Antivirals

Pharmacology 3

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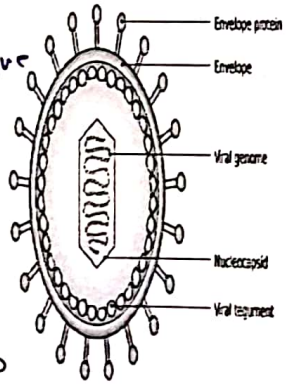
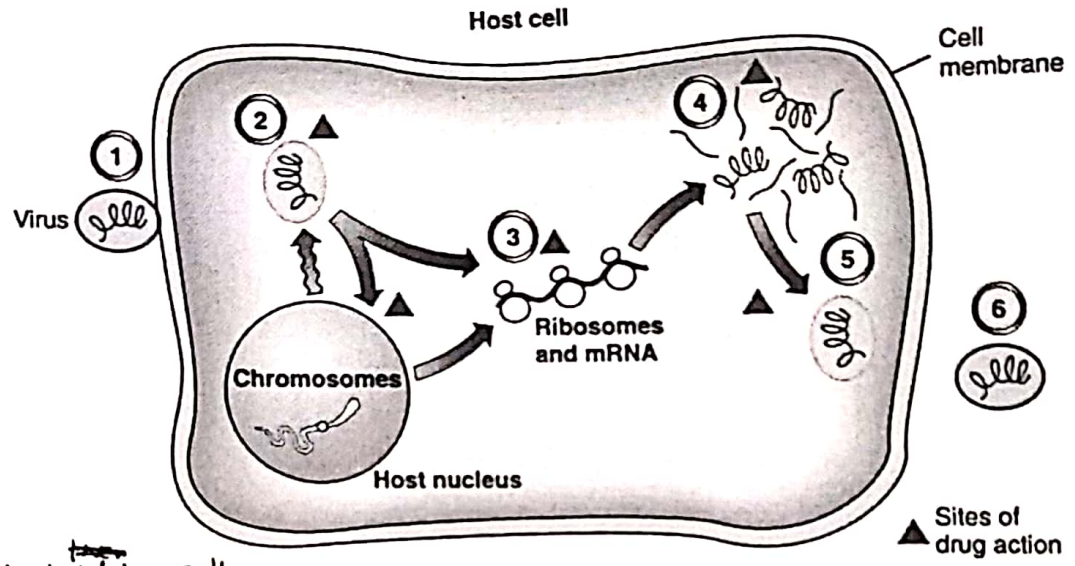
Overview

- Viruses are obligate intracellular parasites. They lack both a cell wall and a cell membrane, and they do not carry out metabolic processes.
- A virus cannot replicate on its own
- It must attach to and enter a host cell
- It then uses the host cell's energy to synthesize protein, DNA, and RNA





1. Attachment to host cell
2. Uncoating of virus, and entry of viral nucleic acid into host cell nucleus
3. Control of DNA, RNA, and/or protein production
4. Production of viral subunits
5. Assembly of virions
6. Release of virions

(Modified from Brody TM, Larner J, Minneman KP. Human pharmacology: molecular to clinical, ed 3. St Louis, 1998, Mosby.)

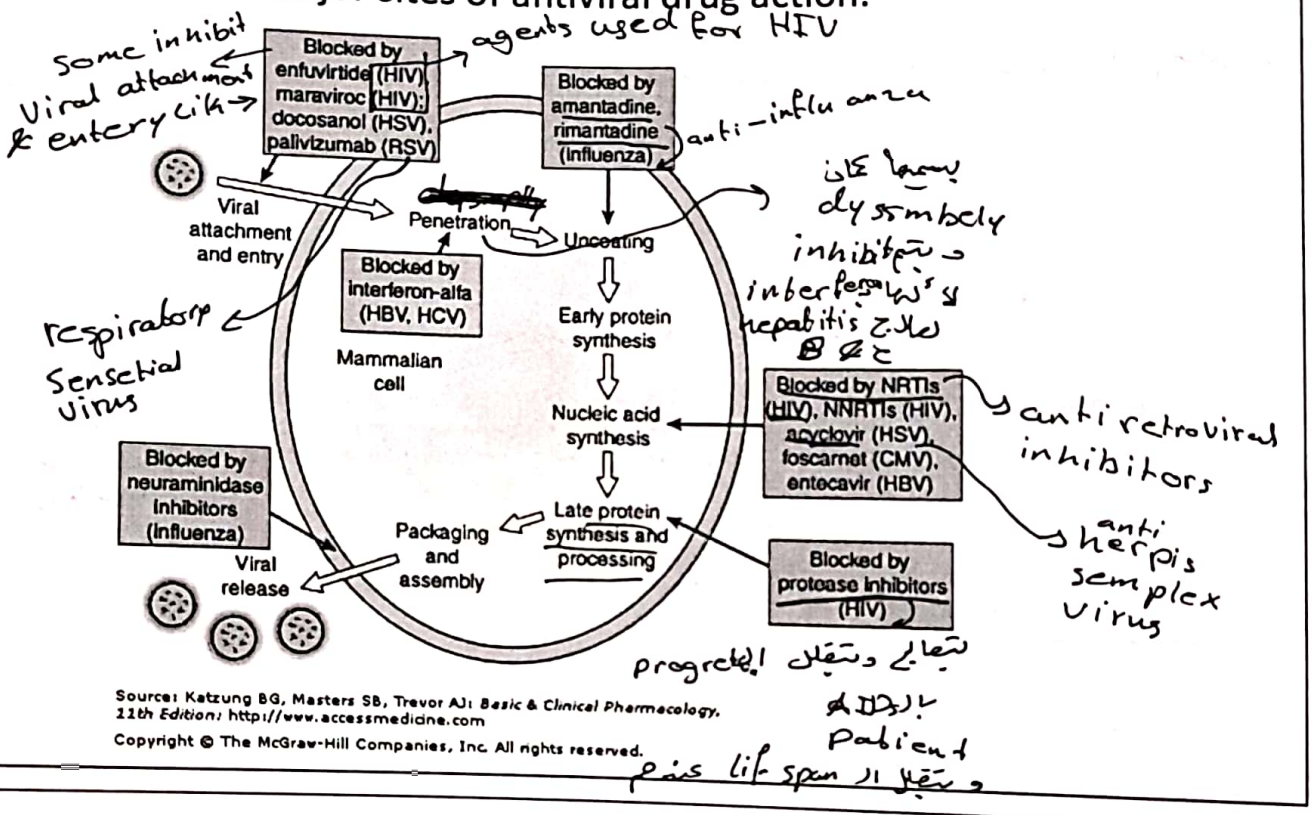
Fig. 39-1. Virus replication. Some viruses integrate into host chromosome with development of latency.

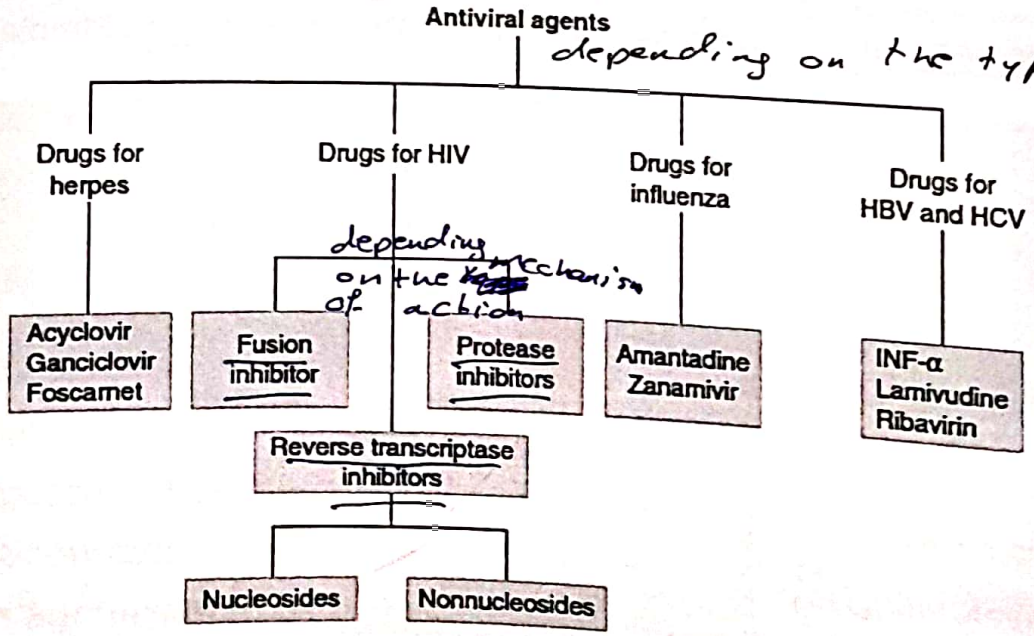
- **Stages of viral replication**

(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 → depend on the type of virus
(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.

الأسماء بالترجمة هو مطلوب بيّ الا إذا مرلعة ام بالسلايد





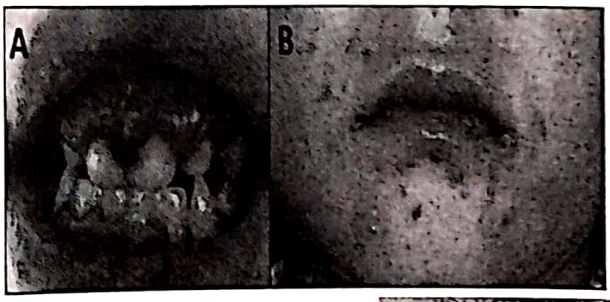
Key characteristics of antiviral drugs

- Able to enter the cells infected with virus.
- Interfere with viral nucleic acid synthesis and/or regulation.
- Some drugs interfere with ability of virus to bind to cells.
- Some drugs stimulate the body's immune system.

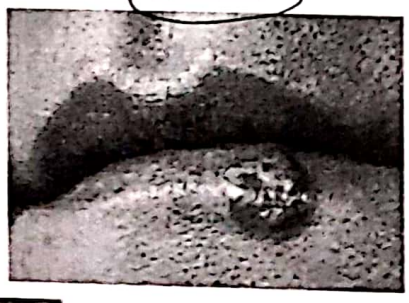
- Best responses to antiviral drugs are in patients with competent immune systems.
- A healthy immune system works synergistically with the drug to eliminate or suppress viral activity.

Herpes virus Infections

Acute primary herpetic gingivostomatitis (APHG).



Recurrent Herpes Simplex Labialis



Ophthalmic shingles

Herpes Zoster (shingles)

Varicella (Chickenpox)

herpes family

TREATMENT OF HERPESVIRUS INFECTIONS

- Acyclovir → means active against virus
- is the prototypic antiherpetic therapeutic agent .
- acyclovir contained in the drug stops the replication of herpes viral DNA.
- Acyclovir is used to treat infections caused by herpes viruses, such as genital herpes, cold sores, shingles, and chickenpox.
- HSV types 1 & 2, VZV & some Epstein-Barr virus infections are sensitive to acyclovir.

herpes simplex — varicella zoster — it is used to treat (dermatological + genital herpes)

- It is the treatment of choice in HSV encephalitis.
- The most common use of acyclovir is in therapy for genital herpes infections.

Acyclovir is administered by IV, oral, or topical routes.

brain tissue

meningis

- High doses effective for adults (shingles) herpes zoster and children (chickenpox) if begun within 24 hours of rash.
- Intravenous acyclovir is the treatment of choice for herpes simplex encephalitis, neonatal HSV infection, and serious HSV or VZV infections
- In immunocompromised patients with VZV infection, intravenous acyclovir reduces the incidence of cutaneous and visceral dissemination.
- ADEs depends on the route of administration:
  - **Oral administration:** NVD and headache
  - **Topical administration:** local irritation

TREATMENT OF HERPESVIRUS INFECTIONS

➢ Ganciclovir : is an analog of acyclovir that has greater activity against CMV.

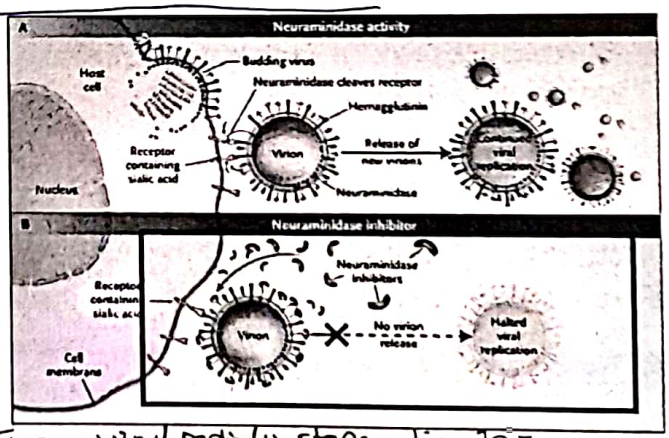
- It is used for the treatment retinitis in immunocompromised patients and for CMV prophylaxis in transplant
- Ganciclovir is carcinogenic as well as embryotoxic and teratogenic in experimental animals

TREATMENT OF RESPIRATORY VIRAL INFECTIONS

- **Viral respiratory tract infections** for which treatments exist include those of influenza A and B and respiratory syncytial virus (RSV) (Respiratory syncytial virus (RSV) causes infection of the lungs and respiratory tract. It's so common that most children have been infected with the virus by age 2. it can also infect adults)
- **Influenza is caused by RNA viruses.**
- **Influenza virus strains are classified** by their core proteins (ie, A, B, or C), species of origin (eg, avian, swine), and geographic site of isolation

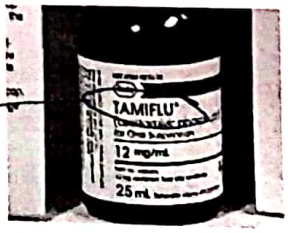
TREATMENT OF RESPIRATORY VIRAL INFECTIONS

Sialic acid analogues
Agents: Oseltamivir & Zanamivir
Active against both **type A & Type B influenza viruses**



MOA: *Oseltamivir* and *zanamivir* selectively inhibit neuraminidase, thereby preventing the release of new virions and their spread from cell to cell.

Early administration is crucial (within the first 24 to 48hrs after the onset of the infection)

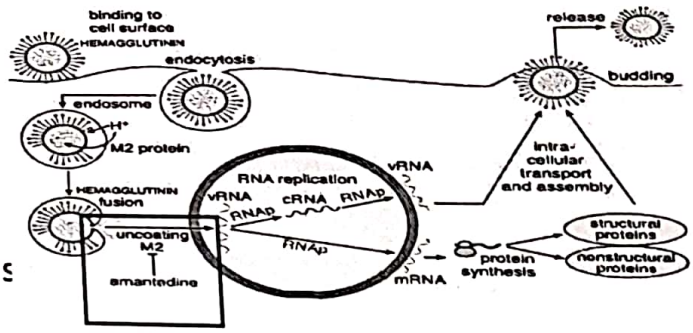


* neuroamidinase الي بصير عليها تغيرات و طفرات اعتماداً ← influenza A هي
الي موجود فيها و اعتماداً على الـ NH و aminoglutin برضه الموجود
(بصرلها subtypes) فيها دبل (H_2N_9) ≠ (H1N1)

TREATMENT OF RESPIRATORY VIRAL INFECTIONS

عكس الي قبل هاد شغال بس على influenza A

- **Amantadine and Rimantadine**
- Are limited to influenza A infections.
- **Mechanism of action:** *Amantadine* and *rimantadine* interfere with the function of the viral M2 protein, possibly blocking uncoating of the virus particle and preventing viral release within infected cells
- are **effective for the prevention and treatment of influenza A virus infections**



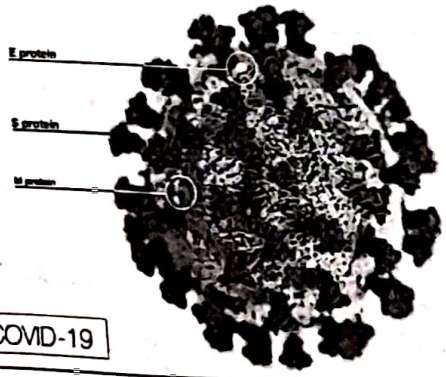
- *Amantadine* distributes throughout the body and readily penetrates into the central nervous system (CNS)

مطلوب تفرق، حيث بتكون طلعته من جوا بدكو انه → increases dopamine release & prevents dopamine reuptake

يعني بيشتغل على الـ parkinson

COVID-19

- ➢ An outbreak of respiratory disease caused by a novel (new) coronavirus that was first detected in China and which has now been detected globally (internationally).
- ➢ The virus has been named "SARS-CoV-2" and the disease it causes has been named "coronavirus disease 2019" (abbreviated "COVID-19").
- ➢ World Health Organization declared the outbreak a "public health emergency of international concern



antibacterial مثل azithromycin و ivermictin (their anti-inflammatory effect بسبب action الي بعمل ا) + other medications + Vitamins بعالج عادة

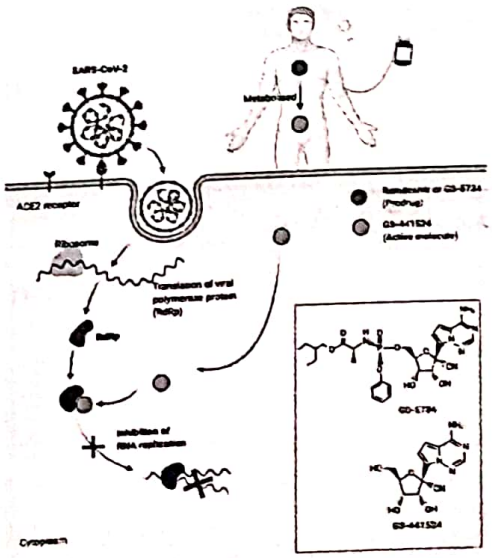
Antivirals for COVID-19

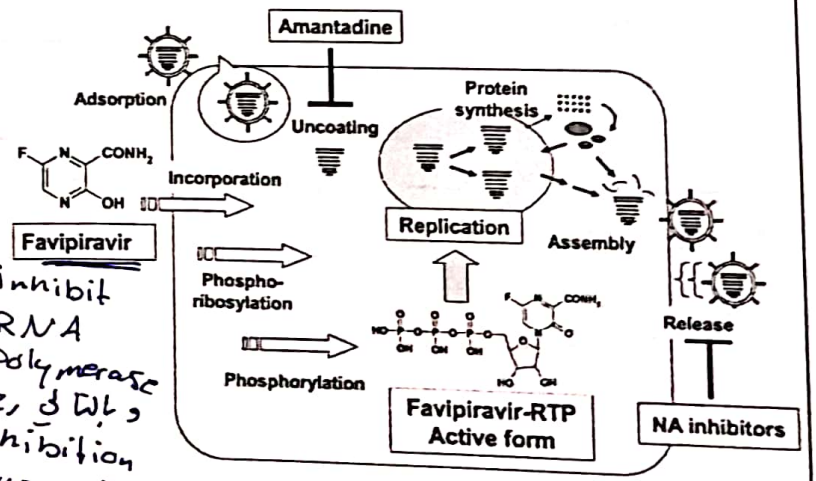
- **Remdesivir** — Remdesivir is a novel nucleotide analog that has in vitro activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
- **Favipiravir** → sancover — is an RNA polymerase inhibitor → as prodrug available in some countries in Asia (including India and Russia) for treatment of non-severe COVID-19.
- **Paxlovid** → givin orally → antiviral وهو عبارة عن ritonavir مع — is a combination of Pfizer's investigational antiviral PF-07321332 and a low dose of ritonavir, an antiretroviral medication traditionally used to treat HIV. The treatment disrupts the replication of SARS-CoV-2 in the body by binding to the 3CL-like protease, an enzyme crucial to the virus' function and reproduction. اليهو بيستخدم لـ AIDS

inhibit the synthesis & replication of viral RNA

Antivirals for COVID-19

activation يعني prodrug موجود

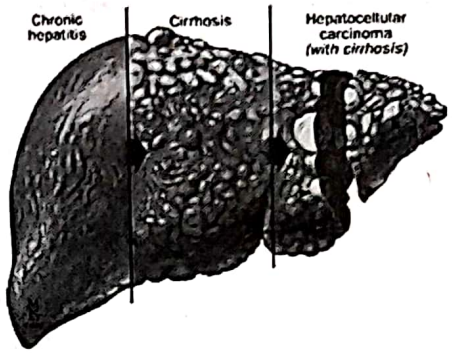


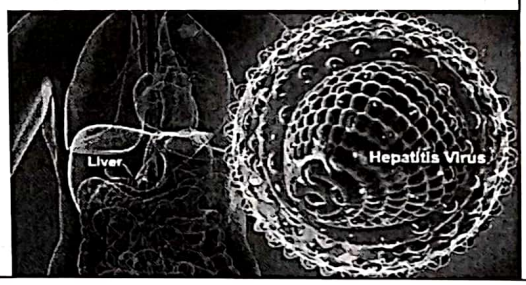


inhibit RNA Polymerase يعني بمنع inhibition virus لـ Protein

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.





TREATMENT OF HEPATIC VIRAL INFECTIONS

- **Most cases of acute hepatitis are due to viral infections**
- hepatitis **B and hepatitis C** are the most common causes of **chronic hepatitis, cirrhosis, and hepatocellular carcinoma**
- Chronic hepatitis **B** is usually treated with interferon alfa. Oral therapy includes lamivudine, adefovir, enetecavir, or telbivudine
- Treatment of chronic **hepatitis C**, the preferred treatment is the combination of **interferon-α plus ribavirin**

Interferon alfa

↳ are endogenes & can be produced in our body and have a role to attack viruses → جسمك بتصنعهم وعندها دور تهاجم بيهم الفيروسات

- Interferons are host cytokines that exert complex antiviral, immunomodulatory, and antiproliferative activities
- **Synthesized by recombinant DNA technology**
- **Interferon (IFN)-alfa appears to function by:** inhibit viral replicabion cycle
  1. Induction of intracellular signals resulting in **inhibition of viral penetration, translation, transcription, protein processing, maturation, and release**
  2. Enhanced **phagocytic activity of macrophages** they help in the servivour of T-Cells
  3. Augmentation of the proliferation and survival of cytotoxic T cells.

Not active orally. Administered SC or IM

Subcoutonsilly — intramuscularly

* الانترفيرون دوره مهم بالـ cellular defense mechanism

Lamivudine → can be given orally

- Cytosine analog that must be phosphorylated by host cellular enzymes to the triphosphate (active) form
- **MOA:** Competitively inhibits HBV DNA polymerase at concentrations that have negligible effects on host DNA polymerase. يعني الدوز لدرجة قاتلة كالايدز
- ADEs: well tolerated with rare occurrences of headache and dizziness

ممكن كثير بكنت عليهم

* عايزين DNA عشان يعملوا DNA جديد (DNA polymerase enzyme) synthesis or replication

دوا جديد ← new nucleic acid bases addition

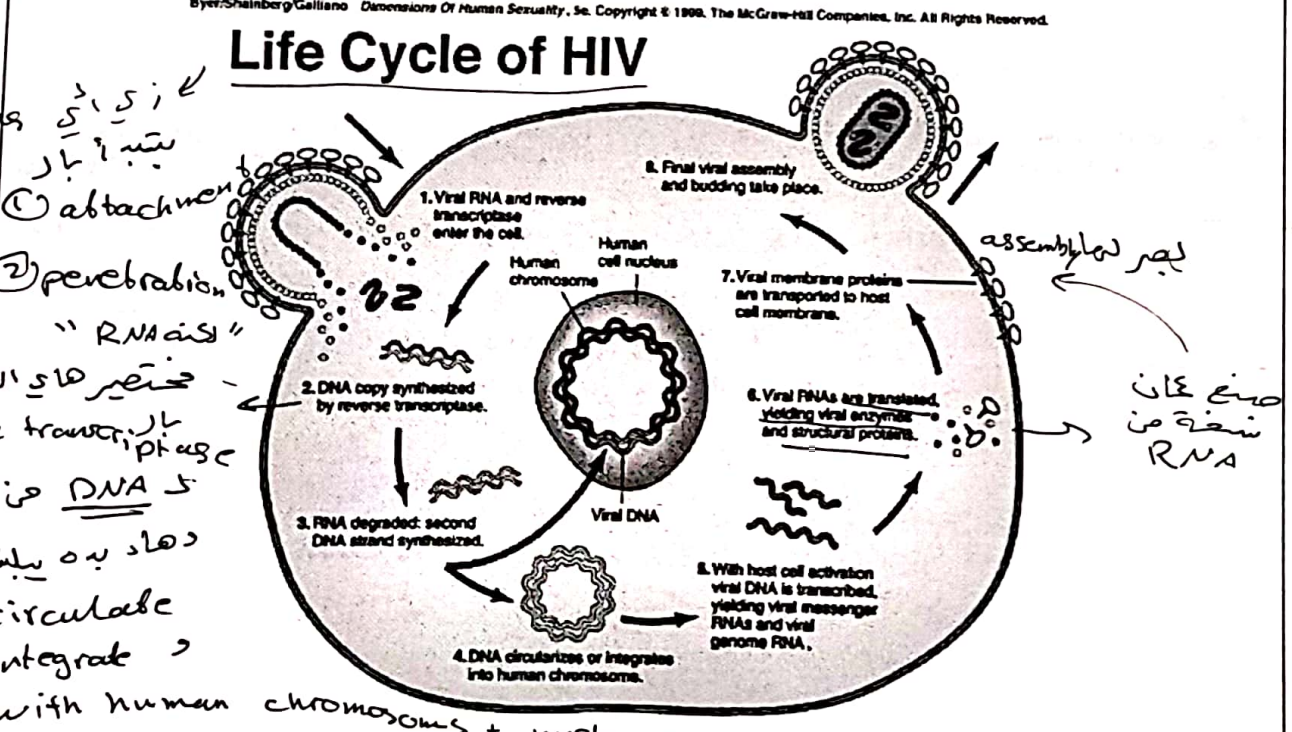
synthesis

Antiviral Drugs (Against HIV)

- RNA retroviruses "HIV" وهو مرض نقص المناعة المكتسبة → وهي فيه HIV 1 & 2 — يعالج
  contain an enzyme(reverse transcriptase)
  making a DNA copy of viral RNA which then enter the nucleus and is integrated into host DNA (genes) and direct the generation of new viruses.

RNA فيه كيرسمة step ← its Component يصنع عالخلية وحتى يبدأ
لازم RNA يتحول لـ DNA وال DNA هاد بده يسيطر
على ال nucleus تبعت الخلية الاساسية ليبدأ تصنعه
ال viral protein وهو بدو enzyme كيرسم الي صو

"reverse transcriptase" → RNA الي بدو لـ DNA
بيلبس الفيروس الي بعدها



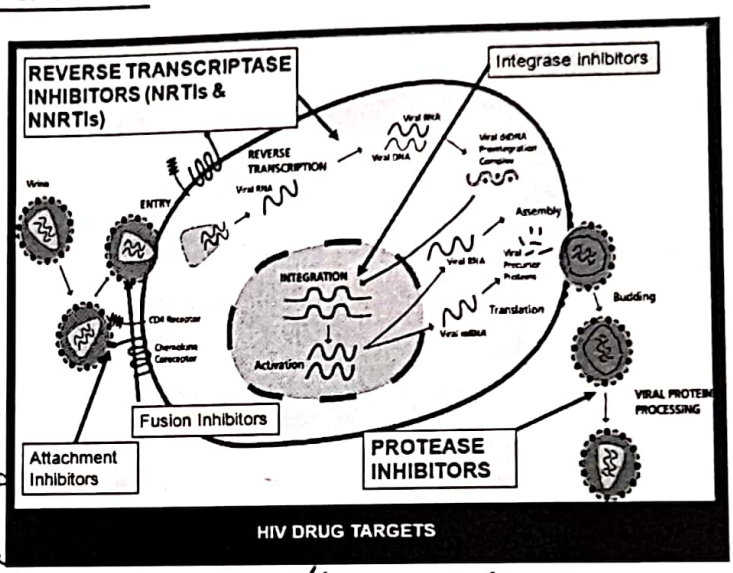
virus زي اللي
بتبين بالا
① attachment
② penetration
" RNA بدخل "
بختصر هاي العملية
reverse transcriptase
RNA. من DNA
دهاد بده يلبس
to circulate
integrate
with human chromosomes + nucleus and giving order to synthesis its particle

assembly يصير هنا

صنع عدان
نسخة من
RNA

Inhibitors of HIV Replication

- A: Nucleoside reverse transcriptase inhibitors(NRTI).
- B: Non- nucleoside reverse transcriptase inhibitors(NNRTI).
- C: Protease inhibitors(PI).
- D:Integrase inhibitors
- E: Entry inhibitors (fusion inhibitors)



+ reverse transcriptase inhibitors (Crabe Limiting step) + fusion inhibitors + attachment inhibitors

عادة بنستخدم 2(NRTI) with(PI)

resistance ↗ بقلل ← (combination بنستخدم) single anti-retroviral عادة بالعلاج ما بنستخدم

TT of AIDS with antivirals:

i. Delay in onset of the disease and death. + increas life span of patient

ii. Improvement in markers of TT outcome as CD4-positive T lymphocyte

1 or 2 agents have been associated with:

- High rate of disease progression.
- Viral resistance.

- Three or more drugs are now used, usually:

2NRTIs + one PI or one NNRTI.

at least → بنستخدم 3 أدوية

Antiretroviral Drugs

HAART - Highly active antiretroviral therapy

هاد اللي بحبوه يدرسوه

- Includes **at least three medications**
  - "cocktails"

- These **medications work in different ways to reduce the viral load**

with diffrent mechanisims to affect the virus in diffrent steps

Anti-AIDs Combination

medication كيف بيختار

1) avoiding the use of two agents of the same nucleoside analog.

يعني ما استخدم cytosin analog مع cytosin analog

2) avoiding overlapping toxicities and genotypic and phenotypic characteristics of the virus.

يعني لو واحد عنده nephrotoxicity لازم اتاني مايكون عنده

3) patient factors, such as disease symptoms and concurrent illnesses.

4) impact of drug interactions.

5) ease of adherence to the regimen.

+ renal + hepatic function + drug-drug interactions

The goals of therapy are to maximally and durably suppress HIV RNA replication, to restore and preserve immunologic function, to reduce HIV-related morbidity and mortality, and to improve quality of life.

active ليه؟ phosphorable nucleotide + nucleoside ← * في فرق بين
Base
↳ S - purin
S - Pyrimidin

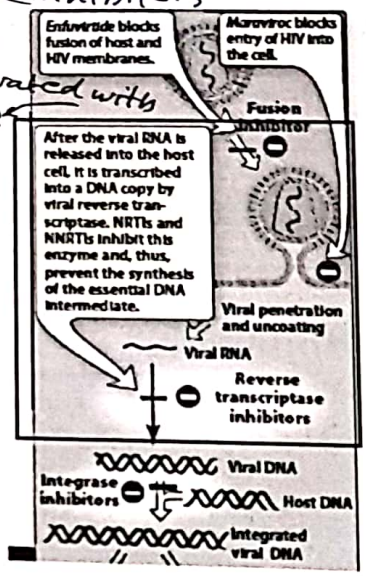
NRTIs (nucleoside- reversed transcriptase inhibitors)

↳ they are not activated they need to be activated with

- They are activated intracellularly by cellular kinase
- The triphosphate forms competitively inhibit RT.
- Incorporated into HIV DNA → chain termination
- More selective to RT than cellular polymerase

virus DNA ← termination

reverse transcriptase



NRTIs

Drug	Elimination	Main ADRs
Zidovudine (T)	H&R (hepatic + renal)	BM suppression → bone marrow suppression
Zalcitabine (C)	R (kidney)	Neuropathy and stomatitis

Zidovudine (T) ← analog of thymidine base

Zalcitabine (C) → analog of cytosin

NNRTIs non-nucleoside

intracellular activation داخل الخلية → by kinase enzymes
Phosphorylation فسفرة

- They are potent inhibitors of HIV-1 RT.
- They do not need IC phosphorelation → intracellular
- RT mutation produces cross resistance to all NNRTIs.

resistance يعني اذا عنده حتى واحد مشكلة حتى باقي

NNRTIs

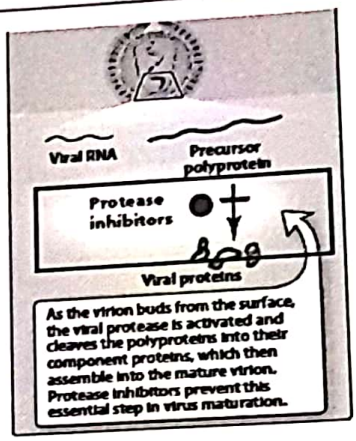
Drug	Main ADRs
Nevirapine* (tab)	Skin rash & hepatitis
Delavirdine (tab)	Skin rash

orally active

Vir فيروس

PIs proteases inhibitors وهو النوع اللي عملت منه فايرز دوا الكورونا

- Reversible inhibitors of HIV1 & 2 protease
  inhibit synthesis of viral proteins
- They do not need IC activation
  they are active
- Marked resistance develops easily, if they are used alone.
  alone لا يستخدمو
- Combination with NRTIs → additive effect and decrease resistance
- Example: Ritonavir (caps)



Antiretroviral Drugs

- **Fusion inhibitors** → وهي الأول step
  تمنع دخول الخلايا
  - Inhibit viral fusion, preventing viral replication
  - Example: enfuvirtide