunavir
- Fosamprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

- The resistance to the RT led to target the HIV protease
- HIV requires specific protease to generate essential structural proteins of the mature virion core as well as RT itself.
- This enzyme is essential for the final step of viral proliferation

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Protease inhibitors

- **Adverse effects:**
- As a class, PIs are associated with mild-to-moderate nausea, diarrhea, and dyslipidemia. A syndrome of redistribution and accumulation of body fat that results in central obesity, dorsocervical fat enlargement (buffalo hump), peripheral and facial wasting, breast enlargement, and a cushingoid appearance has been observed.
- **Drug interactions:**
- Drug interactions are a common problem for all protease inhibitors, because they are not only substrates but also potent inhibitors of CYP isozymes.

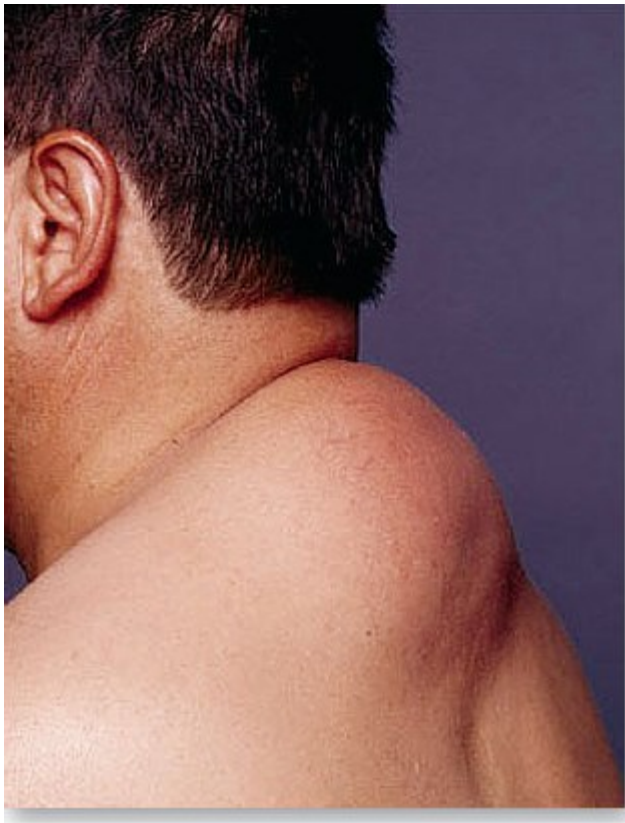

Figure 38.29
Accumulation of fat at the base of the neck in a patient receiving a protease inhibitor.

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- The inhibitory potency of the compounds lies between that of **ritonavir**, the most potent inhibitor, and that of **saquinavir**, the least potent inhibitor of CYP isoenzymes.

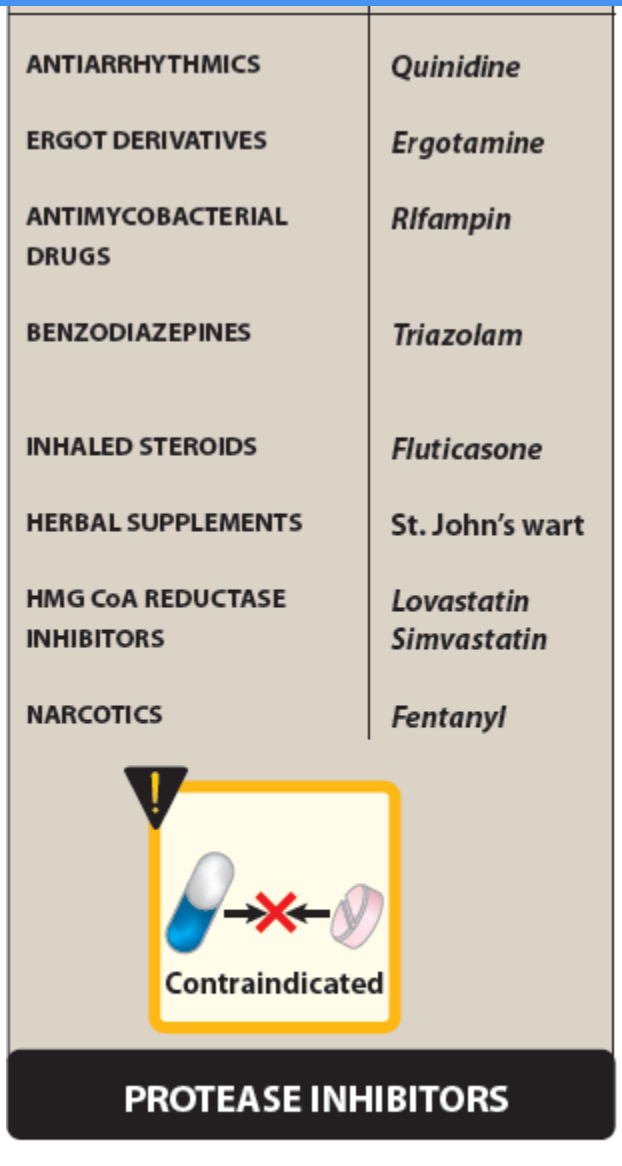

Figure 38.30
Drugs that should not be

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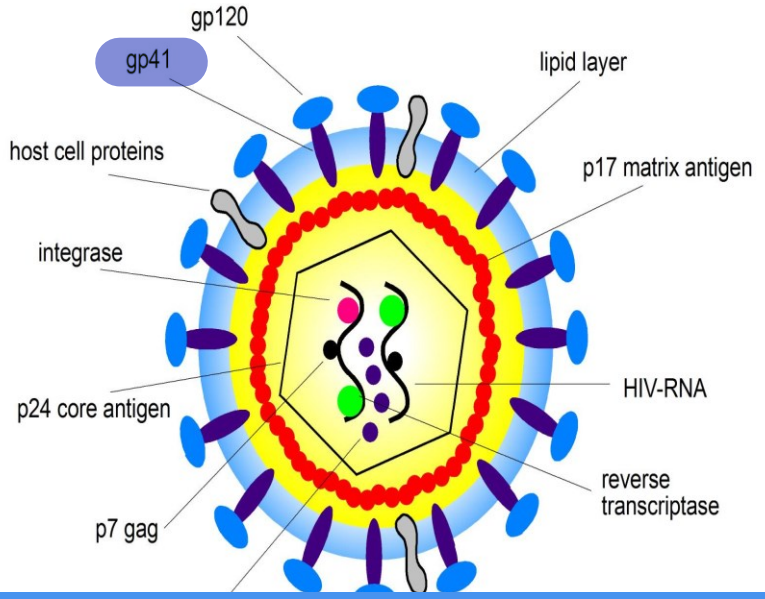
Fusion inhibitor

Enfuvirtide is a 36-amino-acid peptide that binds to the viral transmembrane glycoprotein gp41, preventing viral fusion.

- As a peptide, it must be given subcutaneously.
- Most of the adverse effects are related to the injection, including pain, erythema, induration, and nodules, which occur in almost all patients.



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CCR5 receptor antagonists

Maraviroc

- Because it is well absorbed orally, it is formulated as an oral tablet.
- Maraviroc blocks the CCR5 co-receptor that works together with gp41 to facilitate HIV entry through the membrane into the cell.
- Maraviroc is generally well tolerated.

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Integrase Inhibitor

- **Raltegravir** specifically inhibits the final step in integration of the viral DNA into host cell DNA.
- The route of metabolism is UGT1A1-mediated glucuronidation and, therefore, drug interactions with CYP450 inducers, inhibitors, or substrates do not occur.
- Raltegravir is well tolerated, with nausea, headache, and diarrhea as the most common side effects. More serious side effects reported include elevated CK (creatine kinase) with muscle pain and rhabdomyolysis.

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The End

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