Treatment of viral infection in the hematopoietic system

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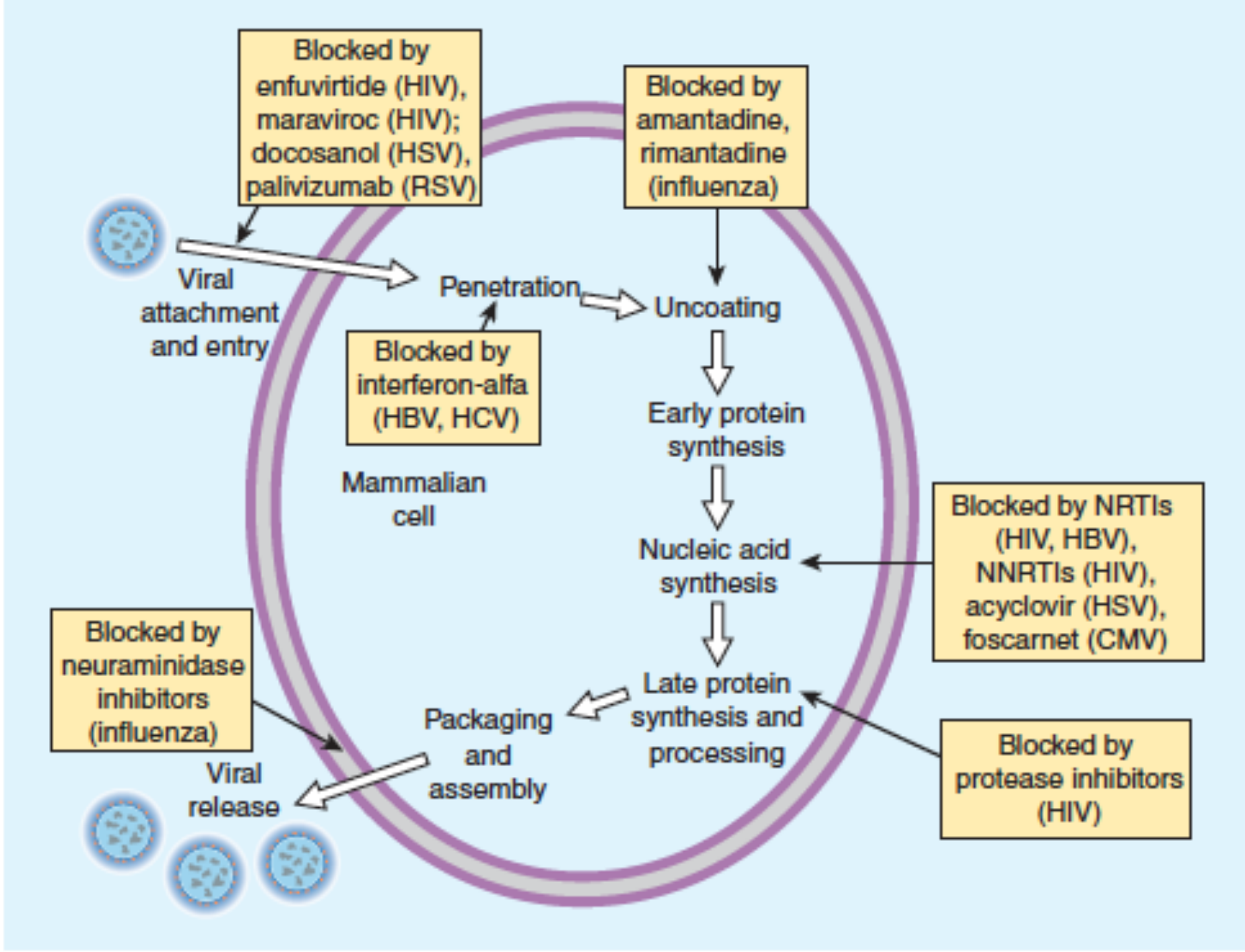

Blocked by enfuvirtide (HIV), maraviroc (HIV); docosanol (HSV), palivizumab (RSV)
Blocked by amantadine, rimantadine (influenza)
Viral attachment and entry
Penetration
Uncoating
Blocked by interferon-alfa (HBV, HCV)
Early protein synthesis
Mammalian cell
Nucleic acid synthesis
Blocked by NRTIs (HIV, HBV), NNRTIs (HIV), acyclovir (HSV), foscarnet (CMV)
Blocked by neuraminidase inhibitors (influenza)
Late protein synthesis and processing
Packaging and assembly
Viral release
Blocked by protease inhibitors (HIV)

Patterns of Viral Infection

Acute infection:

- Complete viral clearance mediated by immune response
- E.g. Influenza, Rubella.

Latent infection:

- Acute infection but followed by virus persistence in non-infectious form.
- Periodic reactivation of infection with viral shedding
- E.g. Chickenpox, Herpes simplex, CMV

Chronic infection (progressive or persistent):

- Acute infection followed by lack of viral clearance
- Virus continuously shed or present in tissues
- e.g. HIV, Hepatitis C

- **Cytomegalovirus**
- **Human Immunodeficiency Virus**

Agents for Cytomegalovirus (CMV)

- CMV infections occur in the setting of advanced immunosuppression, and are typically due to reactivation of latent infection.
- Dissemination of infection results in end organ disease: retinitis, colitis, esophagitis, CNS disease, and pneumonitis.

Agents for Cytomegalovirus

Ganciclovir:

- It is an acyclic guanosine analog that requires activation by triphosphorylation.
- Initial phosphorylation is catalyzed by virus-specified protein kinase in CMV infected cells.
- Because it requires virus enzymes first for activation, it is selectively activated, and the active metabolites accumulate in infected cells.

Agents for Cytomegalovirus

- The activated compound competitively inhibits the viral DNA polymerase and causes termination of viral DNA elongation.
- Resistance with long-term use is due to mutation in the kinase which results in less triphosphorylated active form of ganciclovir.
- Can be administered IV, PO, or via intraocular implant.
- Its clearance is related to creatinine clearance.

Adverse Effects:

1. Myelosuppression.
2. Peripheral neuropathy.
3. CNS toxicity (confusion, seizures, psychosis).
7. Hepatotoxicity.
8. May be carcinogenic, embryotoxic and may cause aspermatogenesis.

Foscarnet

Unlike most antiviral agents, *foscarnet* [fos-KAR-net] is not a purine or pyrimidine analog. Instead, it is a phosphonoformate (a pyrophosphate derivative) and does not require activation by viral (or cellular) kinases.

- Uses: CMV (retinitis and other CMV infections),Herpes simplex, and HIV.

approved for CMV retinitis in immunocompromised hosts and for *acyclovir*-resistant HSV infections.

Foscarnet

works by reversibly inhibiting viral DNA and RNA polymerases, thereby interfering with viral DNA and RNA synthesis.
Mutation of the polymerase structure is responsible for resistant viruses.

***Foscarnet* is poorly absorbed orally and must be injected intravenously.**

It must also be given frequently to avoid relapse when plasma levels fall. It is dispersed throughout the body, and greater than 10% enters the bone matrix, from which it slowly leaves.

The parent drug is eliminated by glomerular filtration and tubular secretion.

Foscarnet

Adverse effects :

- Nephrotoxicity (25%) is the most common side effect
- anemia, nausea, and fever

Due to chelation with divalent cations, hypocalcemia and hypomagnesemia are also seen.
In addition, hypokalemia, hypo- and hyperphosphatemia, seizures, and arrhythmias have been reported

Maribavir (Livtencity)

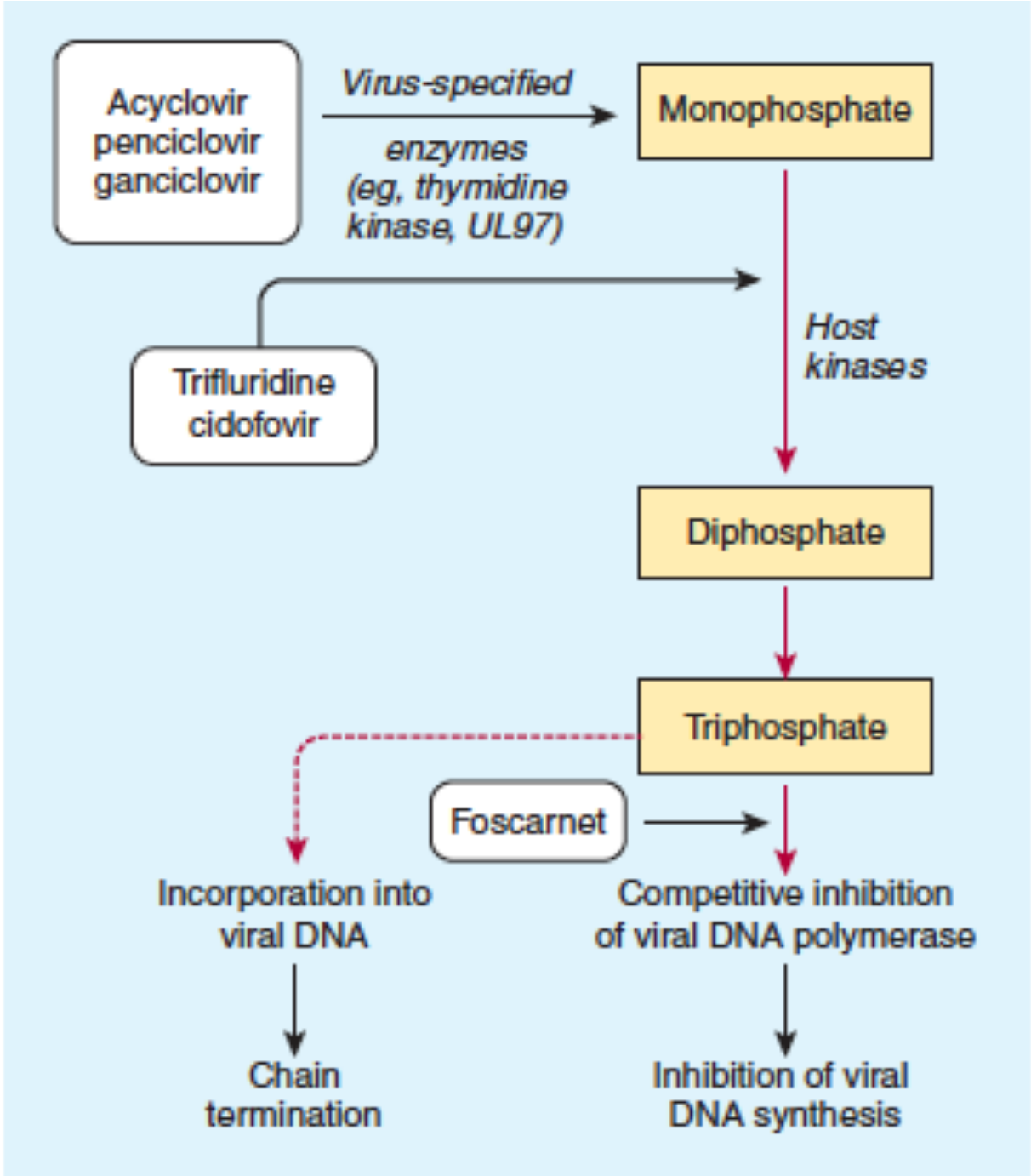
- New agent : Approved in 2021
- **A first-in-class medication**

- Indication: treat post-transplant cytomegalovirus (CMV).

- Mechanism of action: Inhibitor of cytomegalovirus pUL97 kinase thus blocking virus replication.

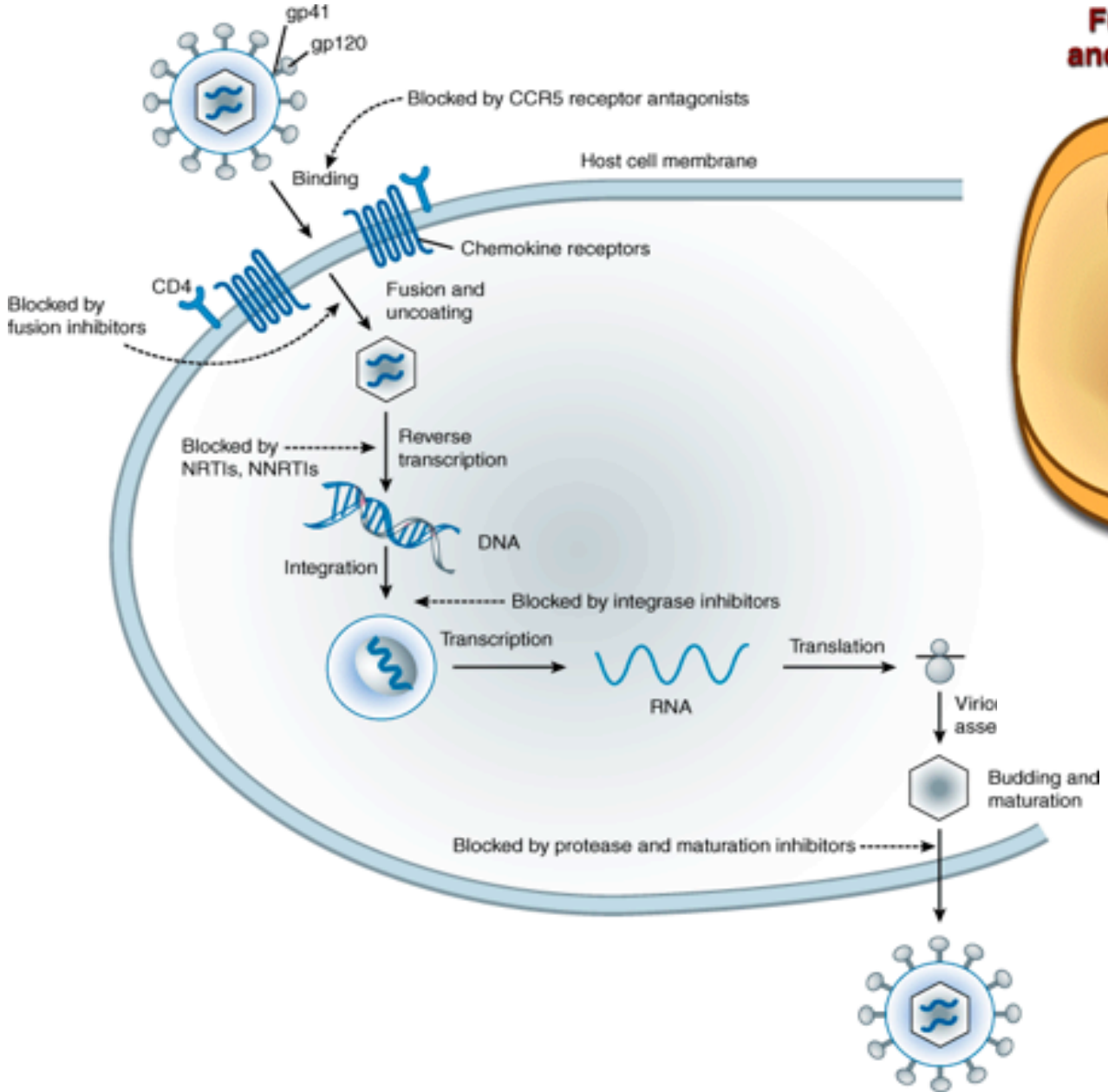
Maribavir

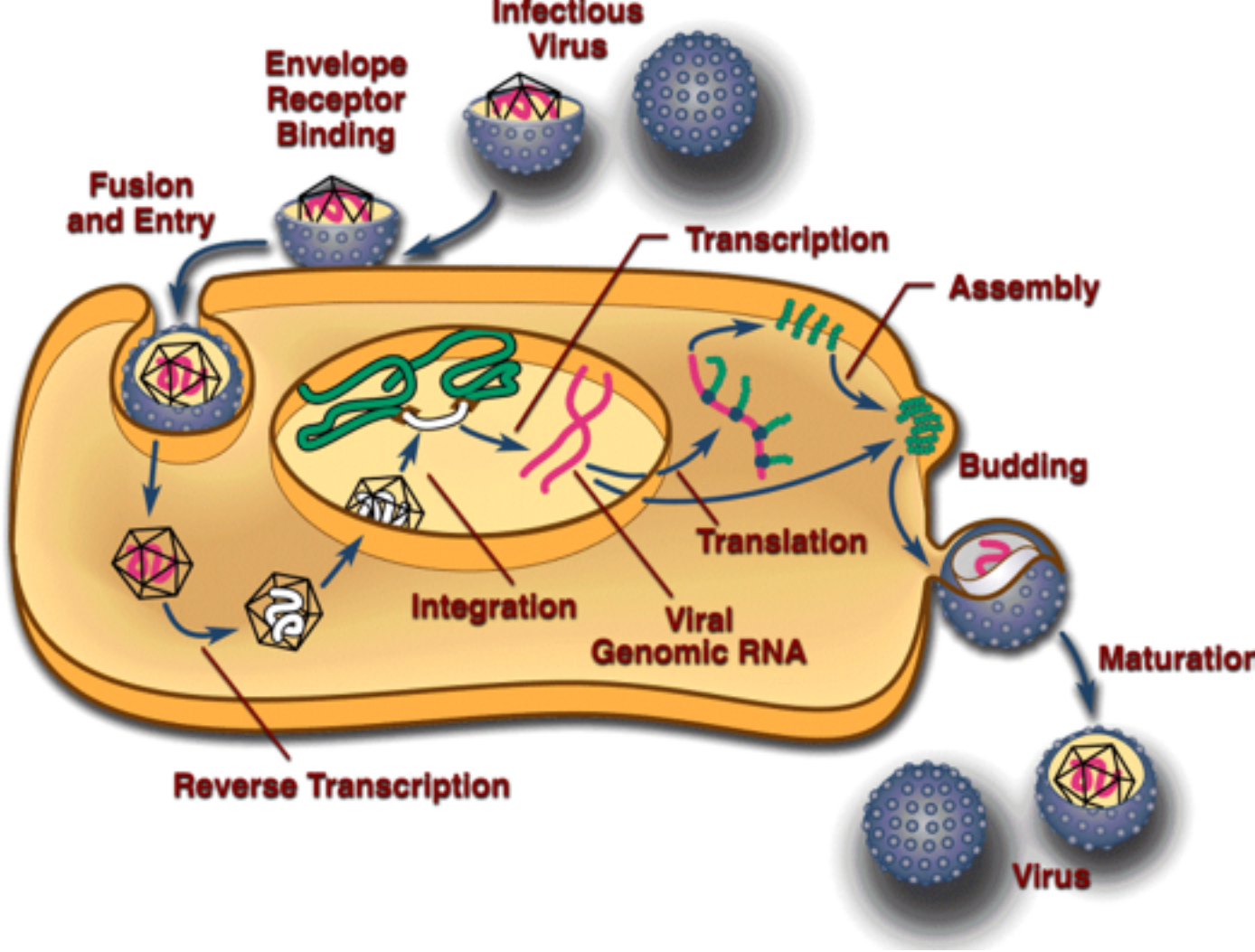
- May antagonize the antiviral activity of ganciclovir and valganciclovir by inhibiting human CMV pUL97 kinase.
- **Coadministration of Maribavir with ganciclovir or valganciclovir is not recommended**
- **Side effects:**
  - **Change of taste**
  - **diarrhea**
  - **loss of taste**
  - **nausea**
  - **unusual tiredness or weakness**
  - **vomiting**


Acyclovir
penciclovir
ganciclovir
Virus-specified
enzymes
(eg, thymidine
kinase, UL97)
Monophosphate
Trifluridine
cidofovir
Host
kinases
Diphosphate
Triphosphate
Foscarnet
Incorporation into
viral DNA
Competitive inhibition
of viral DNA polymerase
Chain
termination
Inhibition of viral
DNA synthesis

Agents for Human Immunodeficiency Virus

- Combination therapy with maximally potent agents reduce viral replication to the lowest possible level and decrease the likelihood of emergence of resistance.
- Typically 3-4 antiretroviral agents, has become the standard of care.


gp41
gp120
Blocked by CCR5 receptor antagonists
Binding
Host cell membrane
Chemokine receptors
CD4
Blocked by
fusion inhibitors
Fusion and
uncoating
Blocked by
NRTIs, NNRTIs
Reverse
transcription
DNA
Integration
Blocked by integrase inhibitors
Transcription
RNA
Translation
Budding and
maturation
Blocked by protease and maturation inhibitors


Infectious
Virus
Envelope
Receptor
Binding
Fusion
and Entry
Transcription
Assembly
Budding
Translation
Integration
Viral
Genomic RNA
Maturation
Reverse Transcription
Virus

Agents for Human Immunodeficiency Virus

1. Nucleoside & Nucleotide Reverse Transcriptase Inhibitors (NRTIs): Abacavir, Didanosine, Emtricitabine, Tenofovir.
2. Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs): Delavirdine, Nevirapine, Efavirenz.
3. Protease Inhibitors (PIs): Atazanavir, Indinavir, Ritonavir, Saquinavir.
4. Fusion Inhibitors: Enfuvirtide.
5. Entry Inhibitors: Maraviroc.
6. Integrase Strand Transfer Inhibitors (INSTIs): Raltegravir, Elvitegravir.

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

- Act by competitive inhibition of HIV-1 reverse transcriptase.
- Incorporation into the growing viral DNA chain results in premature chain termination due to inhibition of binding with the incoming nucleotide.
- All NTRIs may produce mitochondrial toxicity due to inhibition of mitochondrial DNA polymerase gamma.
- Can produce fatal lactic acidosis with hepatic steatosis (fatty liver).
- There may be an increased risk of myocardial infarction (MI) (?).

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

Abacavir:

- It is a guanosine analog.

Adverse Effects:

- Hypersensitivity reaction, occasionally fatal have been reported in 3-5% of patients. Test HLA-B*5701 allele before use.
- Symptoms which occur in the first 6 weeks of therapy: fever, vomiting, diarrhea, and anorexia.

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

- Respiratory symptoms (dyspnea, pharyngitis, and cough).
- Elevation of aminotransferases and creatine kinase levels.
- Pancreatitis
- Risk of MI.

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

- They bind directly to HIV-1 reverse transcriptase, resulting in allosteric inhibition of RNA- and DNA-dependent DNA polymerase.
- Do not require phosphorylation to be active.
- As a class NNRTIs tend to be associated with GIT intolerance and skin rash that can be serious (Steven-Johnson syndrome).
- Metabolized by CYP3A4 → tremendous drug-drug interactions.

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Delavirdine:

Adverse effects:

- Skin rash develops in ~ 40% of patients during the first 1-3 weeks of therapy.
- Severe rash – erythema multiforme and Steven-Johnson syndrome – is rare.
- Headache, fatigue, vomiting, diarrhea, and elevated serum aminotransferase levels.
- Pregnancy should be avoided.
- Extensively metabolized by CYP3A and CYP2D6 and also inhibits CYP3A4 and CYP2C9 → drug interactions.

Protease Inhibitors

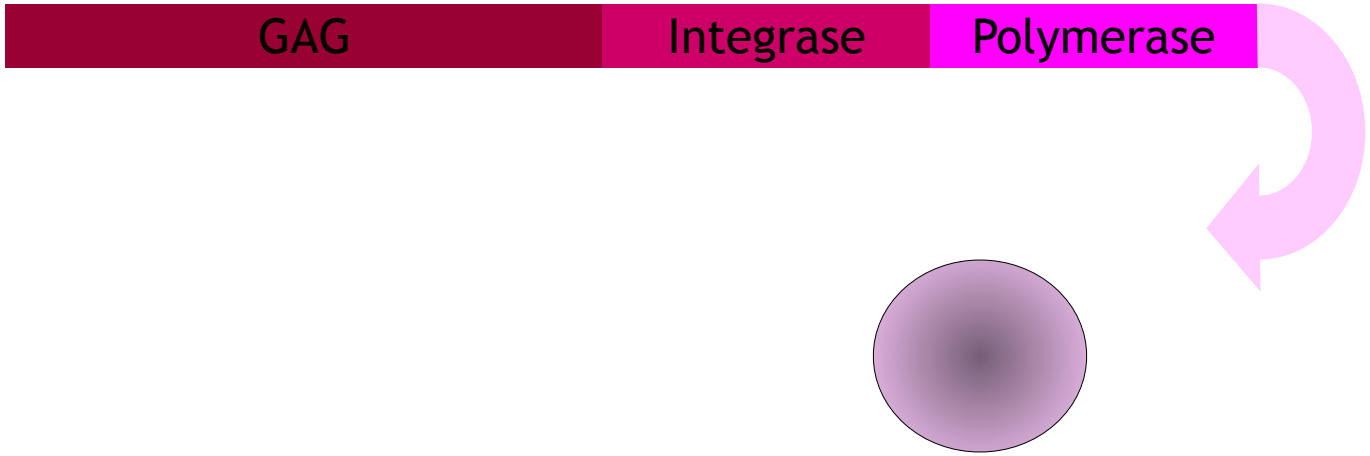
- During the later stages of HIV growth cycle, polyproteins that become immature budding particles are formed.
- Protease is responsible for processing of these proteins to produce the final structural proteins of the mature virion core.
- Protease inhibitors inhibit this post-translational cleavage of polyproteins, resulting in the production of immature, noninfectious viral particles.
- They are active against HIV-1 and HIV-2.
- They do not need intracellular activation.

Anti-Viral Chemotherapy

GAG/POL polyprotein

Retrovirus --- HIV

Anti-Viral Chemotherapy

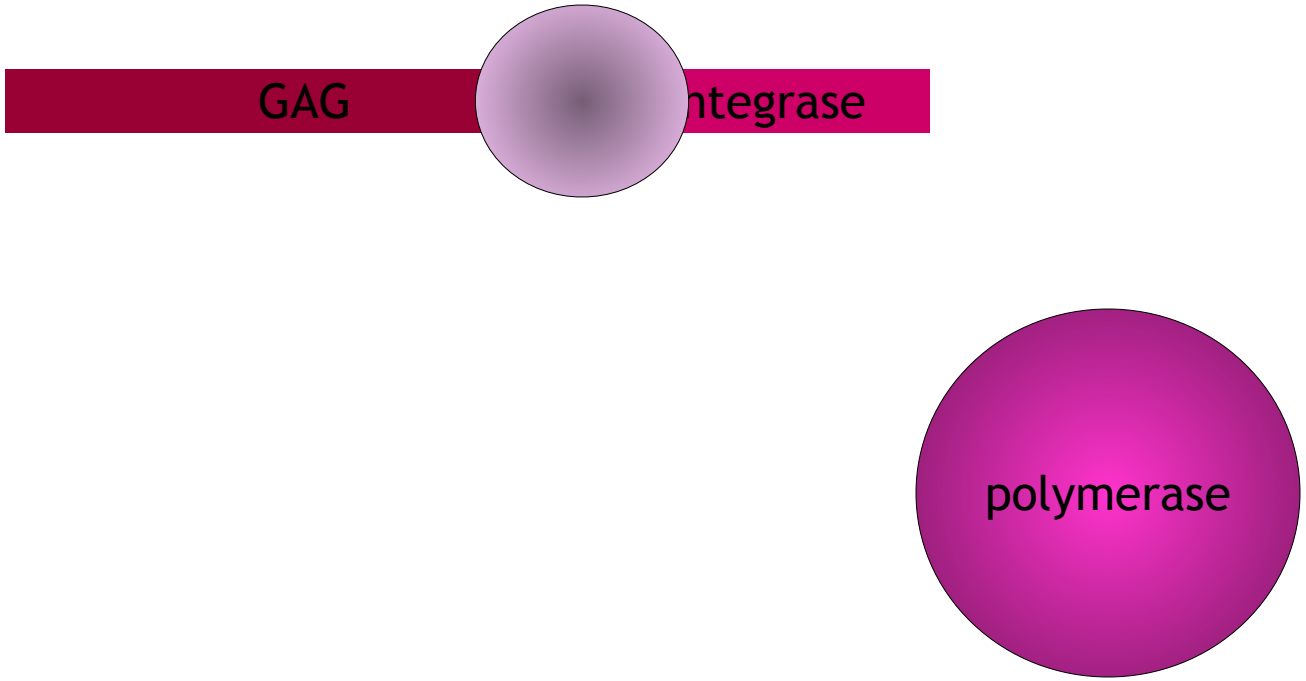


Protease folds and cuts itself free

Anti-Viral Chemotherapy

Protease cuts at a site between the integrase and polymerase

Anti-Viral Chemotherapy



Protease Inhibitors

- A syndrome of redistribution and accumulation of body fat, resulting in central obesity, dorso-cervical fat enlargement (buffalo hump), peripheral and facial wasting, breast enlargement, and a Cushingoid appearance has been observed with the use of these drugs.
- This has been concomitantly associated with elevated LDL and triglycerides, hyperglycemia and insulin resistance (except atazanavir). Cause is unknown.
- All are extensively metabolized by CYP3A4.

Protease Inhibitors

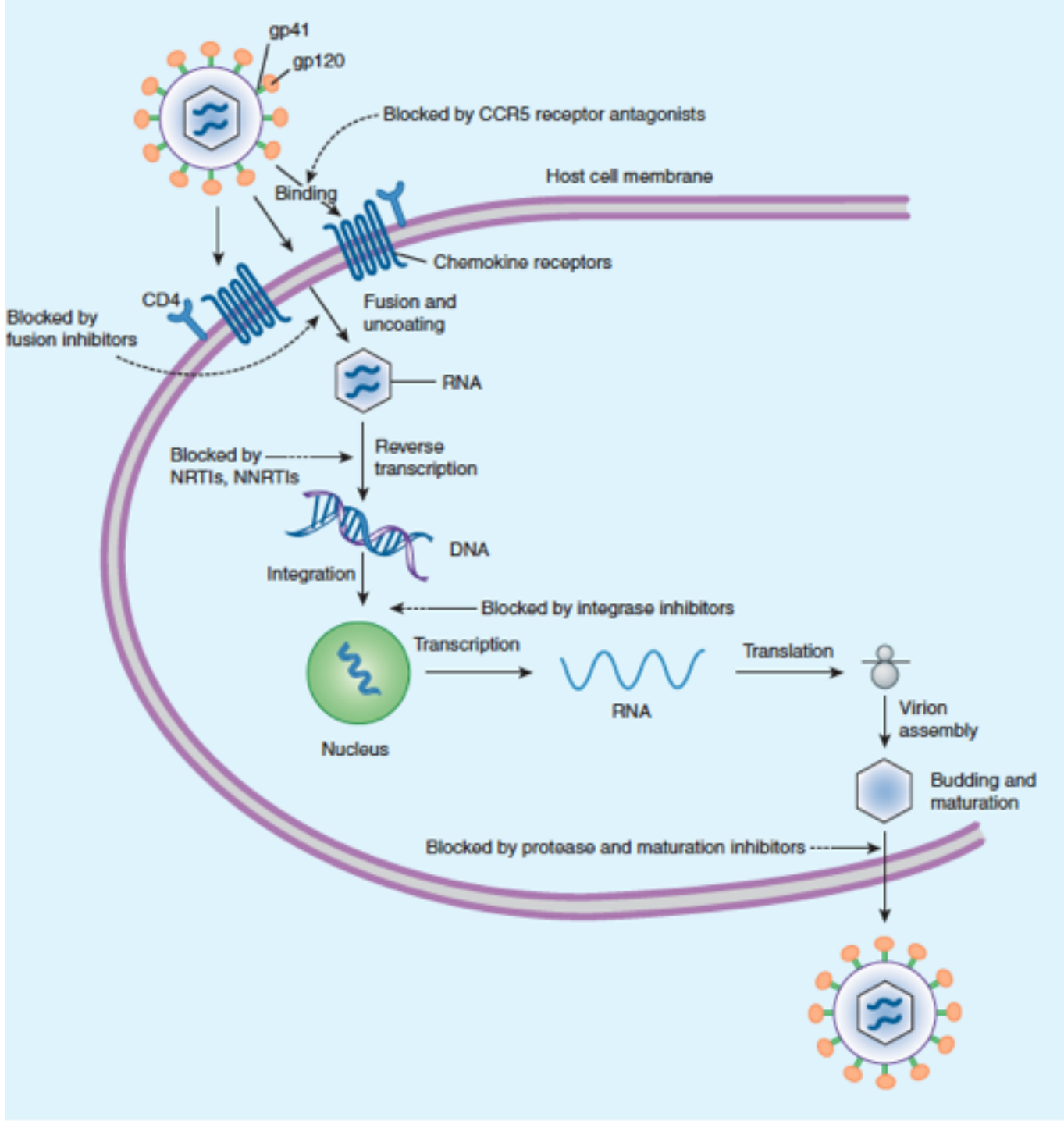
Atazanavir:

Adverse effects:

- Diarrhea, nausea, and vomiting.
- Peripheral neuropathy.
- Indirect hyperbilirubinemia and jaundice due to inhibition of UGT1A1 glucuronidation enzyme.
- Prolongation of PR interval and QTc interval.

Fusion Inhibitors

- The process of entry of HIV-1 into host cells entails binding of the viral envelope glycoprotein complex (gp120 & gp41) to its cellular receptor CD4.
- This binding induces conformational changes in gp120 that enable access to the chemokine co-receptors.
- Co-receptor binding induces further conformational changes in gp120, allowing exposure to gp41 → leading to fusion of the viral envelope with the host cell membrane → entry of viral core into cellular cytoplasm.


gp41
gp120
Blocked by CCR5 receptor antagonists
Binding
Host cell membrane
Chemokine receptors
CD4
Blocked by
fusion inhibitors
Fusion and
uncoating
RNA
Blocked by
NRTIs, NNRTIs
Reverse
transcription
DNA
Integration
Blocked by integrase inhibitors
Transcription
Translation
RNA
Nucleus
Virion
assembly
Budding and
maturation
Blocked by protease and maturation inhibitors

Fusion Inhibitors

Enfuvirtide:

- It is a synthetic peptide fusion inhibitor that blocks entry into the cell.
- It binds to gp41 subunit of the viral envelope preventing the conformational changes required for the fusion of the viral and cellular membranes.
- Must be administered by sc injection.
- Eliminated by proteolytic hydrolysis.

Adverse effects:

- Injection site reactions
- Hypersensitivity and eosinophilia.
- Increased rate of bacterial pneumoni

Integrase Strand Transfer Inhibitors

Raltegravir:

- It is a pyrimidine analog that binds integrase.
- Integrase is a viral enzyme essential to the replication of both HIV-1 and HIV-2.
- It inhibits strand transfer, the third and final step of provirus integration, thus interfering with the integration of reverse-transcribed HIV DNA into the chromosomes of host cells.

Integrase Strand Transfer Inhibitors

- Polyvalent cations (Ca^{2+}, Mg^{2+}, Fe^{2+}) may bind the drug and interfere with its activity.
- Adverse effects include diarrhea, nausea, headache.
- Increased creatine phosphokinase