Antimicrobial therapy for Sexually transmitted diseases (STD)

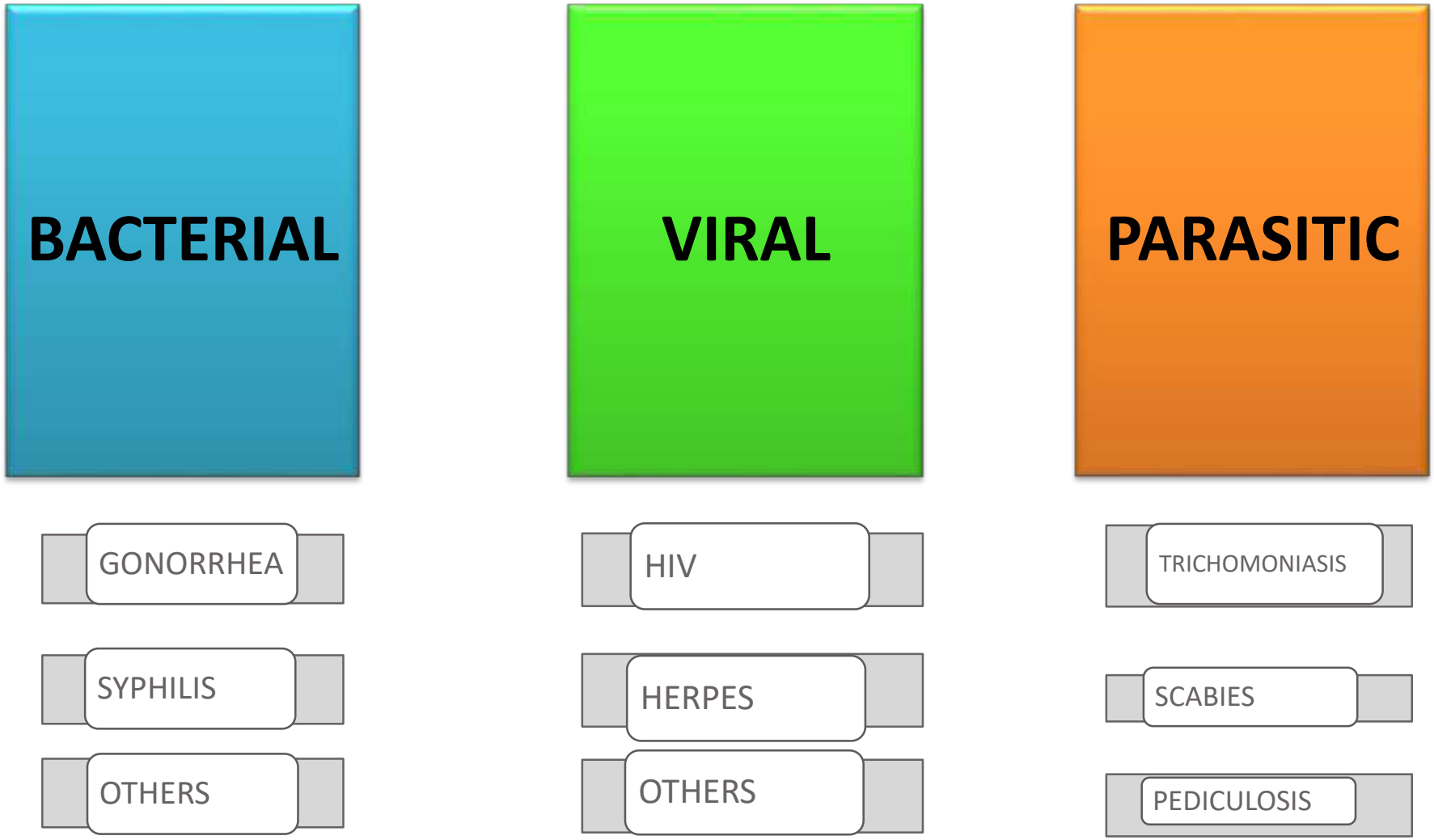
❌ dose
✅ duration
✅ MOA (most important)

Dr/ Heba Ahmed Hassan

nt professor of clinical pharmacology,
faculty of medicine, mutah university

Definition and classification

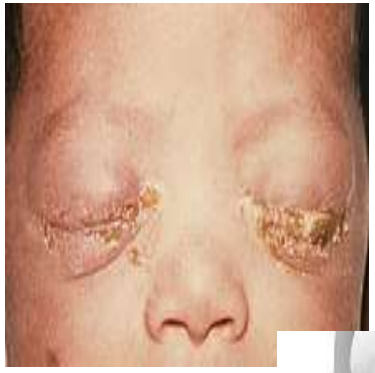
Diseases that are transmitted **MAINLY** by sexual contact



Gonorrhea Urethritis

genital - track inf.

- **Causative agent:-** Neisseria gonorrhoeae (G-)
- **Symptoms and Signs:-**



Asymptomatic (10-20%)

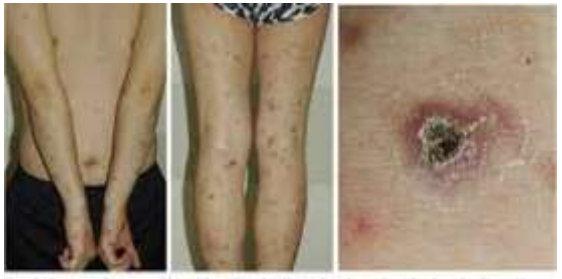
1. Male urethritis*
2. Female Cervicitis* and Urethritis
3. Ophthalmia neonatorum — transmitted during birth : give antibiotic to newborn & wash their eyes w/ saline

- **Complications**

1. Epididymitis and inflammations of urethral glands:-
   - Usually, epididymitis causes unilateral scrotal pain, tenderness, and swelling.
2. Pelvic inflammatory disease(PID) — mixed [aerobic] inf
   - It occurs in 10-20% of infected women.
3. Disseminated gonococcal infection (DGI)] very severe

Arthritis- dermatitis syndrome, bacteremia

Joint Skin blood



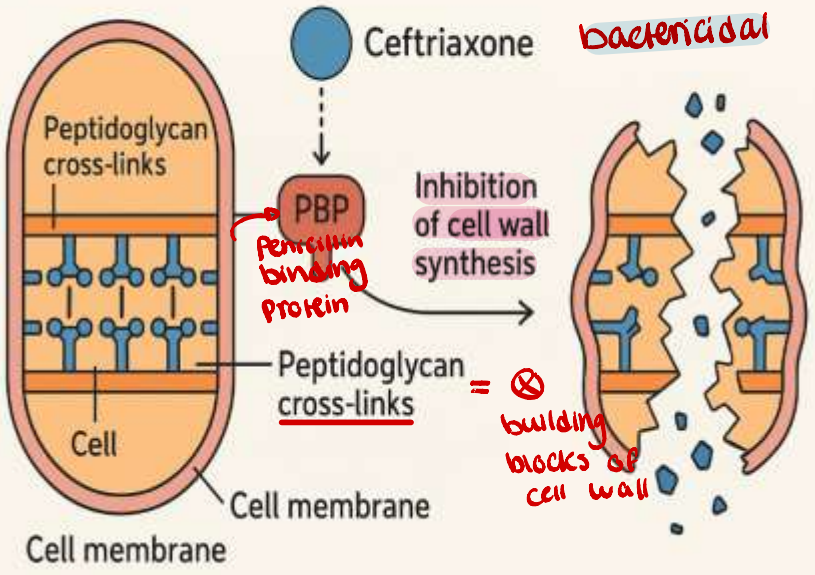
Presentation of infection	treatment
1. **Uncomplicated Gonococcal Infections**	Ceftriaxone or cefotaxime (IM) PLUS Azithromycin 1g orally in a single dose In the case of azithromycin allergy:- Doxycycline 100 mg orally twice a day for 7 days
2.Prophylactic measures to prevent ophthalmia neonatorum	All newborns are given one of these ttt:- • 0.5% erythromycin ointment. • 1% solution of silver nitrate or • 1% tetracycline ointment.
3.Treatment of complicated gonorrhea:- • **Gonococcal Conjunctivitis:-** • **Gonococcal Epididymitis:-** • **PID:-** • **DGI:-**	• (Single dose of ceftriaxone 1 g IM + Azithromycin 1 g PO with saline irrigation + Topical antibiotic solution). • (Single dose of ceftriaxone 250 mg IM.+ Doxycycline 100 mg orally twice daily for 10 days). • (Single dose of ceftriaxone 2 g IM+Doxycycline 100 mg orally twice daily for 14 days+With or without Metronidazole 500 mg PO twice daily for 14 days). • (Ceftriaxone 1 g IM/IV every 24 hours + Single dose of azithromycin 1 g PO)
Sex partners:-	❑All sex partners with sexual contact with patient within 60 days should be tested for gonorrhea & other STDs and treated if results are positive. ❑Sex partners with sexual contact within two weeks should be treated presumptively for gonorrhea

Standard for all cases

antibiotic prophylactic treatment

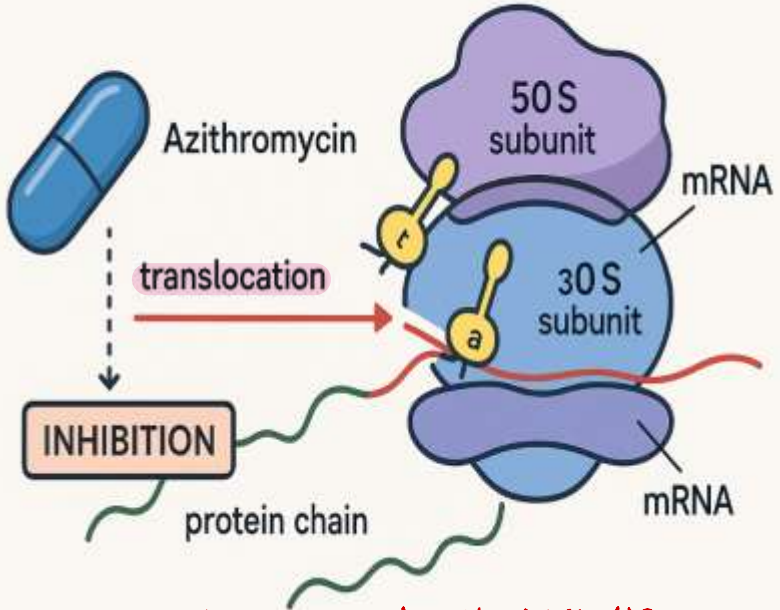
only diff is dose & duration

MECHANISM OF ACTION OF CEFTRIAXONE

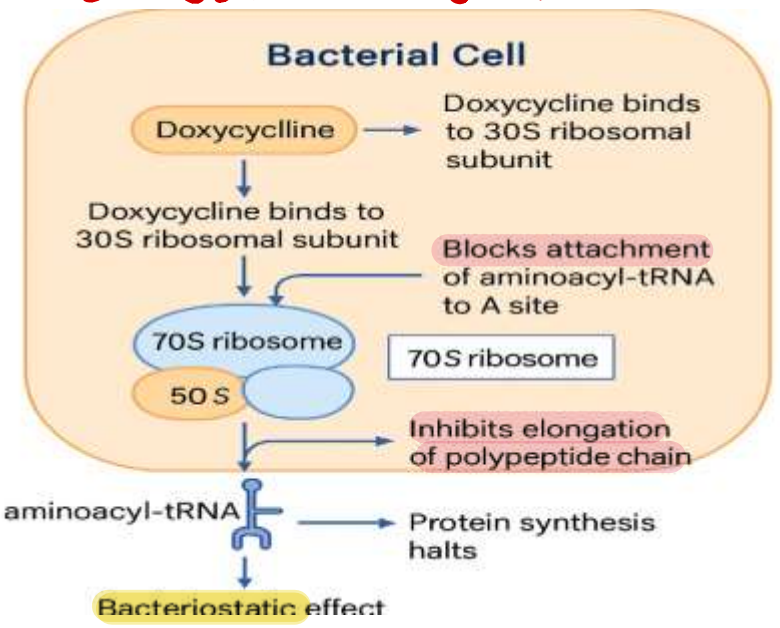


[كأنها حيط بدون داعمات، بتوقع بسرعة]

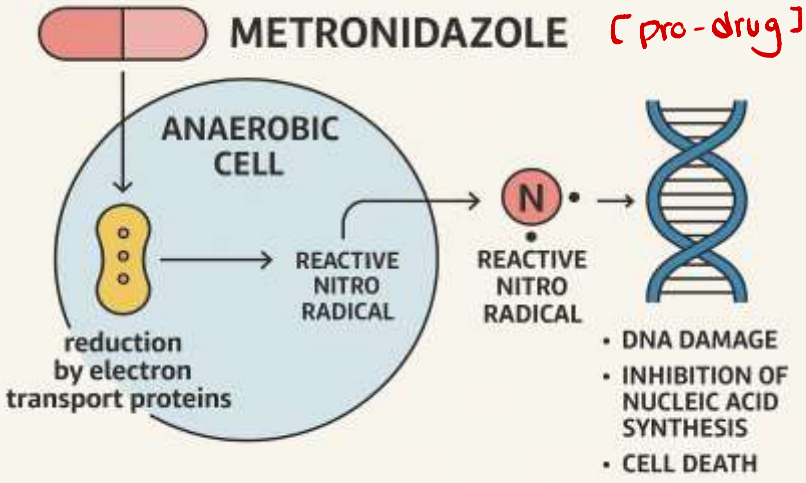
Azithromycin: Mechanism of Action



protein inhibitor, bacteriostatic



METRONIDAZOLE [pro-drug]



activated when oxidized in cell

NON-GONOCOCCAL URETHRITIS (NGU)

- NGU is much more common than gonococcal urethritis.
- The most common causes are:

1. **Bacterial infections:-**

Chlamydia trachomatis (most common).

2. Viral(rare):-

- Herpes simplex virus.

3. Parasitic(rare):-

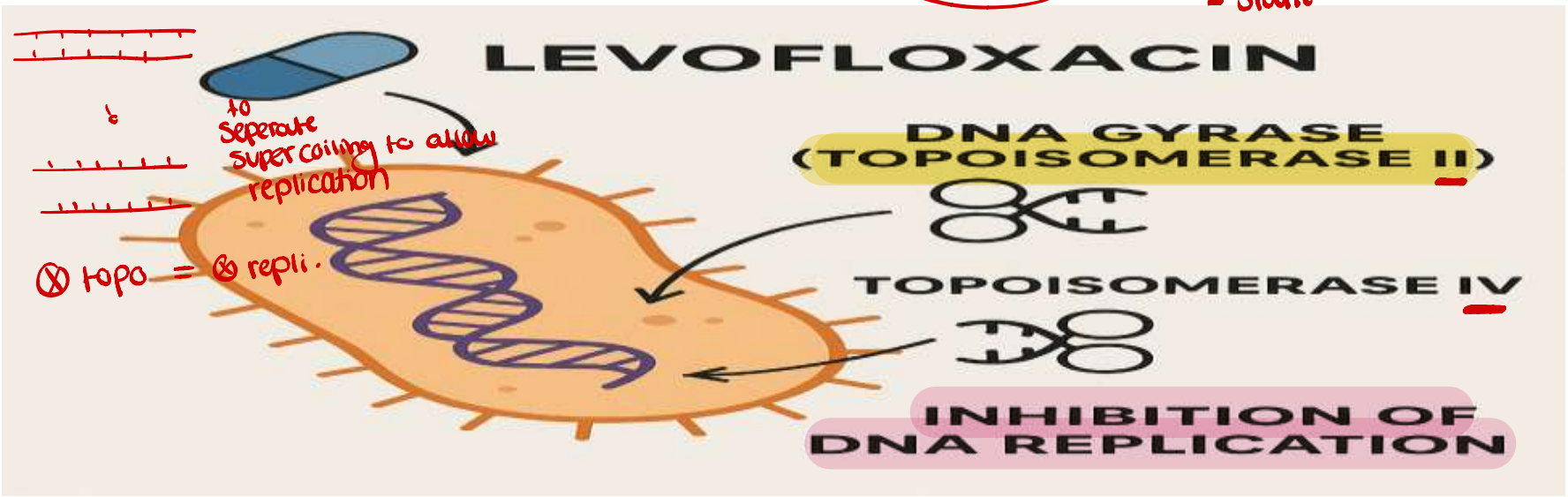
- Trichomonas vaginalis

4. **Non-infectious**

- Mechanical injury (from a urinary catheter or a cystoscope).

Chlamydial URETHRITIS

- **Treatment:-**
  - Azithromycin 1 g orally in a single dose OR
  - Doxycycline 100 mg orally twice a day for 7 days
- **Alternative Regimens**
  - Erythromycin 500 mg orally four times a day for 7 days OR
  - Levofloxacin 500 mg orally once daily for 7 days OR
  - Ofloxacin 300 mg orally twice a day for 7 days



Syphilis

all w/ Penicillin unless allergy !

- **Etiology:-**

Causative agent:- Spirochete Treponema pallidum (T. pallidum).

- **Classification:-**

1- Acquired syphilis

2- Congenital syphilis

1. Acquired syphilis :

Classified into 4 stages:-

A. Primary B. Secondary C. Tertiary D. Latent] depending on duration

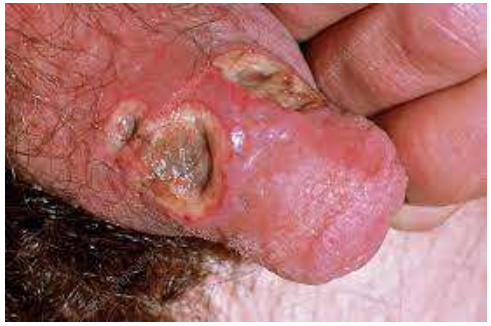
A. Acquired Primary Syphilis	The initial lesion is **a papule** that rapidly ulcerates to make a chancre. It may occur on any skin or mucous membrane surface	Benzathine penicillin G 2.4 million units IM in a single dose.
B. Acquired Secondary syphilis	Develops **4-10 weeks** after the appearance of the primary lesion. During this stage, spirochetes multiply and spread throughout the body (general manifestation plus skin manifestations).	Benzathine penicillin G 2.4 million units IM in a single dose
C. Acquired Latent syphilis	There are no clinical lesions, but the disease is detectable by positive serological tests. (early latent and late latent)	**Early latent syphilis:-** ➢ Benzathine penicillin G 2.4 million units IM in a single dose. **Late latent syphilis or latent syphilis of unknown duration:-** ➢ Benzathine penicillin G 2.4 million units IM weekly for 3 weeks.
D. Acquired Tertiary syphilis	Tertiary syphilis disease is rare. It mainly affects CVS (80-85%) & CNS (5-10%) Cardiovascular syphilis:- Occurs at least 10 years after primary infection. (Aneurysm in ascending aorta Or Aortic valve insufficiency). Neurosyphilis:- Meningiovascular syphilis and Parenchymal neurosyphilis	**Neurosyphilis:** **crystalline penicillin G** •18–24 million units per day (IV) for **10–14 days** **Cardiovascular syphilis:** Benzathine penicillin G 2.4 million units IM/Once weekly/3 weeks **Surgical intervention** may be required for aneurysms or valve dysfunction. •**Cardiology follow-up** is essential

* لانه حسب الـ pen. هو الي فعّال

Congenital syphilis	▪ **Treponemes** cross the placental barrier and infect the fetus	➢ **Benzathine penicillin G 50,000 units/kg IM, in a single dose.** 1. **In patients with a history of penicillin allergy →** ➢ **Skin testing is recommended.** ➢ **Skin test positive patients should be desensitized in the hospital.**
For patients allergic to penicillin if older age	depending on culture ←	1. Tetracycline:- for 14 0r 28 days 2. Erythromycin:- for 14 0r 30 days 3. Azythromycin:- for 14 days 4. Ceftriaxone: for 10 days

Other Bacterial STIDs

- **Chancroid (Soft sore)**



Causative agent:- Hemophilus ducreyi → Gram -ve coccobacilli.

Treatment

- The main treatment is erythromycin, given for 7 days.
- Ceftriaxone or azithromycin is an alternative given as a single dose.

mass in lymph nodes around genitalia

- **Lymphogranuloma venereum**
- **Causative agent**: It is caused by Chlamydia trachomatis types L1, L2, L3
- **Treatment**
  - Tetracycline:- 500 mg 4 times daily for 14 days.
  - Erythromycin or doxycycline, or azithromycin are effective.
  - Most cases require repeated courses. ↑↑ recurrance

Human Immunodeficiency Disease

- **Etiology:-**

Causative agent:- Caused by infection with HIV-1 or HIV-2, which is a single-stranded RNA virus.

- -It was identified as the cause of AIDS in 1983.

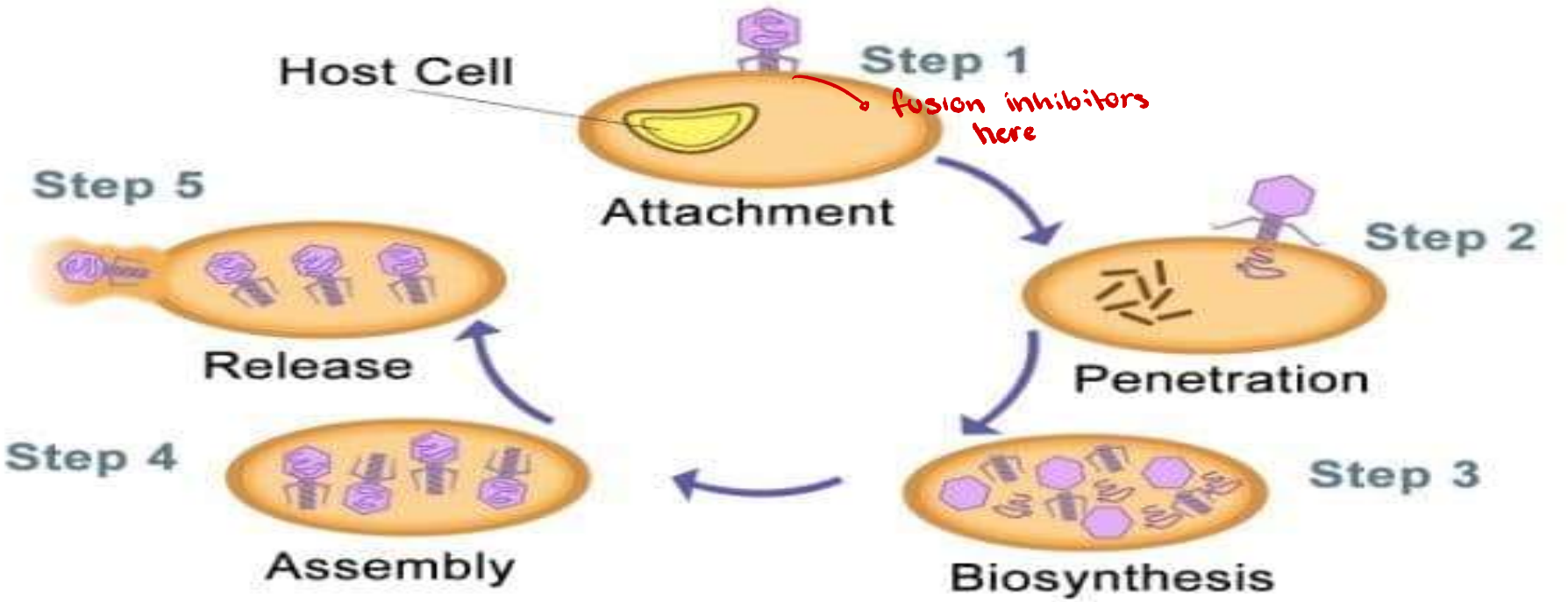
Mode of transmission:-

- HIV is blood-borne virus transmitted via:-
- 1.Sexual intercourse including anal intercourse.
- 2.Use of contaminated injecting equipment.
- 3. Mother-to-child transmission, during birth process or during breastfeeding

Treatment of HIV

عطول بدأ

- **Highly active antiretroviral therapy (HAART)** is often initiated at the time of diagnosis. The strongest indication is for patients with AIDS-defining illness, low CD4+ (< 500 cells/mm^3), or high viral load.
- Regimen consists of 3 drugs (to prevent resistance):
- 2 NRTIs &1 of the following (NNRTIs, protease inhibitors, or integrase inhibitors)



Nucleoside reverse transcriptase inhibitors (NRTIs)

- zidovudine, didanosine, lamivudine
- **Mechanism**

Phosphorylated by host kinases, competitive inhibition of reverse transcriptase and chain termination of DNA.

- **Clinical use**

Main component of HAART.

Zidovudine is used for general prophylaxis and for prevention of vertical transmission in pregnancy.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

- Efavirenz, Etravirin.
- ***Mechanism:***
  - Bind to and inhibit reverse transcriptase, inhibiting DNA synthesis.
  - No need for phosphorylation
  - Not competitive (binds to a site other than the site of NRTIs).
- ***Toxicity:*** Rash & hepatotoxicity (common with all members).

- Efavirenz causes vivid dreams and is contraindicated during pregnancy.

Integrase inhibitors

- **Raltegravir and Elivtegravir**
  - Inhibit integration of viral genome in host cell DNA.

Protease inhibitors (PIs)

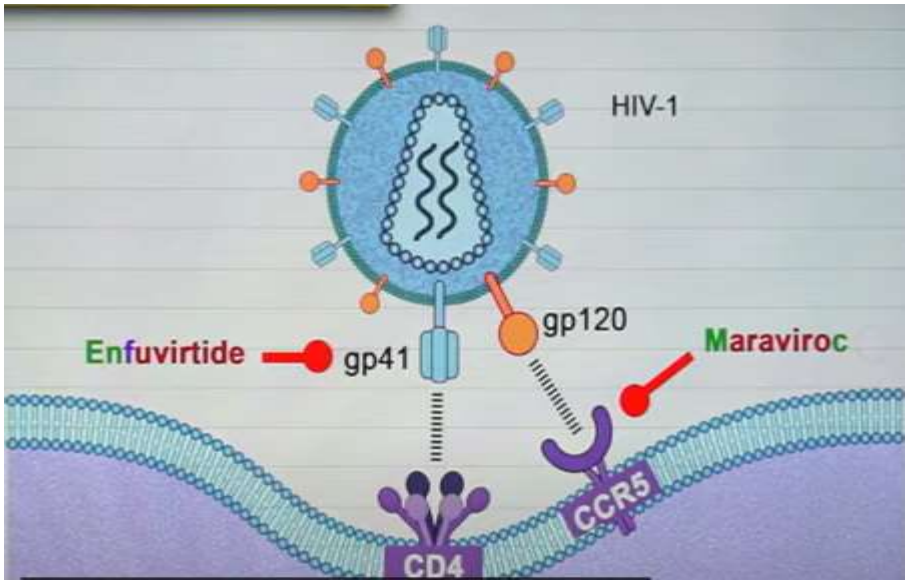
- ***atazanavir, lopinavir, ritonavir***
- **Mechanism**
- HIV-1 protease cleaves the polypeptide products of the viral mRNA into functional parts → assembly & maturation of new viruses.
- PIs act by inhibiting this enzyme.

Fusion inhibitors

Enfuvirtide

Mechanism of action:

- It binds to the gp41 subunit of the viral envelope glycoprotein, preventing the fusion of the viral and cellular membranes.



Maraviroc

Mechanism of action:

- binds specifically and selectively to the membrane host protein CCR5, one of two chemokine receptors necessary for entry of HIV into CD4+ cells
- So, it inhibits binding and entry of the virus into immune cells

Genital Herpes

↓ severity
↓ duration

Etiology:- Causative agent: Herpes simplex virus (HSV)

- It is a DNA virus.
- HSV has been classified into two types, HSV-1 & HSV-2.

- **Treatment**

- **Aim of treatment:-**
- With the first episode, → to reduce the duration and severity of symptoms.
- With recurrent infections, → to reduce the duration and severity of symptoms, and the likelihood of further recurrences

Antiviral drugs

1-Acyclovir- famciclovir- valacyclovir

1. Acyclovir: Guanosine analogs. need phosphorylation since nucleotide

- Mono-phosphorylated by HSV/VZV thymidine kinase (TK) (not phosphorylated in uninfected cells → few adverse effects). → activated in affected cell
- They are further activated by host-cell kinases to the triphosphates

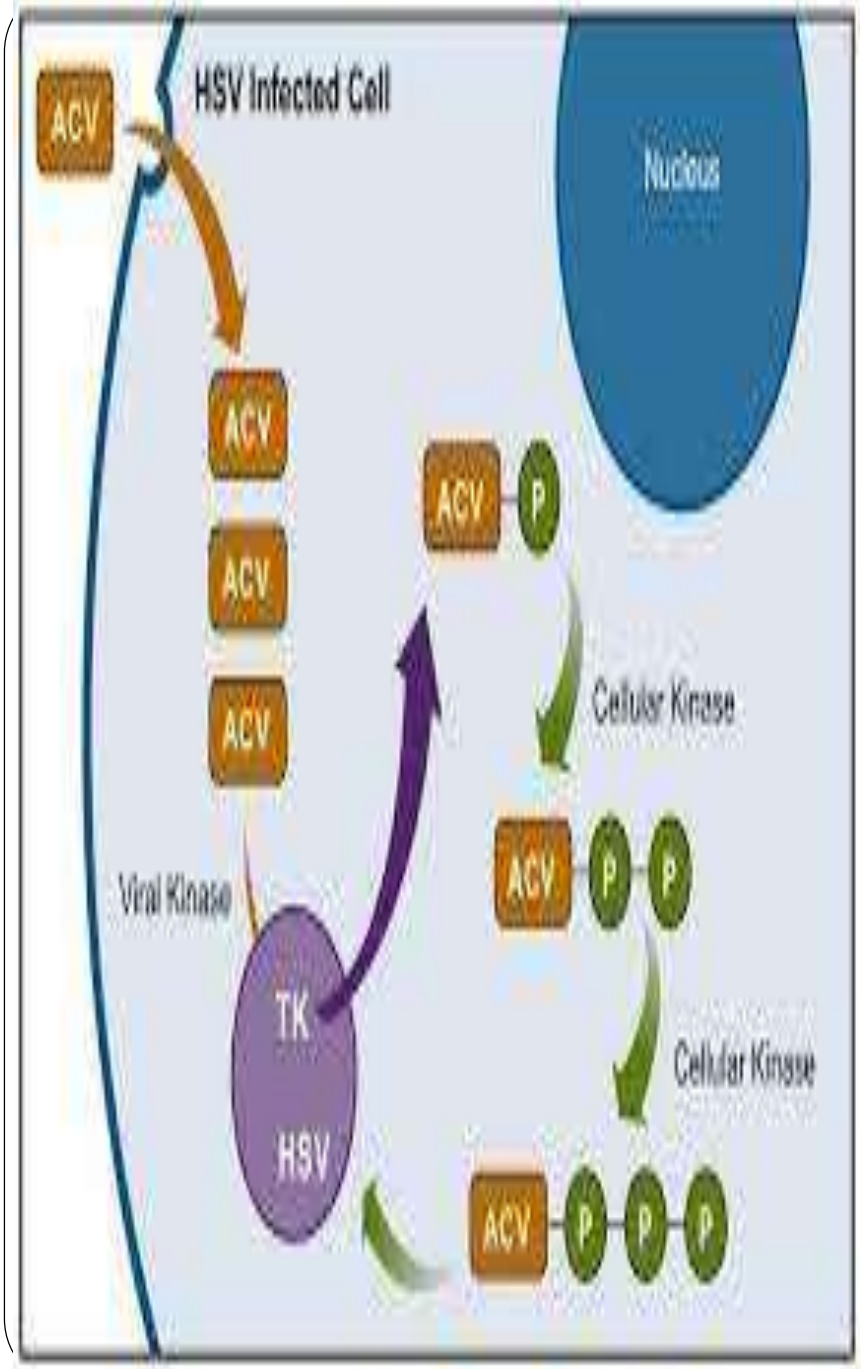
2- Valaciclovir

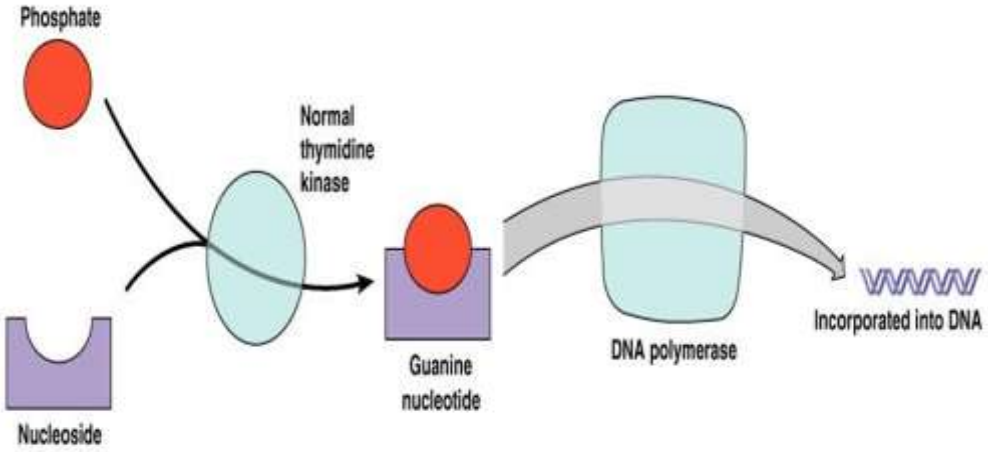
- Valaciclovir is the pro-drug of acyclovir.
- Valaciclovir is converted into acyclovir by intestinal & liver enzymes resulting in improved bioavailability of acyclovir.

Mechanism of action:-

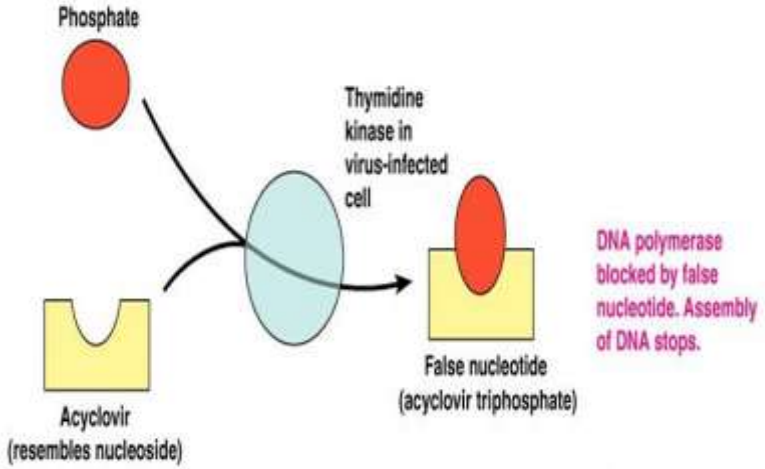
Triphosphates are substrates for viral DNA polymerase → incorporated into the DNA molecule → chain terminations

Mechanism of Action of Acyclovir





(b) The enzyme thymidine kinase combines phosphates with nucleosides to form nucleotides, which are then incorporated into DNA.



(c) Acyclovir has no effect on a cell not infected by a virus, that is, with normal thymidine kinase. In a virally infected cell, the thymidine kinase is altered and converts the acyclovir (which resembles the nucleoside deoxyguanosine) into a false nucleotide—which blocks DNA synthesis by DNA polymerase.

Fig 20.16

2-Foscarnet

Doesn't require activation by viral or human kinases

Mechanism of action:

Inhibition(-) of Viral DNA polymerase ①

(-) RNA polymerase ②

(-) HIV reverse transcriptase ③

clinical uses:

Acyclovir-resistant **HSV infection**

Toxicity:

Nephrotoxicity

Electrolyte disturbances that may cause seizures (hypocalcemia & hypomagnesemia)

Hepatitis B

Causative organism: Hepatitis B virus (HBV) is a double-stranded DNA virus.

Treatments:-Currently there are seven approved drugs for treating HBV:-

- Interferon2b&2a, Lamivudine, Adefovir, Entecavir, Telbivudine and Tenofovir

A·E:
↓ immunity + recurrance ✱

Interferon2b&2a

drug symptoms are very aggressive !

Glycoproteins are normally synthesized by virally infected cells.

They have a wide range of antiviral and antitumor effects.

The exact mechanism is unclear, but possibly they may act through:

- Inhibition of viral penetration, translation, transcription, protein processing, maturation, and release.] everything
- Enhanced phagocytic activity.
- ↑↑ proliferation and survival of cytotoxic T cells.

all against infected cells

- **Lamivudine :** This cytosine analog is an inhibitor (HBV) DNA polymerase. Lamivudine must be phosphorylated by host cellular enzymes to the triphosphate (active) form.

قراءة بس

- **Adefovir:** Adefovir dipivoxil is a nucleotide analog that is phosphorylated to adefovir diphosphate, which is then incorporated into viral DNA. This leads to the termination of further DNA synthesis and prevents viral replication.
- **Entecavir:** is a guanosine analog . Following intracellular phosphorylation to the triphosphate, it competes with the natural substrate, deoxyguanosine triphosphate, for viral reverse transcriptase.

Entecavir is effective against lamivudine-resistant strains of HBV

- **Telbivudine** is a thymidine analog. The drug is phosphorylated intracellularly to the triphosphate, which can either compete with endogenous thymidine triphosphate for incorporation into DNA or else be incorporated into viral DNA, where it serves to terminate further elongation of the DNA chain.

Hepatitis C

Causative organism: Hepatitis C virus, which is a single-stranded RNA virus.

Mode of transmission:-

- The main form of transmission is parenteral.
- However, vertical transmission, sexual contact, and other forms have been reported.

Treatments:-

a combination of antivirals that can be used according to liver condition and type of hepatitis C virus, e.g.:-

- Ribavirin: Competitive inhibition of IMP (inositol monophosphate) dehydrogenase → inhibition of guanine nucleotide synthesis.

Inhibition of viral RNA polymerase.

= ⊗ guanine base

HCV protease inhibitor → ↓↓ viral replication. **Toxicity:** photosensitivity & rash.	***NS3/4A Protease inhibitors*** **e.g. simeprevir**
Inhibition of HCV RNA-dependent polymerase. **Toxicity:** sofosbuvir (Sovaldi) → headache & fatigue.	***NS5B polymerase inhibitors*** a. Nucleoside (sofosbuvir) b. Non-nucleoside (dasabuvir)
Inhibition of HCV NS5A replication complex (replicase) → ↓↓ viral replication.	***NS5A (replicase)inhibitors*** e.g. daclatasvir & ledipasvir

[MOA w/ example for all]

Parasitic STIs

• Trichomoniasis

Causative agent:- It is caused by Trichomonas vaginalis.

Treatment

1. **Oral metronidazole** (Flagyl 250 & 500 mg tab):-

-Cure rates are >95%.

-Treatment should include infected persons & their partners due to:-

High rates of infection in asymptomatic partners.

High rates of re-infection

2. **Oral Tinidazole** (Fasygen, 500 mg tab)

-Single-dose therapy consists of 2 g taken with food.

-Cure rates range from 86-100%.

-For resistant infections → 2 g twice daily for 14 days.

-When metronidazole fails, tinidazole may be used.


Thank
you