MUNI
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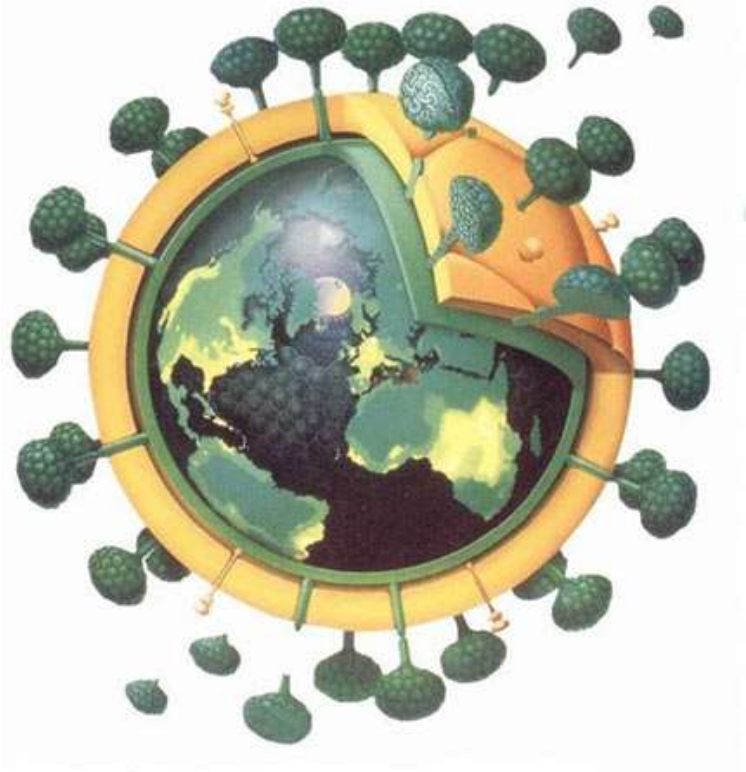
Antivirals

Viruses

obligatory intracelular parasites, their replication depends on synthetic processes of the host cell

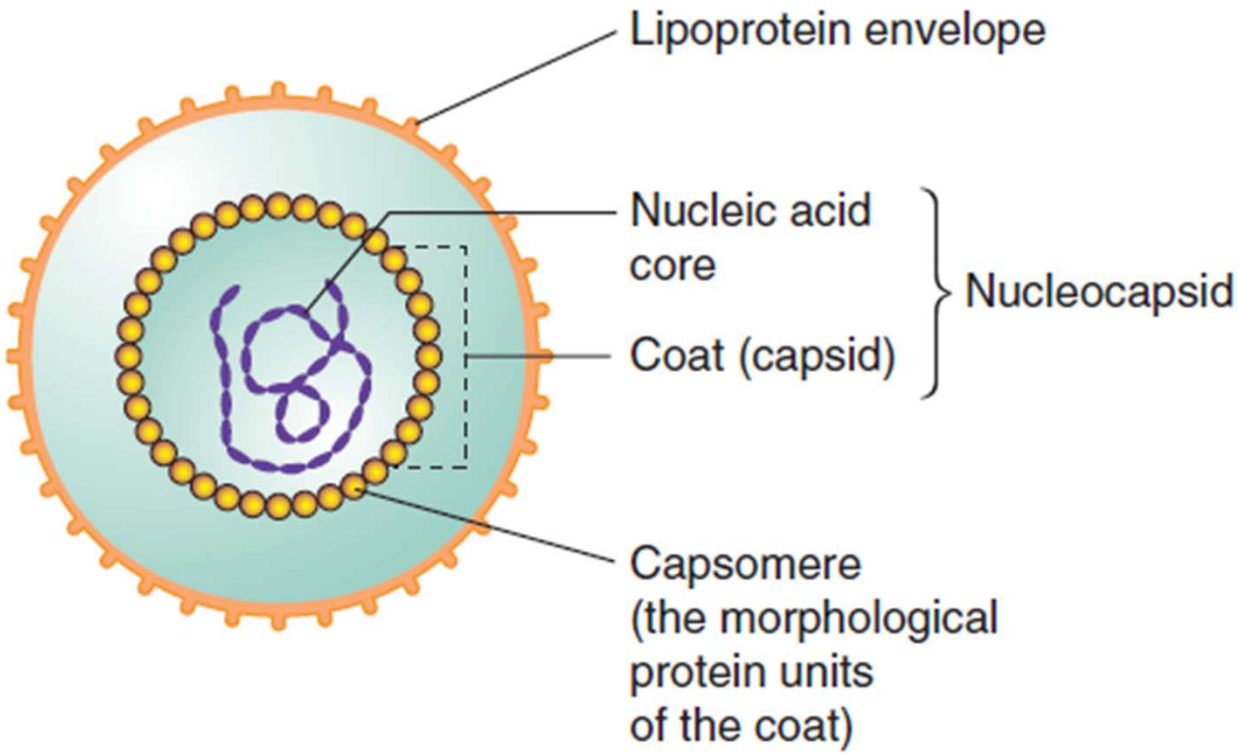
Non-cell particles of size 20 – 300 nm

Antigenous protein capsule called capsid + NA → nukleokapsid



Components of virion

- DNA
- RNA
- RNA retroviruses



Taxonomy of viruses

RNA

- Paramyxovirus – measles, mumps
- Rabdovirus – rabbies
- Retrovirus – HIV, viruses causing malign tumors
- Pikornavirus – poliomyelitis, common cold
- Ortomyxovirus – flu
- Togavirus – yellow fever,tick-borne meningoencephalitis, rubella

DNA

- Herpesvirus – HS I and II, Varicella zoster (small pox, herpes zoster), EBV, CMV
- Adenovirus – respiratory infections
- Poxvirus – pox
- Papovavirus – human warts virus
- Parvovirus

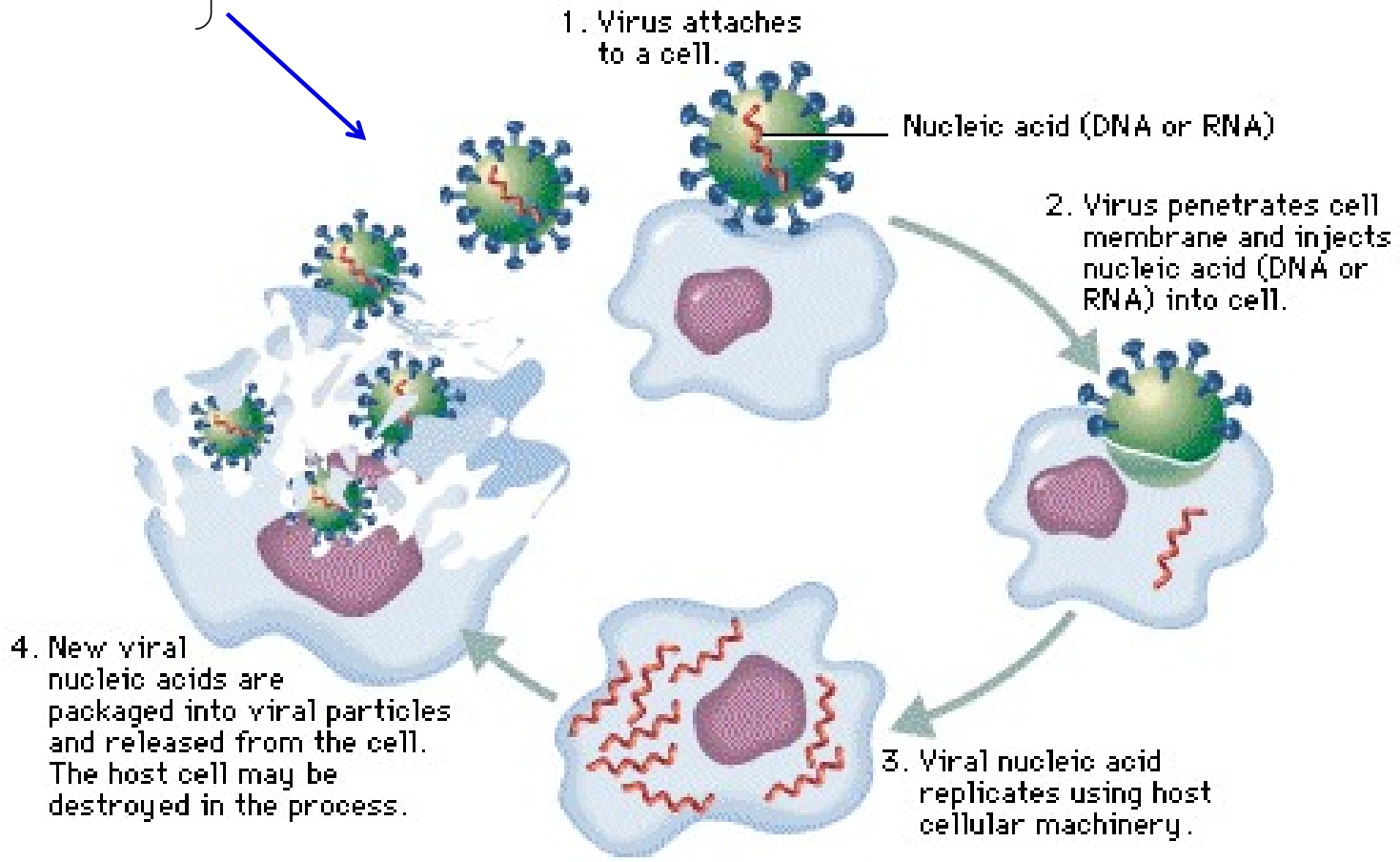
ANTIVIRALS

1) Influenza viruses
2) Herpes viruses
3) Respiratory viruses (RSV+ coronaviridae - SARS, MERS, COVID)
4) Retroviruses – HIV
5) Viral hepatitis
6) Immune response modulators

Viral replication cycle

viral enzymes
+regulation proteins
+structural proteins
+viral NA

} mature viral particle

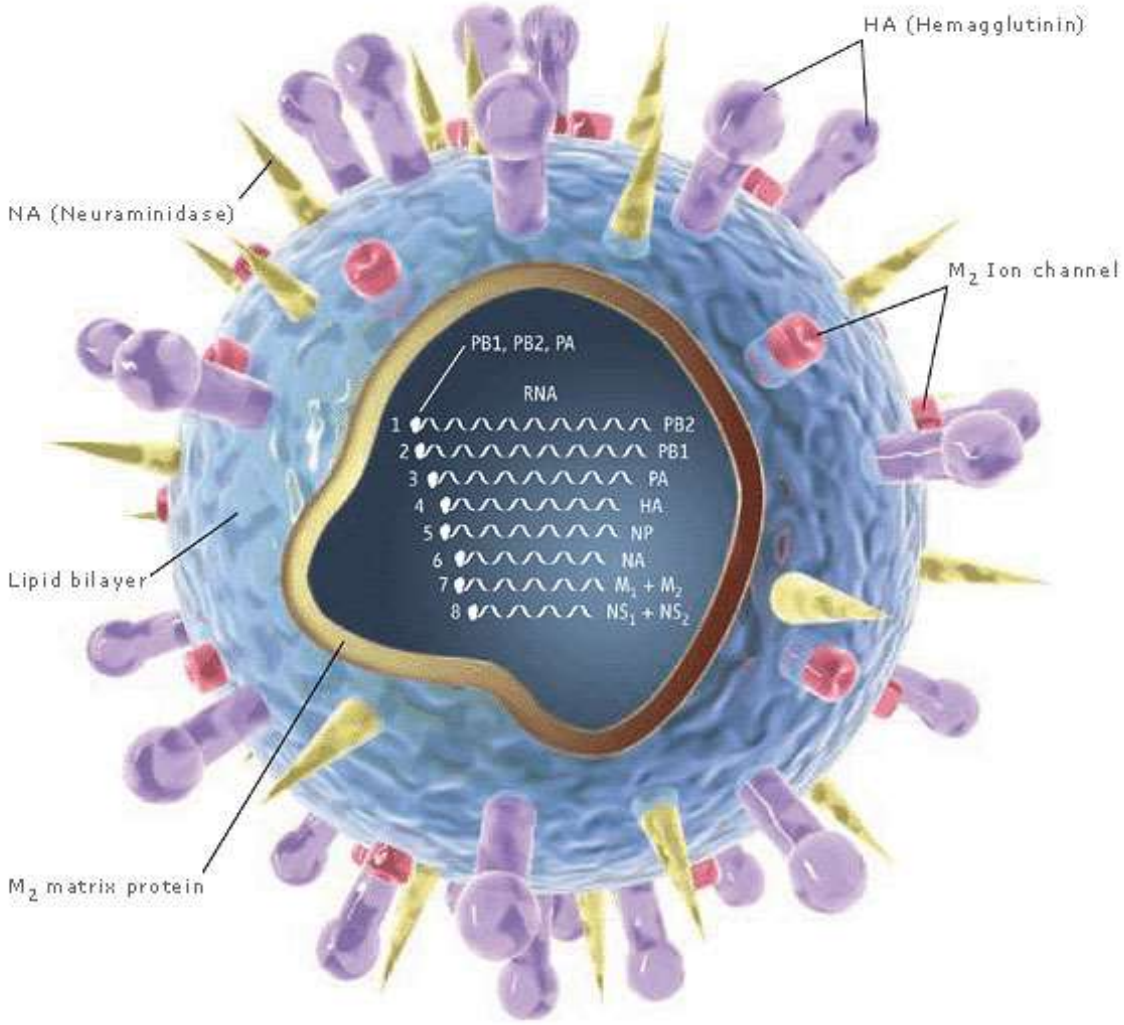


Virus use endogeneous proteins for penetration into the cell

Host cell structures that can function as receptors for viruses	Virus
Th lymphocytes CD4 glycoprotein	HIV
CCR5 receptor for chemokines MCP-1 and RANTES	HIV
CXCR4 chemokine receptor for cytokine SDF-1	HIV
Acetylcholine receptor on skeletal muscle	Rabies virus
B lymphocyte complement C3d receptor	Glandular fever virus
T lymphocyte interleukin-2 receptor	T-cell leukaemia viruses
β Adrenoceptors	Infantile diarrhoea virus
ACE2	Coronaviridae (SARS, MERS, COVID-19)
MHC molecules	Adenovirus (causing sore throat and conjunctivitis) T-cell leukaemia viruses

MCP-1, monocyte chemoattractant protein-1; MHC, major histocompatibility complex; RANTES, regulated on activation normal T-cell expressed and secreted; SDF-1, stromal cell-derived factor-1.

1) INFLUENZA (FLU) ANTIVIRAL DRUGS



Influenza viruses (ortomyxoviruses) = RNA viruses

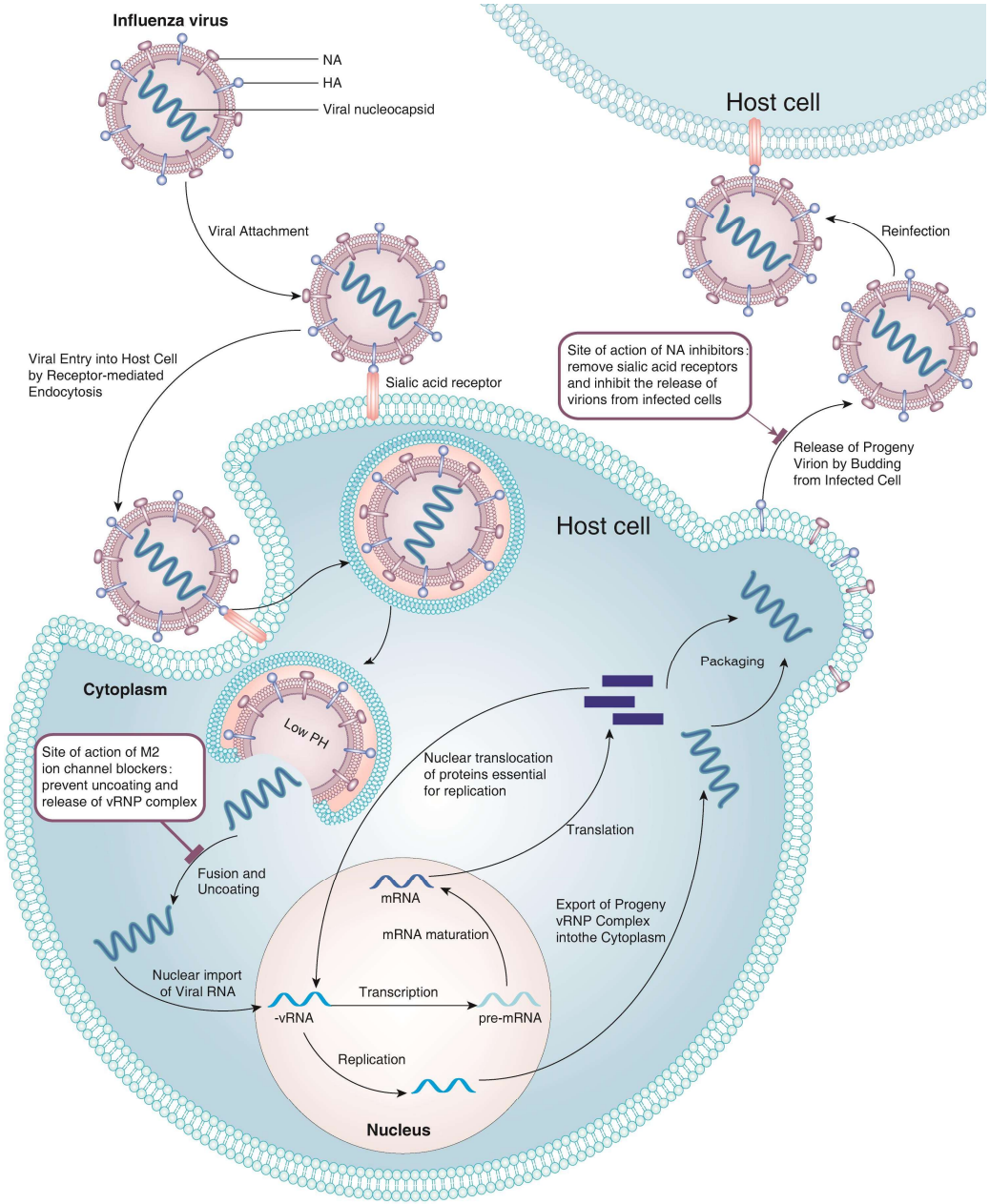
A – causes epidemia, many potential hosts, quickly mutate in bird hosts

B – not widespread, host: human, mutate 2-3x slowly
C – less dangerous

• ***Hemagglutinin*** **-** membrane glycoprotein, binds to sialic acid radicals on the surface of the host cell

• ***Neuraminidase*** **-** enzyme cleaving mucous secrete and preventing clustering of newly created virions

1) influenza antivirals



ANTI-INFLUENZA DRUGS

1. Inhibition of uncoating and release:
amantadin, rimantadin

Antimetabolites:
ribavirin

2. Inhibition of neuraminidase:
zanamivir
oseltamivir

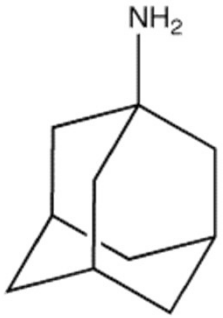
1) influenza antivirals

Amantadine

↑ dopaminergic aktivity in striatum (Parkinson´s dis.)

MA: inhibition of **viral membrane M2-protein** (H^+ channel) – prevention of ribonucleoprotein complex dissociation =) inhibiting the alignment of new virions at the membrane

- rapid resistance in 30 % patients.



I: influenza A prophylaxis (Ag types: H1N1, H2N2, H3N2)

- good oral absorption ($T_{1/2}$ 17 – 29h)

CI: renal failure, age under 15 years, pregnancy, lactation

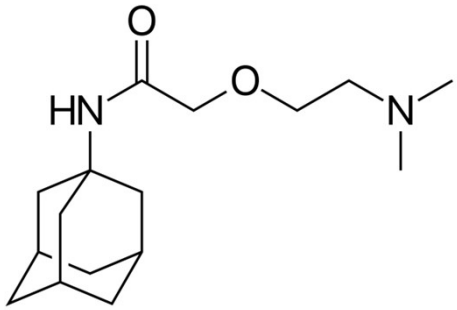
AE: orthostatic hypotension, GIT disorders, CNS influencing (psychosis, dizziness), CVS disorders

Amantadine derivates

Rimantadine

–structural analog of amantadine – similar effect and use

Tromantadine (Viru-Merz)

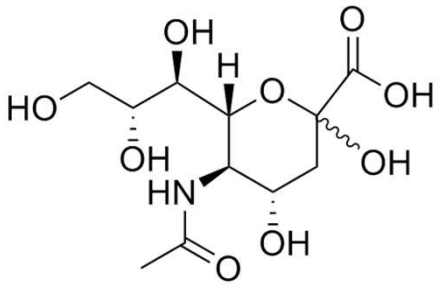


–syntetic derivate of aminoadamantane

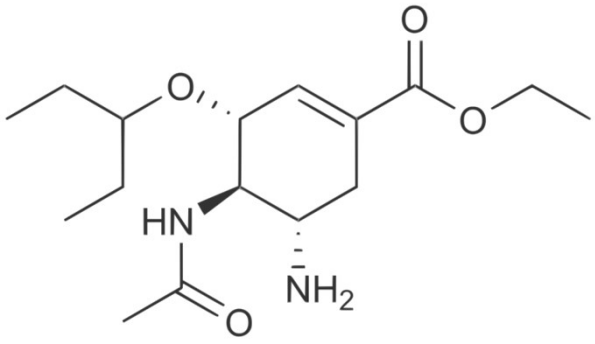
–local therapy of skin and mucosal symptoms of HSV I and II

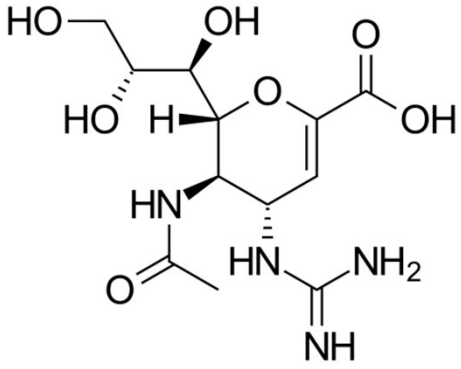
Neuraminidase inhibitors

Sialic acid – N-acetylneuraminic acid

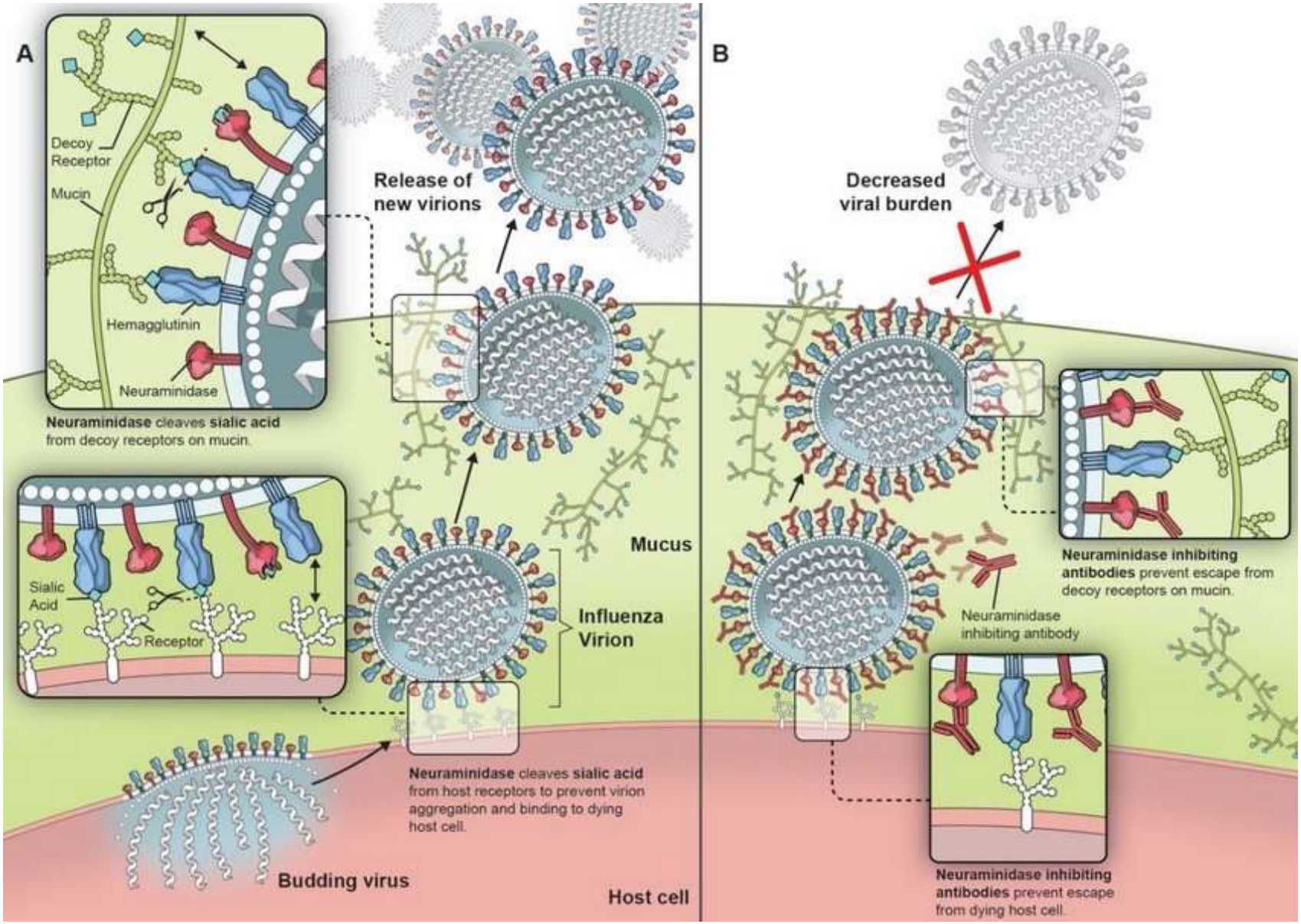


Sialic acid
(*N*-acetyl neuraminic acid)

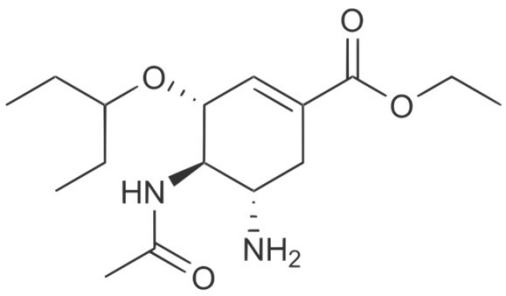




- part of glycoproteins of cell surface
- Pleiotropic effects, role in immune response, role in synaptogenesis


A
Decoy Receptor
Mucin
Hemagglutinin
Neuraminidase
Neuraminidase cleaves sialic acid from decoy receptors on mucin.
Release of new virions
Sialic Acid
Receptor
Mucus
Influenza Virion
Neuraminidase cleaves sialic acid from host receptors to prevent virion aggregation and binding to dying host cell.
Budding virus
Host cell
B
Decreased viral burden
Neuraminidase inhibiting antibodies prevent escape from decoy receptors on mucin.
Neuraminidase inhibiting antibody
Neuraminidase inhibiting antibodies prevent escape from dying host cell.

1) Anti-influenza antivirals



Neuraminidase inhibitors

Sialic acid analogs

MA: competitive inhibition of viral neuraminidases of influenza A and B

oseltamivir- prodrug
max. effect: in first 2-3 days of acute illness
mitigate and shorten symptoms

Oseltamivir

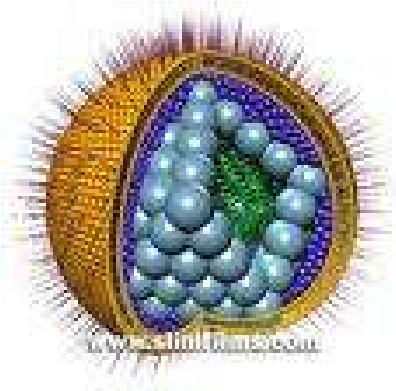
rapid development of resistance!

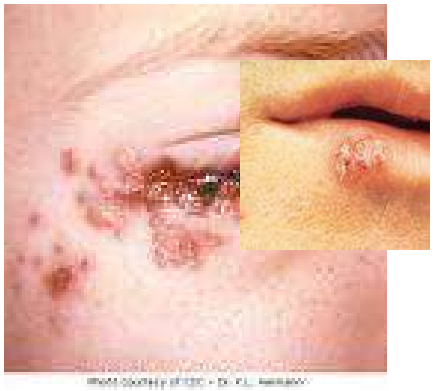
Zanamivir:

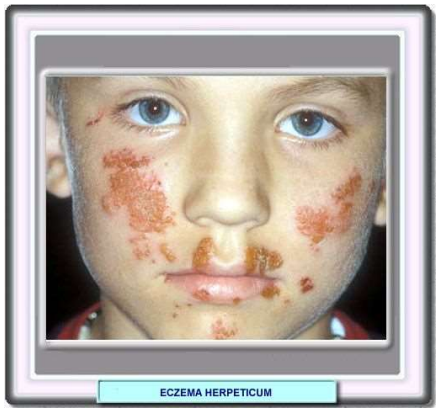
inhalation (low p.o. bioavailability)
AE:
cough, bronchospasm, headache, confusion, nausea

AE: nausea, epigastric discomfort, diarrhea, insomnia, skin reactions, transaminse elevation, neuropsychiatric AE (confusion, agitation, halucination, abnormal behavior)

2) Herpetic viruses







Herpes viruses (= double-string DNA viruses)

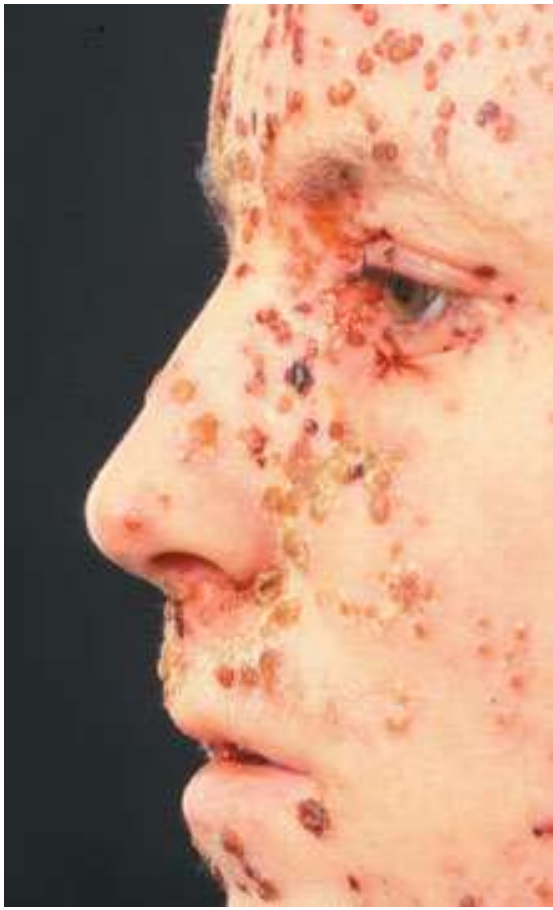
1+2 Herpes simplex virus I and II – lesion in face (lip, cornea) or genital area

3 Varicella-zoster virus – small-pox, herpes zoster

4 EBV infectious mononucleosis

5 Cytomegalovirus (CMV) – infectious mononucleosis, infections in imunosupressed patients

6-8 HHV (human herpes viruses)



Anti-herpetic antivirals

1. virostatic antimetabolits *(purines, pyrimidines)*

– ***aciclovir, valaciclovir, famciclovir, penciclovir, ganciklovir, cidofovir, idoxuridin, trifluridin, vidarabin***

2. fusion inhibitors ***- docosanol***
3. antisense oligonukleotides ***- fomivirsen***
4. DNA polymerase inhibitors ***- foscarnet***

Anti-herpetic drugs

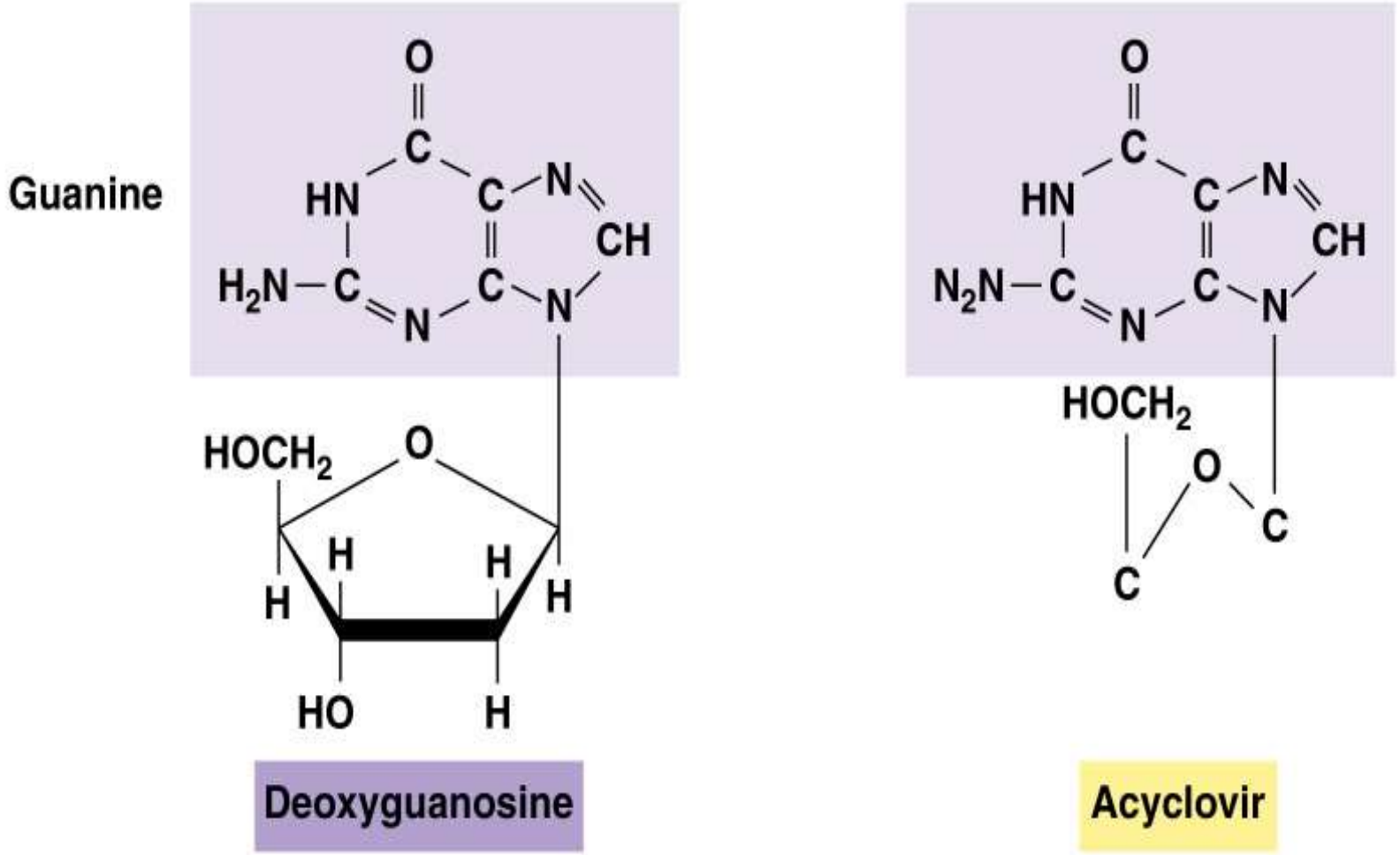
Virostatic antimetabolites

syntetic nucleosides, so called nucleoside analogues (antimetabolites)

fosforylation → active drug:

substitution of carbohydrate → **block of enlongation of nucleic chain**

substitution of base → **nonfunctional DNA matrix**



(a) Structural resemblance between acyclovir and guanine-containing nucleoside

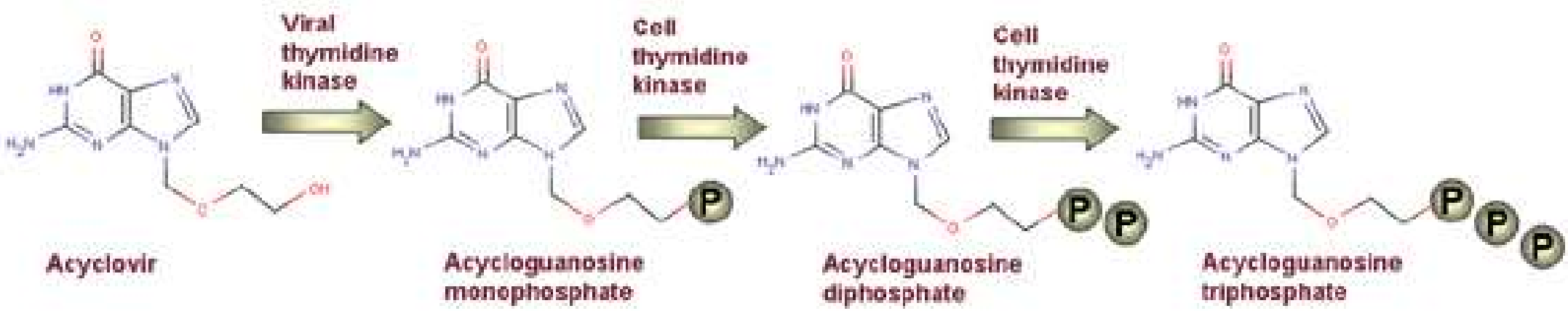
Virostatic antimetabolites I.

Aciclovir (syntetic analogue of guanosine)

specific, well tolerated antiviral

effective in form of aciclovir triphosphate

- monophosphate – viral thymidinkinase
- di- and triphosphate –kinases of host cell



Virostatic antimetabolites

Aciclovir

- **anti- HSV-1,2 + VZV** >> CMV and EBV
- i.v. herpetic encephalitis
- profylaxis of CMV infection in BMT recipient (tbl., inj.)
- in severely immunocompromised (AIDS)

– local, oral, i.v. application

AE:

p.o. – GIT intolerance
i.v.: tromboflebitis (3%), renal dysfunction, neurotoxic, mental symptoms

Resistance caused by changes in the viral genes coding for thymidine kinase or DNA polymerase has been reported and aciclovir-resistant HSV has been the cause of pneumonia, encephalitis and mucocutaneous infections in immunocompromised patients

Virostatic antimetabolites

Aciclovir, Valaciclovir, Famciclovir → Penciclovir

– similar efficacy **anti- HSV-1,2 + VZV**
– generics available

– ***aciclovir*** – best safety, bioavailability 10-20 %

– ***penciclovir*** - only topical drug in herpes labialis

– ***valaciclovir*** – aciclovir prodrug (L-Valin), better absorption after oral administration (F=77%), less frequent dosing

Virostatic antimetabolites

Ganciclovir (Valganciclovir = prodrug)

I: severe CMV infections in immunodeficiency patients in AIDS patients
transplantation: **prevention of CMV transmission** from CMV+ donors

AE: haematologic: up to 40 % (anaemia, neutropenia, trombocytopenia)
GIT, neurotoxic, teratogenic – spermatogenesis inhibition

Cidofovir

effective against CMV (also in case of ganciclovir resistance)
– CMV retinitis in AIDS patients

AE: nefrotoxicity (proteinuria, glykosuria, azotemia), neutropenia, teratogenic, kancerogenic

Virostatic antimetabolites - topical

- ***Idoxuridin***

– inhibits NA synthesis in both viruses and human cells → toxic also for host!!!

– corneal herpetic infections (in case of impossible systemic application)

- ***Trifluridin***

I: (systemic use - colorectal carcinom)

locally in herpetic eye infections and chronic skin ulcerations

Other anti-herpetic drugs

Docosanol

fusion inhibitor

HSV, CMV, RSV, influenza

I: initial phase of HSV-1 infection, h. labialis

Fomivirsen

antisense oligonukleotide

I: CMV retinitis

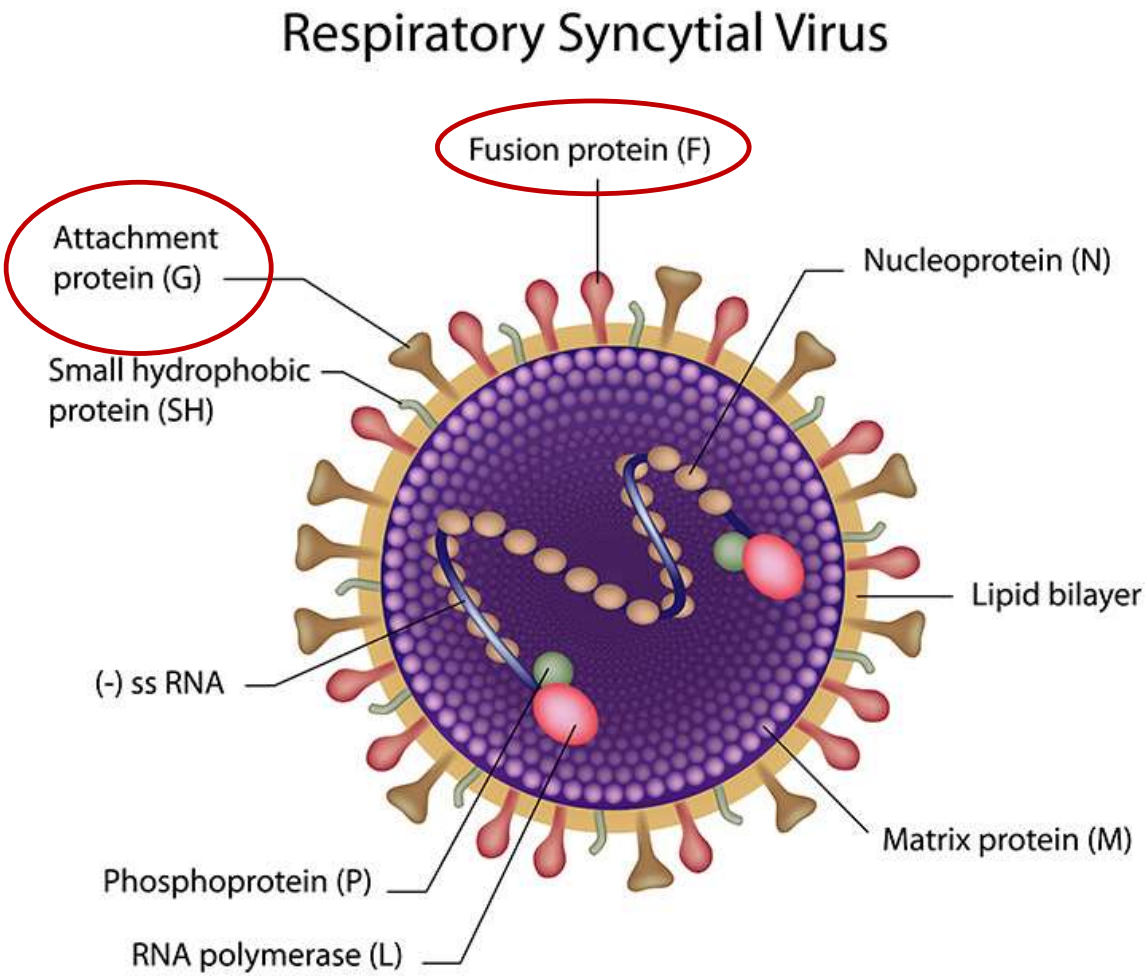
- injection into intraocular fluid – cummulation in retina and iris for 3-5 days

Foscarnet

inhibits DNA polymerase

I: immunodeficient pacients with CMV, HV infection resistant to aciclovir and ganciclovir

3) Respiratory viruses (RSV + coronaviridae - SARS, MERS, COVID)



RSV

- antigenic types A and B
- mortality **1-3 % in hospitalized infected children**
- correlation with SIDS (25 % post mortem)

- early RSV infections are independent risk factor for AB

- **Mab immunoprophylaxis** in preterm infants with high risk of bronchopulmonary dysplasia and in children under 4 years of age with congenital heart disease

RSV

Palivizumab, Motavizumab

- humanized Mab (95 % human Mab) against the fusion protein F
- effective against both types of RSV

Ribavirin

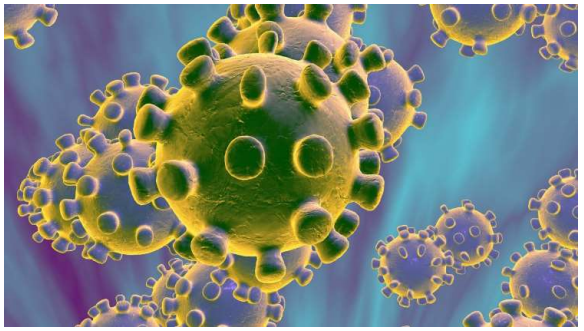
- syntetic nucleoside

- I: HVC
- off label: viral pneumonia in children and immunocompromised patients
- concerns about efficiency

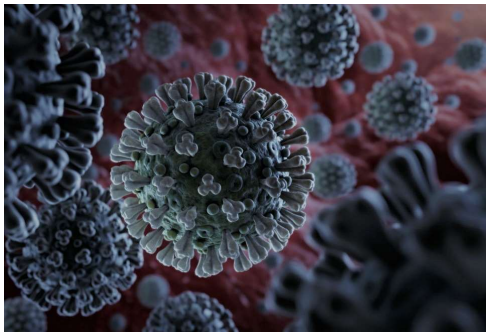
SARS, MERS, COVID

(Severe Acute Respiratory Syndrome, Middle East Respiratory Syndrome , Coronavirus disease

- supplemental oxygen (respiratory distress, hypoxemia, or shock)
- fluid management
- empiric antimicrobials
- **do not routinely use corticosteroids** for viral pneumonia or ARDS
- closely monitor
- tailor supportive management based on comorbidities



Monoclonal Ab



- recombinant human IgG MAbs against the spike protein of SARS-CoV-2
- bind to the spike protein, block attachment to the human ACE2 receptor

Bamlanivimab, etesivimab, casirivimab + imdevimab, sotrovimab

I: SARS-CoV-2 positive at **high risk for progression** to severe disease or hospitalization

NOT: hospitalized or require new or increased oxygen therapy due to COVID-19;

Only when the patient is likely to have been infected with or exposed to a variant that is susceptible to these treatments

- highly unlikely to be active against the omicron

Remdesivir

MoA:

- nucleotide prodrug metabolized to nucleoside metabolite
  → incorporation into the viral RNA template
- inhibition of RNA-dependent RNA polymerase

- used in combination with dexamethasone or baricitinib (Jak Tki)
  → prevents the activation of STAT transcription factors and reduces serum IgG, IgM, IgA, and C-reactive protein

World Health Organization **recommends against** the use of remdesivir in hospitalized patients, regardless of disease severity within 72 hours of a positive SARS-CoV-2 test

Molnupiravir

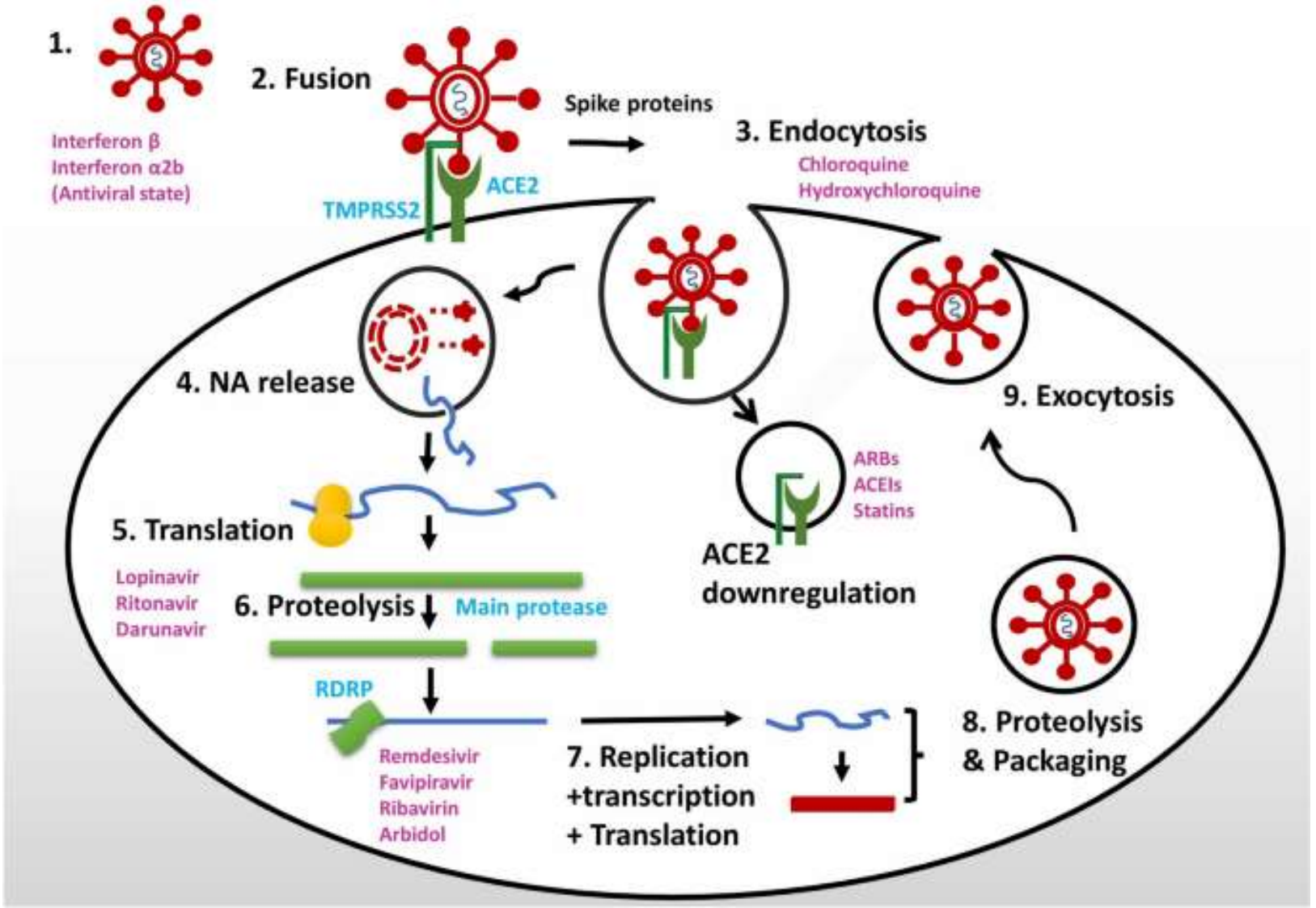
- orally available antiviral, which was originally designed as an **influenza treatment**, although not approved
- inhibits replication of SARS-CoV-2 similar to remdesivir, and was re-purposed early in development as an antiviral for SARS-CoV-2

I: OFF label: COVID-19, treatment, mild to moderate (outpatients with high risk of progression to severe illness) (alternative agent)

MoA

metabolized → cytidine nucleoside, phosphorylated to triphosphate, incorporated into SARS-CoV-2 RNA by viral RNA polymerase,

→→errors in viral genome, inhibition of replication


1.
Interferon β
Interferon α2b
(Antiviral state)
2. Fusion
TMPRSS2
ACE2
Spike proteins
3. Endocytosis
Chloroquine
Hydroxychloroquine
4. NA release
5. Translation
Lopinavir
Ritonavir
Darunavir
6. Proteolysis
Main protease
RDRP
Remdesivir
Favipiravir
Ribavirin
Arbidol
7. Replication
+transcription
+ Translation
8. Proteolysis
& Packaging
9. Exocytosis
ARBs
ACEIs
Statins
ACE2
downregulation

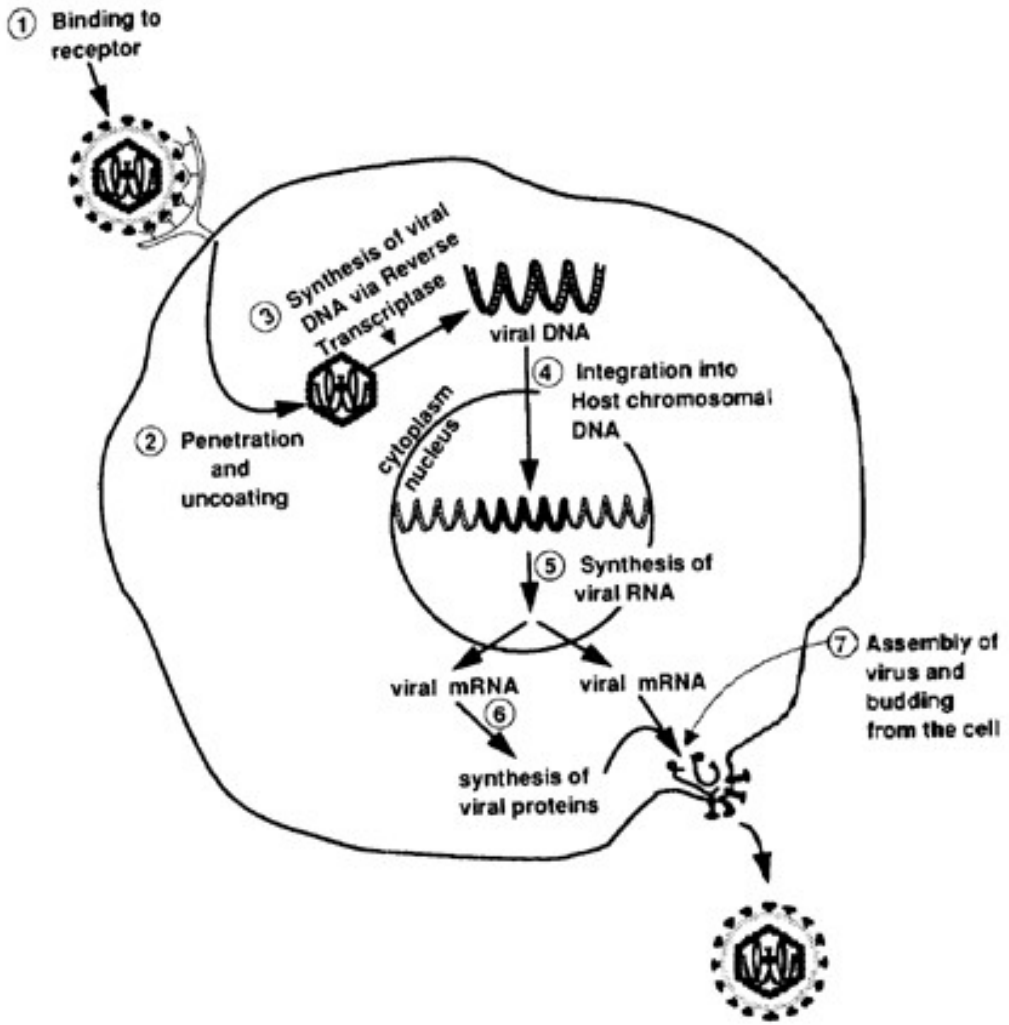
Anticoagulation intensity in people hospitalized for COVID-19 *(March 2021)*

- Thromboembolic complications of severe COVID-19 are common in hospitalized patients, especially in ICU
- optimal approach to venous thromboembolism (VTE) prophylaxis has been unclear
- RCT: prophylactic dose anticoagulation is equally effective as higher doses of anticoagulation in reducing VTE risk, including in patients in the ICU, with trends towards lower rates of bleeding
- Standard prophylactic dosing is appropriate for patients hospitalized for COVID-19 who do not have a VTE.

4) Antiretrovirals

Retroviruses

RNA viruses able to transcribe their genetic code into DNA using enzyme called reverse transcriptase



5) Antiretrovirals

Retroviruses

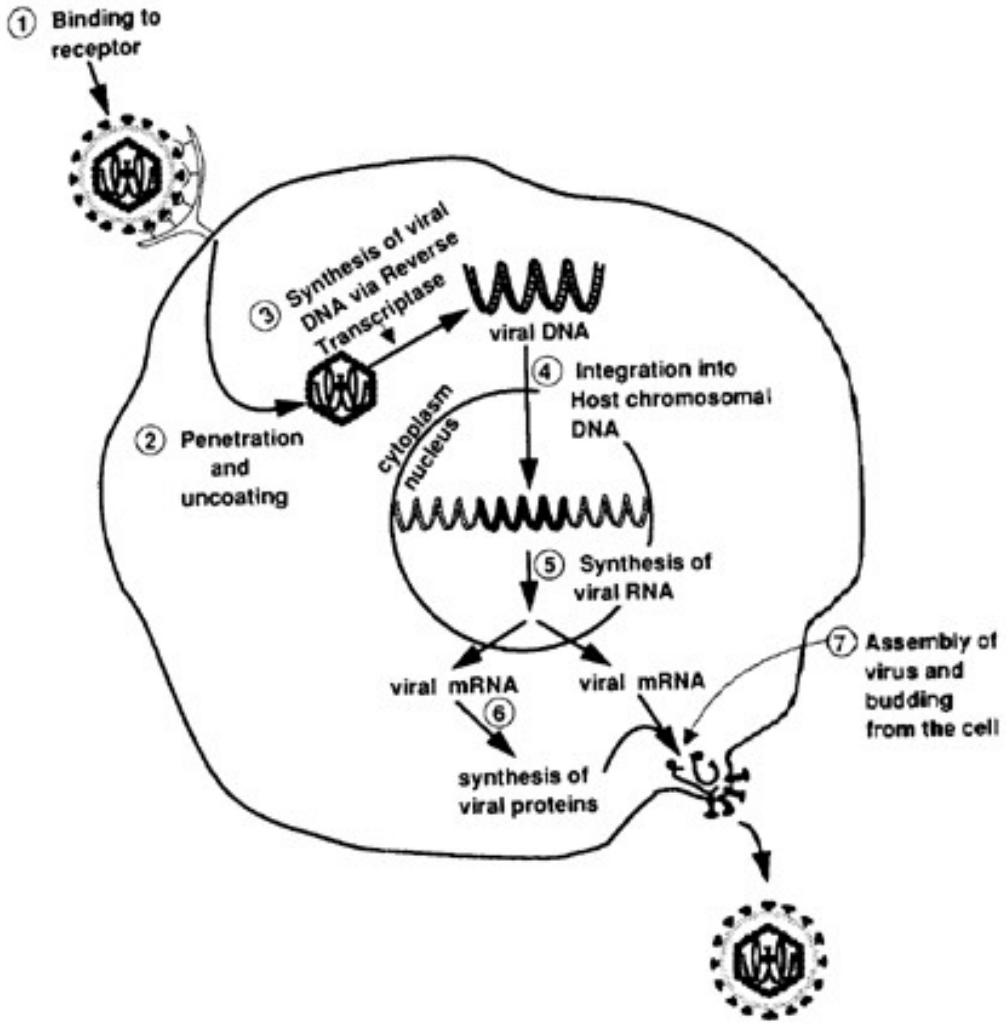
HIV cause pandemic of AIDS

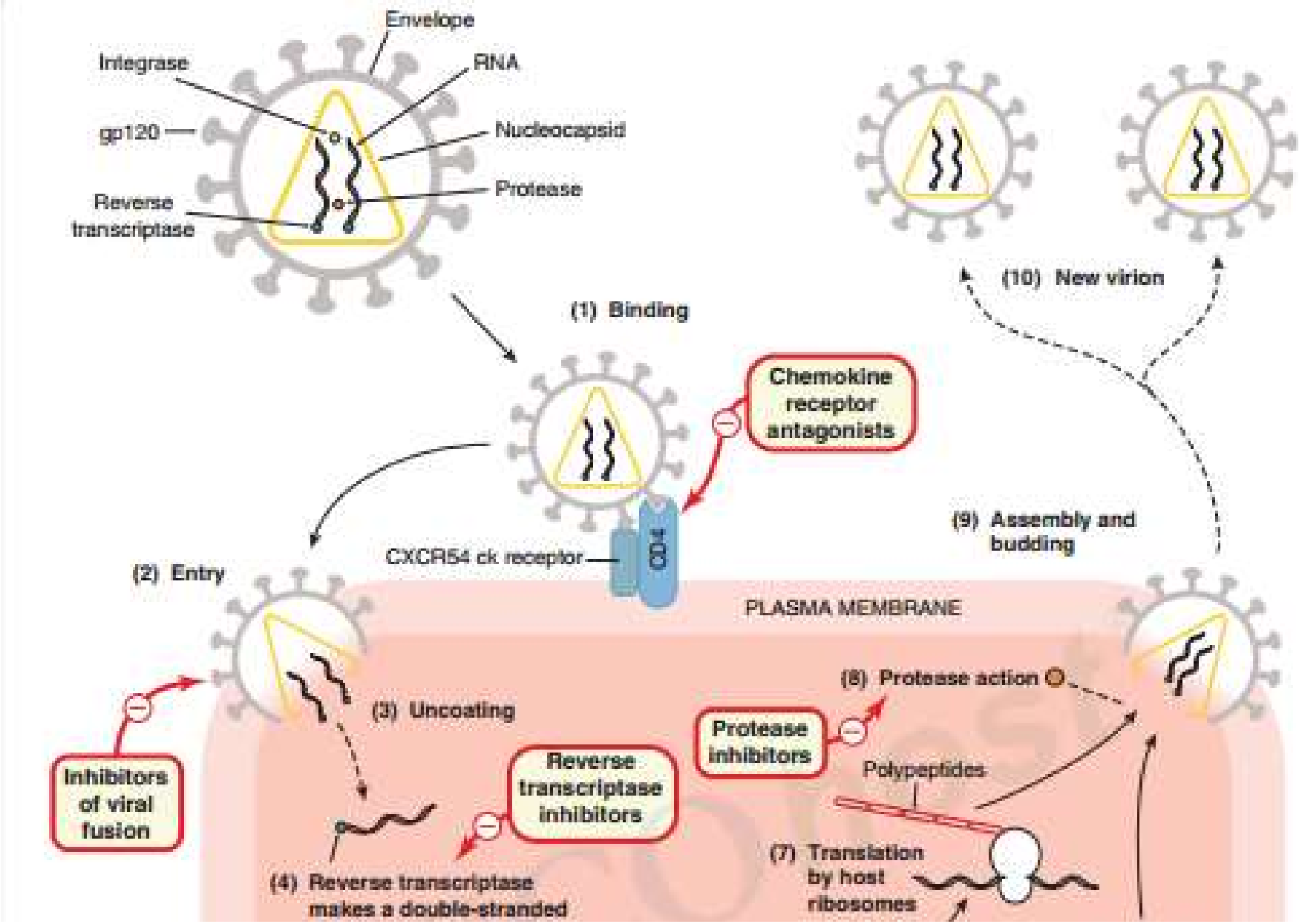
this infection leads to lower levels of CD4+ T-lymfocytes → immunodeficiency

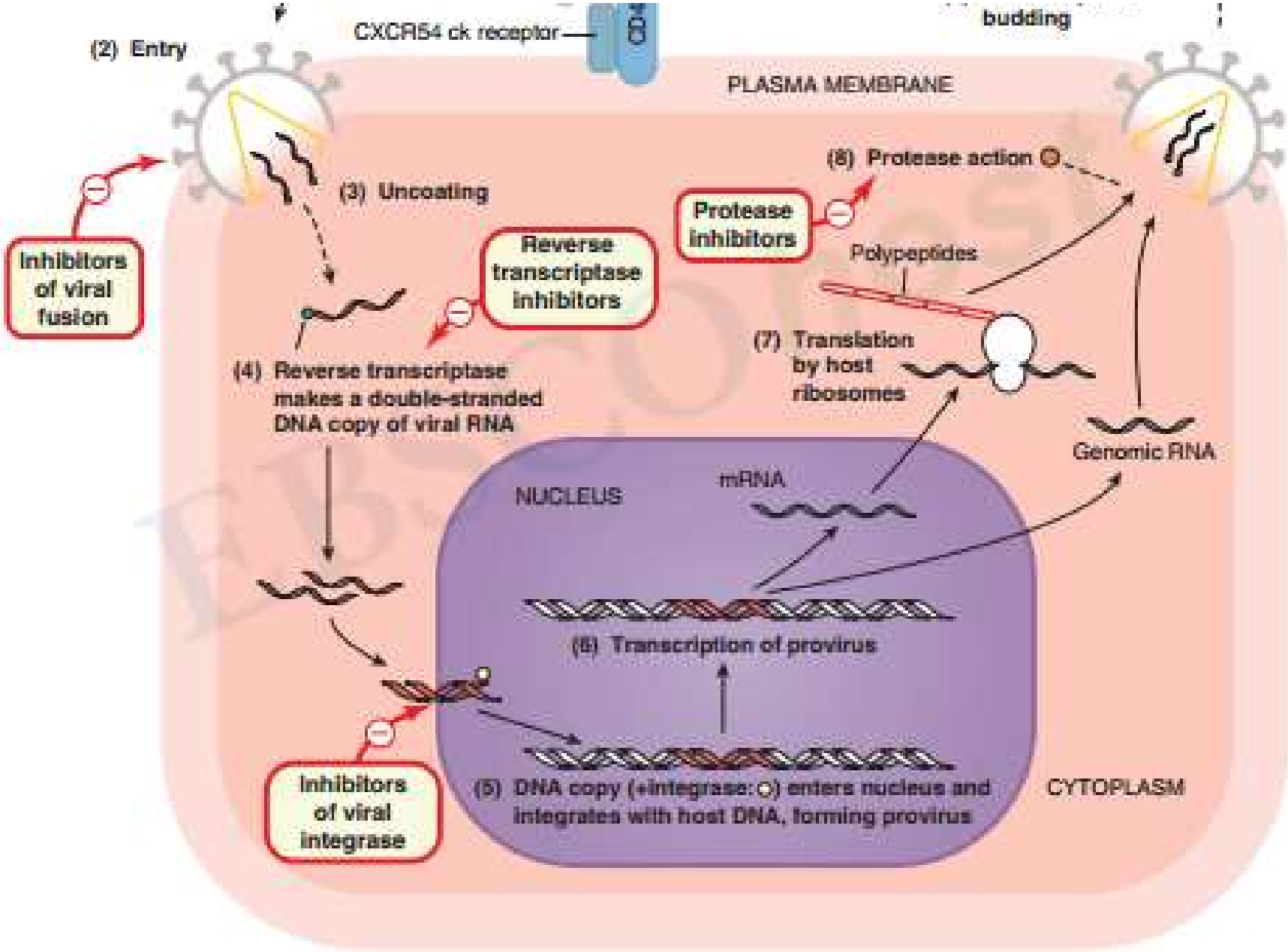
WHO estimate in 2018: 38 mil HIV+, 23 mil. receive treatment

1,7 mil deaths/year, Africa : 4,4 % adults

effective AR therapy since 1996, transmission prevention strategy (PEP)




Envelope
Integrase
RNA
gp120
Nucleocapsid
Protease
Reverse transcriptase
(10) New virion
(1) Binding
Chemokine receptor antagonists
CXCR54 ck receptor
CD4
(9) Assembly and budding
(2) Entry
PLASMA MEMBRANE
(8) Protease action
(3) Uncoating
Protease inhibitors
Polypeptides
Inhibitors of viral fusion
Reverse transcriptase inhibitors
(7) Translation by host ribosomes
(4) Reverse transcriptase makes a double-stranded


(2) Entry
CXCR54 ck receptor
CD4
budding
PLASMA MEMBRANE
(8) Protease action
Protease inhibitors
Polypeptides
(3) Uncoating
Inhibitors of viral fusion
Reverse transcriptase inhibitors
(7) Translation by host ribosomes
(4) Reverse transcriptase makes a double-stranded DNA copy of viral RNA
Genomic RNA
mRNA
NUCLEUS
(6) Transcription of provirus
Inhibitors of viral integrase
(5) DNA copy (+integrase: ○) enters nucleus and integrates with host DNA, forming provirus
CYTOPLASM

Antiretrovirals

Classical:

Reverse transcriptase inhibitors	**RTIs:**
Nucleoside	**NRTI** zidovudin, stavudin, zalcitabin, lamivudin, didanosin
Nucleotide	**NtRTI** tenofovir
Non-nucleoside	**NNRTI** nevirapin, efavirenz, delavirdin

Newer:

Protease inhibitors	**PI** indinavir, saquinavir, ritonavir, nelfinavir
Fusion inhibitors	**FI**
Integrase inhibitors	**InSTI**

Maturation inhibitors (IFN + research)

NRTI

- the oldest class of antiretrovirotics
- synthetic dideoxynucleosides → competitive inhibition of viral reverse transcriptase (block of replication)
- nucleoside analogs, sometimes called „nukes“ or „backbone“
- higher affinity for the virus enzyme than the host cell → specific effect

MoA: phosphorylation by viral kinases: triphosphate → → **reverse transcriptase inhibition**
→ binding as false precursors – **inhibition of DNA synthesis**

NRTI

zidovudine (azidothymidine)
the first substance delaying the manifestation of AIDS
reduces the risk of transmission of the infection to the fetus in pregnant women

AE: **bone marrow suppression**, anemia, leukopenia, myalgia, headache, fatigue, insomnia

stavudine, didanosine, lamivudine, abacavir, emtricitabine

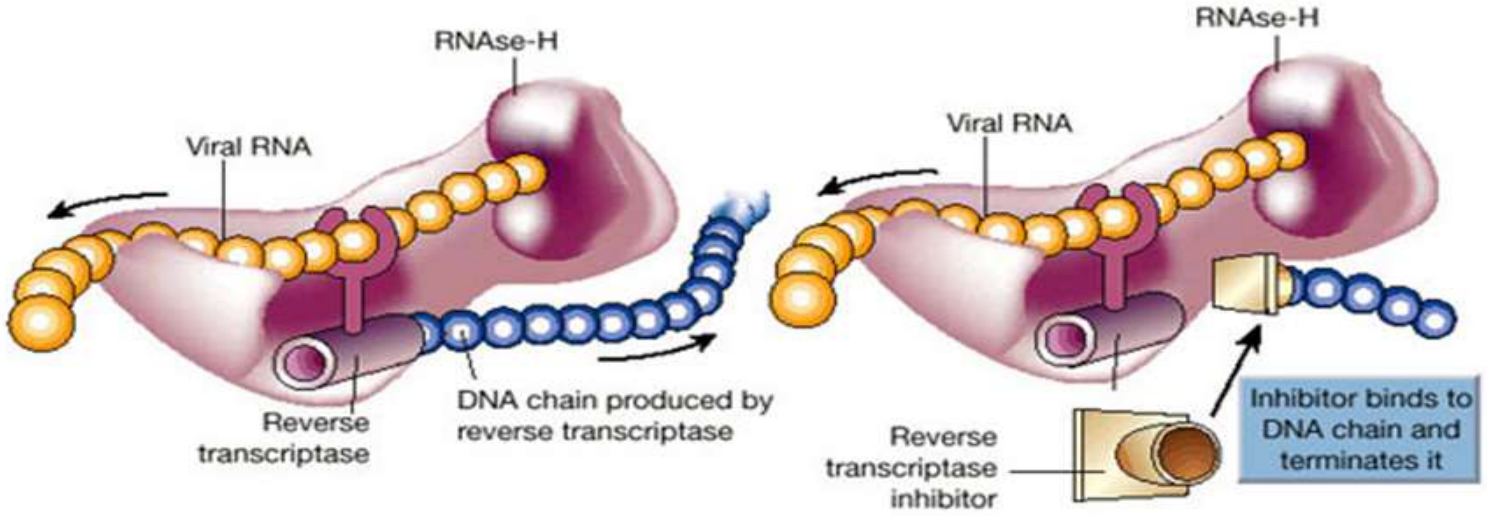
AE: hepatomegaly with steatosis, lactic acidosis, hyperglycaemia, lipodystrophy, insulin resistance, pancreatitis, peripheral neuropathy, retinal damage, hyperuricemia

Nucleotide Reverse Transcriptase Inhibitors (NtRTI)

tenofovir

part of combination therapy in patients with NRTI resistance

2015: tenofovir alafenamid: reduced nephrotoxicity, bone toxicity

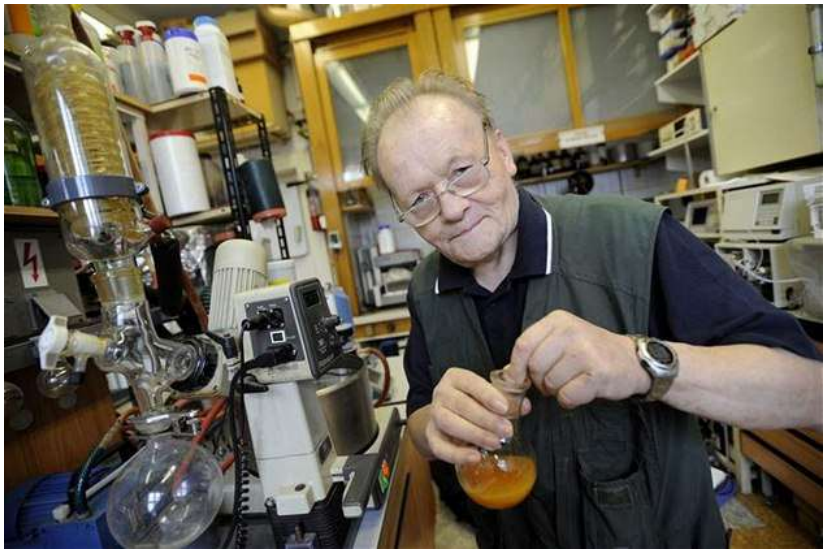


Prof. Holý, UACHB AV ČR
*1936 † 2012

Cidofovire

Tenofovire disoproxil

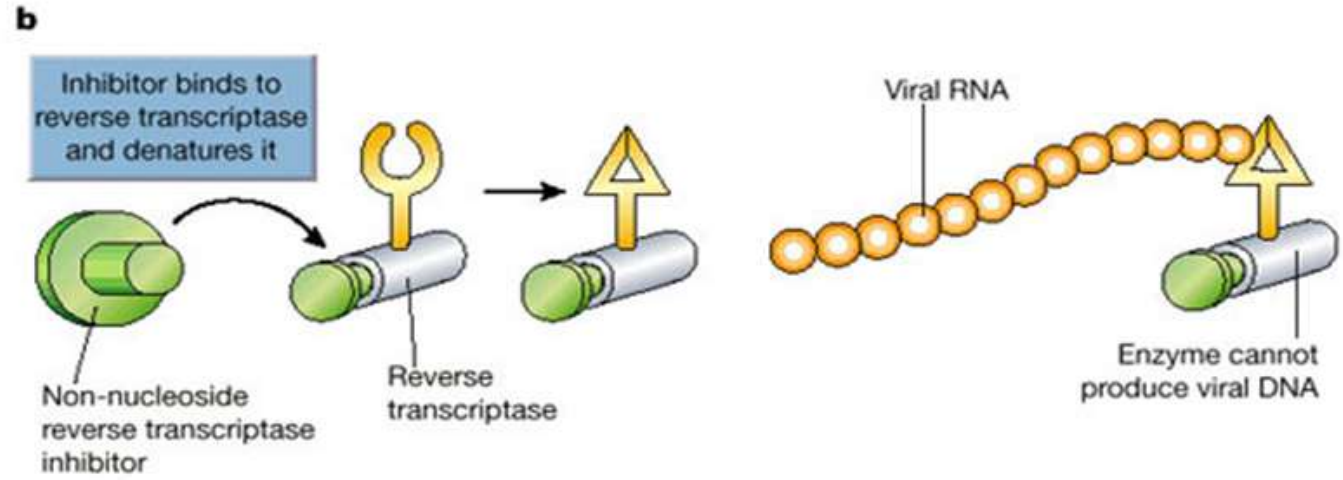
Adefovire



Non-nucleoside RTI (NNRTI)

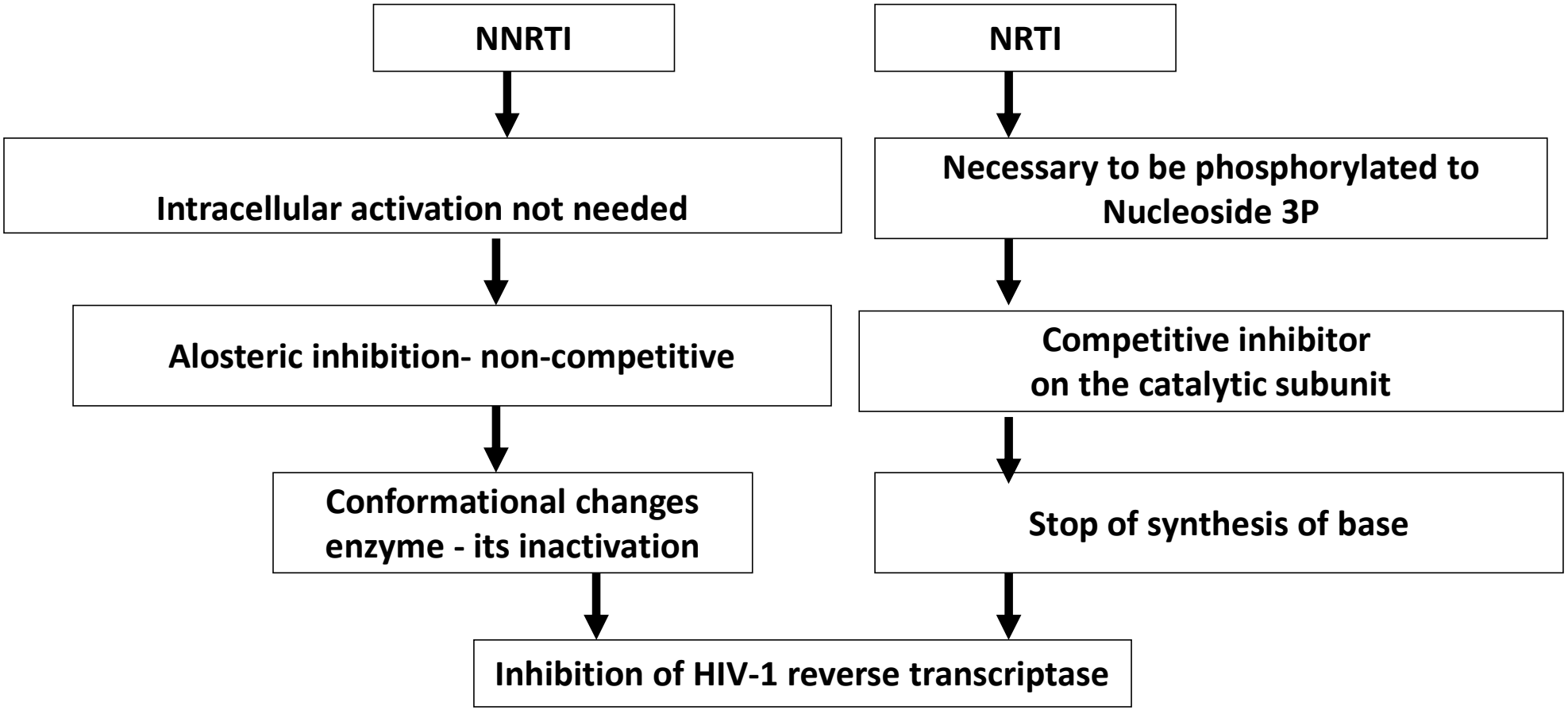
- direct effect (without intracellular phosphorylation)
- inhibition of RT by change of its conformation
- only in combination therapy

nevirapine
efavirenz
etravirine
rilpivirine
delavirdine



AE: rashes, liver failure
–Frequent DDI interactions (inducers of CYP 450)

Differences in the mechanism of action of NNRT and NRTI



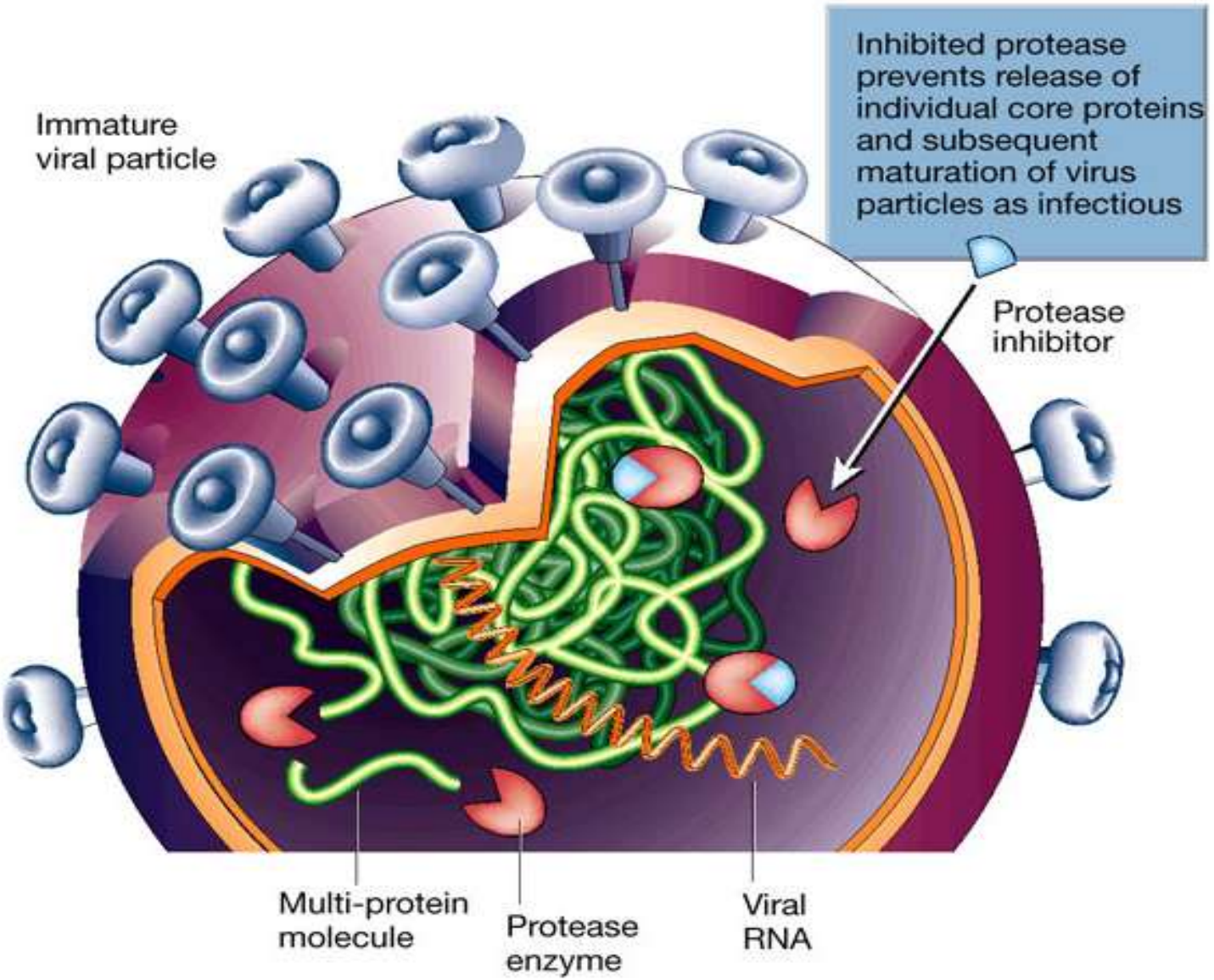
retroviral Protease inhibitors (PI)

- bind to active site of HIV protease and inhibit its function → blockade of completing the capsid and release of virions
- they are very effective and well tolerated

darunavir, ritonavir, atazanavir
oral administration

AE: especially **common in GIT** (nausea, vomiting, anorexia, diarrhea), hematopoietic depression, neuropathy

Metabolic: mtch toxicity, DM, dislipidemia (LPV, ATV less)
D-D interactions (CYP inhibition)

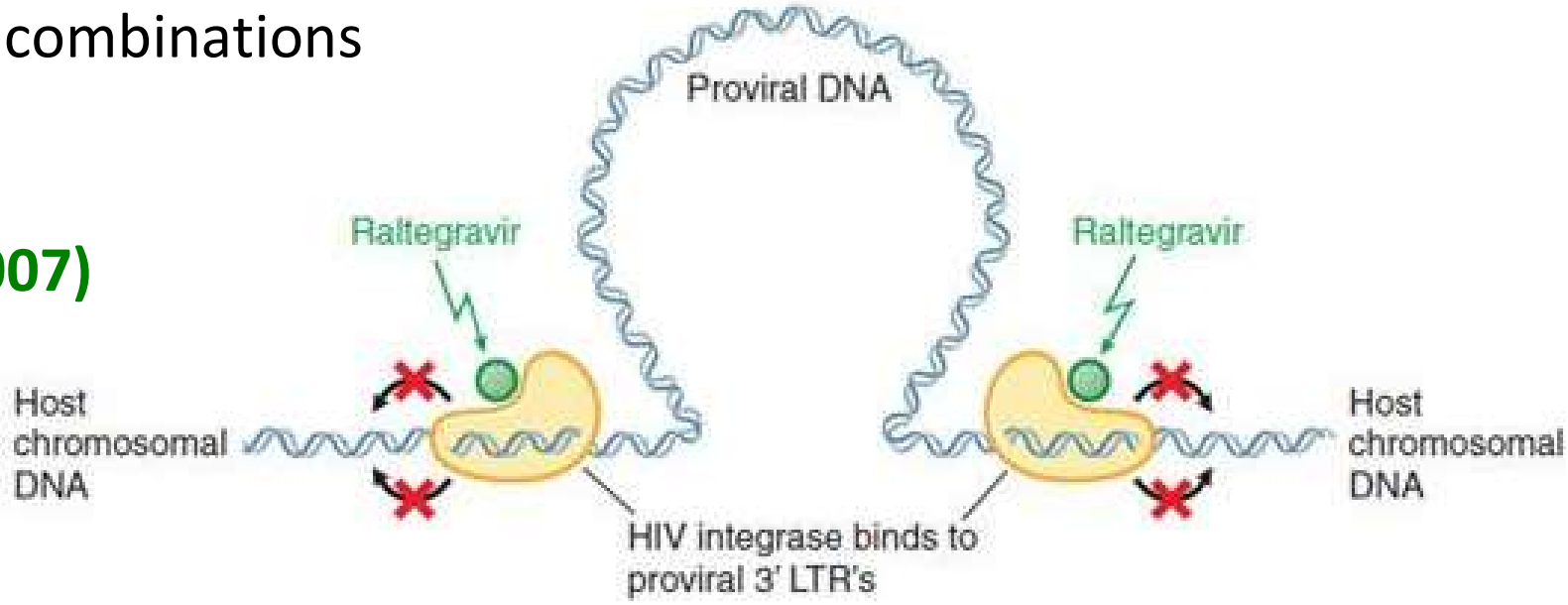

Inhibited protease prevents release of individual core proteins and subsequent maturation of virus particles as infectious
Immature viral particle
Protease inhibitor
Multi-protein molecule
Protease enzyme
Viral RNA

Integrase inhibitors (InSTI)

inhibit insertion of the viral genome into the host cell genome without negative metabolic effects of PI

Ideal for (fixed) combinations

Raltegravir (2007)
Dolutegravir
Elvitegravir



Fusion inhibitors (FI)

after failure/intolerance of combined NRTI, NNRTI and protease inhibitors
no cross-resistance among NRTI, NNRTI, NtRTI

Maraviroc

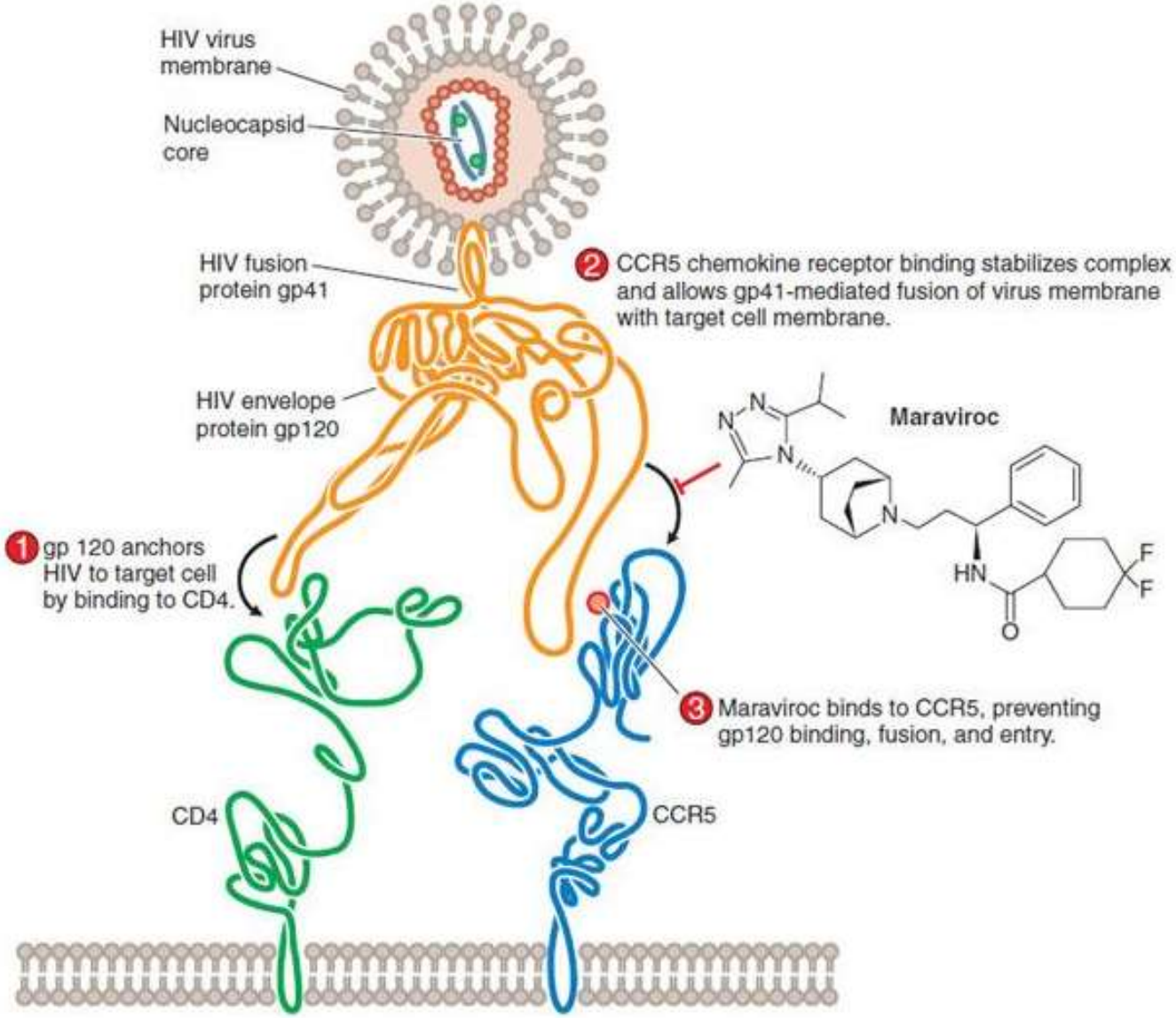
binding to human CCR5 receptor preventing CCR5-tropic HIV-1 from entering the cell

I: only CCR5- tropic HIV-1, not the CXCR4
CYP3A4 substate

Enfuvirtide (2003)

- peptidic structure – s.c. administration, 2x daily ($T_{1/2}$ 3.8 h)
- blocks viral membrane fusion and penetration
- expensive, used in resitant patients

Fusion inhibitors



Strategy of AIDS therapy

1. Antiretroviral therapy

2. Treatment of associated diseases:

opportunistic infections (pneumonia, mycobacterial and fungal infections) and tumors (lymphomas, Kaposi's sarcoma)

1996, the triple fixed combination

HAART (Highly Active Antiretroviral Therapy

[(1 NRTI + 1 NtRTI) or 2 NRTI**]** **+** (INSTI or PI/r)

Simply: 2 transcriptase inhibitors + inhibitor of protease or integrase

Effect evaluation: accordingly to viraemia

Change in the combination: prevents accumulation of resistant mutants

5. Antivirals in hepatitis

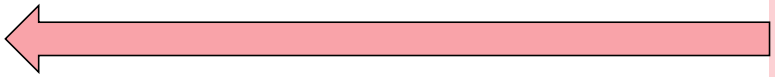
- Viruses are in liver replicated via RNA – similarity with retroviruses

- A, B, C, D
- Different: virulence, healing, transition to chronicity

Drugs used in HBV infection

- Pegylated interferon alpha-2a (PEG-IFN)
- Conventional interferon alfa (IFN) .

- **RTI:**
  - lamivudin (LAM)
  - adefovir dipivoxil (ADV)
  - tenofovir (TDV)



Viruses are in liver replicated via RNA – similarity with retroviruses

Drugs in the treatment of HCV

Ribavirin

DAA – „Directly acting antivirals“

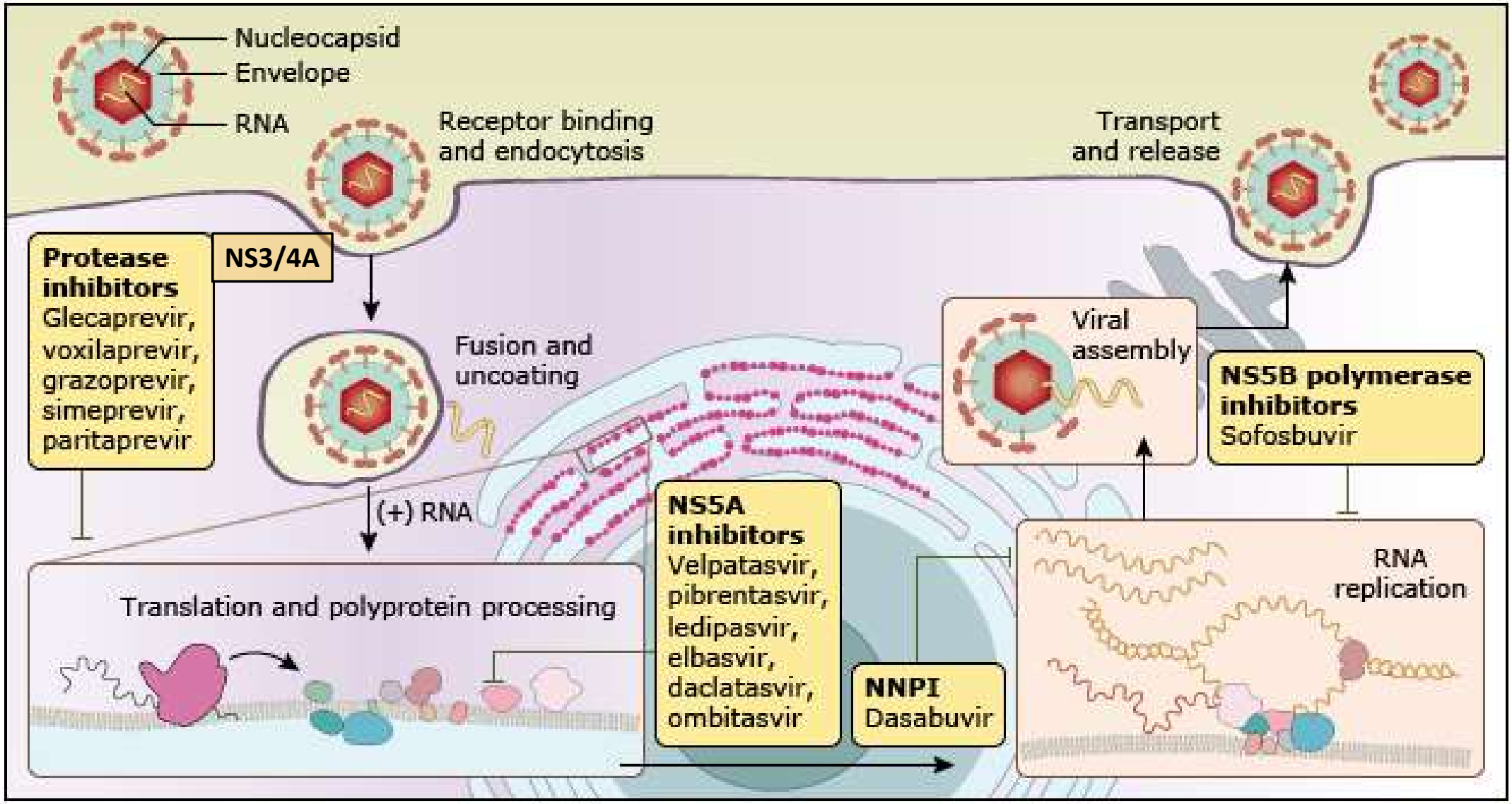
- **HCV RNA polymerase inh.**

  daclatasvir, sofosbuvir, ledipasvir, velpatasvir, elbasvir, pibrentasvir, ombitasvir

- **HCV protease inh.**

  boceprevir, telaprevir, simeprevir, grazoprevir, voxilaprevir , glecaprevir, paritaprevir

- **Non-nucleotide polymerase inhibitor -** dasabuvir


Nucleocapsid
Envelope
RNA
Receptor binding and endocytosis
Transport and release
Protease inhibitors
Glecaprevir, voxilaprevir, grazoprevir, simeprevir, paritaprevir
NS3/4A
Fusion and uncoating
Viral assembly
NS5B polymerase inhibitors
Sofosbuvir
(+) RNA
NS5A inhibitors
Velpatasvir, pibrentasvir, ledipasvir, elbasvir, daclatasvir, ombitasvir
NNPI
Dasabuvir
Translation and polyprotein processing
RNA replication

Ribavirin (HCV)

- **Wide-spectrum antiviral, essential drug WHO**
- acts as guanosine analog in RNA viruses, in DNA viruses is MoA unknown,
- used to treat RSV infection, hepatitis C and some viral hemorrhagic fevers (Lassa fever, Crimean–Congo hemorrhagic fever, and Hantavirus infection)
- Oral or inhaled adm.

Interferons – Immunomodulatory cytokines

- cytokines, intracellular messengers, they do not affect virus itself but infected cells

= virostatic, antiproliferative, immunomodulant effect

Interferon α	**(IFN α)** – leukocytic
Interferon β	**(IFN β)** - fibroblast
Interferon γ	**(IFN γ)** - T cell

Interferons

α – produced by leukocytes after stimulation by viruses, bacterias or mitogens

β – produced by fibroblasts after stimulation by viruses and inhibitors of NA and protein synthesis

γ – produced by NK cells a T-cells after stimulation by antigens, mitogens and cytokines

=> α and β have similar antiviral effects, γ is imunomodulant

Interferons

I:

- chronic hepatitis B or C
- severe infections, encephalitis, generalized herpes zoster
- treatment and prevention of viral infection in immunodeficient patients
- tumors and autoimmune diseases

AE: flu-like syndrom, leukopenia, GIT, skin

Local therapy in oropharyngeal cavity

Local therapy in oropharyngeal cavity

Hexetidine (Stopangin)

- bacteriostatic, fungistatic effect

Chlorhexidine digluconate (Corsodyl)

- against G+,G-, Candida, viruses

Other antiseptics

- *Benzydamin hydrochlorid* - Tantum Verde
- *Oktenidin dihydrochlorid -* PHYTENEO Neocide gel
- *Benzalkonium chlorid* – Septolette
- *Benzoxonium chlorid* – Orofar
- *Cetylpyridinium chlorid* – Neo Septolette, Calgel (+lidokain)
- *Dichlorobenzenmethanol* – Neoangin, Strepsils (2-složˇ.)
- *Tridekanamin* - Septisan

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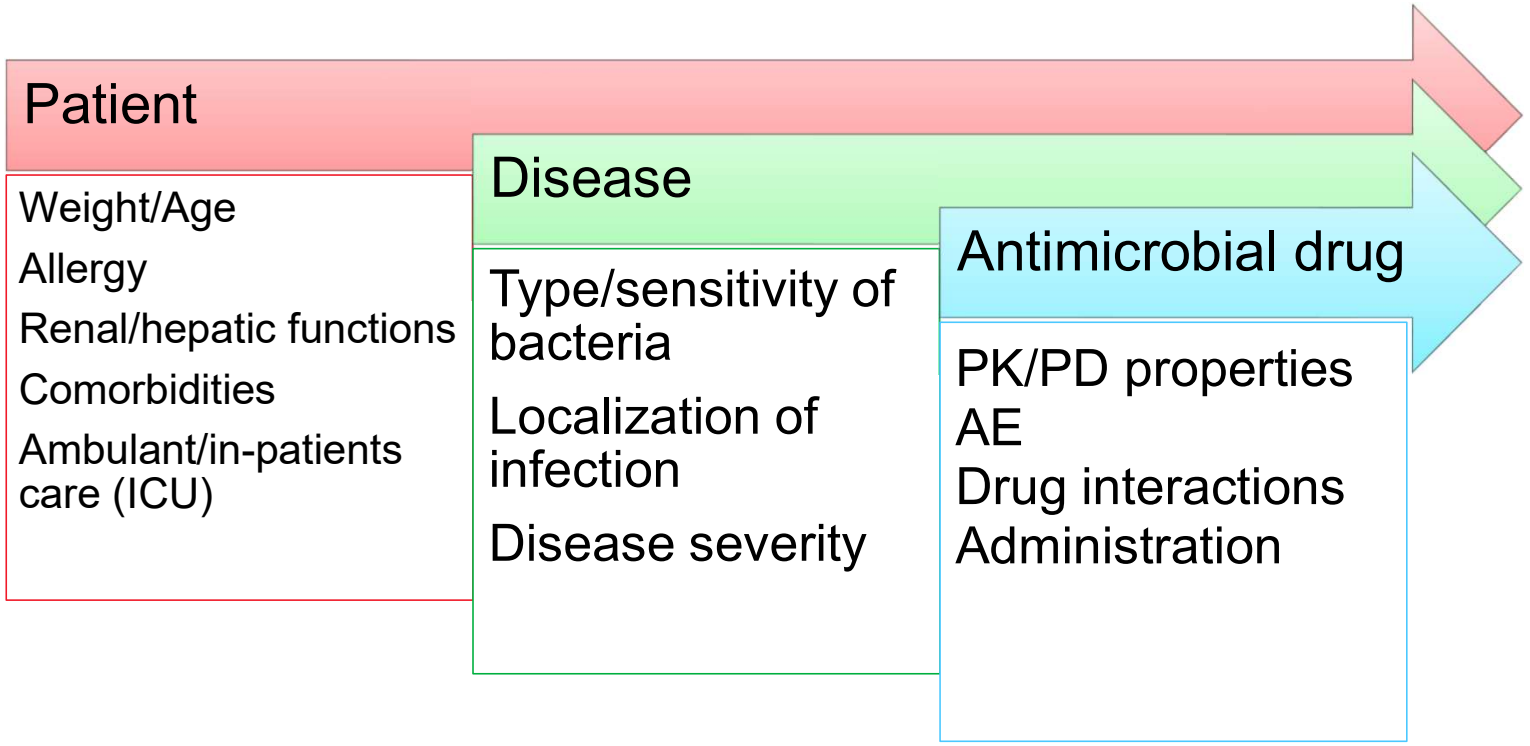
Selection of antibacterial drugs

Depends on:



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Selection of antibacterial drugs

ATB policy in Czechia

Antibiotic centers, free and bound ATB

National reference centre for healthcare associated infections (NRC-HAI)

EARS-NET

Antibiotic prophylaxis

single dose in perioperative period

during immunosuppression

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ATBs in dentistry

Use

- prevention – for risk patients (due to ADA)
    - artificial heart valves
    - a history of ineffective endocarditis
    - a cardiac transplant with developed valve problem
    - some of congenital heart conditions

- in some types of stomatosurgeries
    - for all dental procedures that involve manipulation of gingival tissue or the periapical region of the teeth, or perforation of the oral mucosa

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ATBs in dentistry

Drugs

- penicillin 1,5-3 mil. IU
- amoxicillin/clavulanic acid 1,2 g i.v. /1g p. o.
- ampicillin/sulbactam 2 g i.v./ 750 mg p.o.
- beta lactams allergic patients
    - clindamycin 600 mg p.o./i.m./i.v.
    - vancomycin 500 mg/i.v.

    - oral administration is recommended at least 1 hr before procedure and parenteral administration 15-30 mins before. In long lasting interventions can ATB be administered repeatedly after 4-6 hrs

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Local antiviral drugs

- ***aciclovir***
- Herpesin®, Zovirax®
- ***penciclovir***
- Vectavir®
- ***docosanol***
- Erazaban
- ***tromantadin***
- Viru-Merz

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Antifungals in dentistry

Indications

- oral fungal infections due to
  - » immunosuppression
  - » inadequate oral hygiene
  - » wide spectrum antibiotics, glucocorticoids, chemotherapy

- most often candidosis

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Antifungals in dentistry

Drugs

- topically: nystatin, natamycine, clotrimazole, miconazole
- systemically: fluconazole, itraconazole, posaconazole

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Thank You for attention!