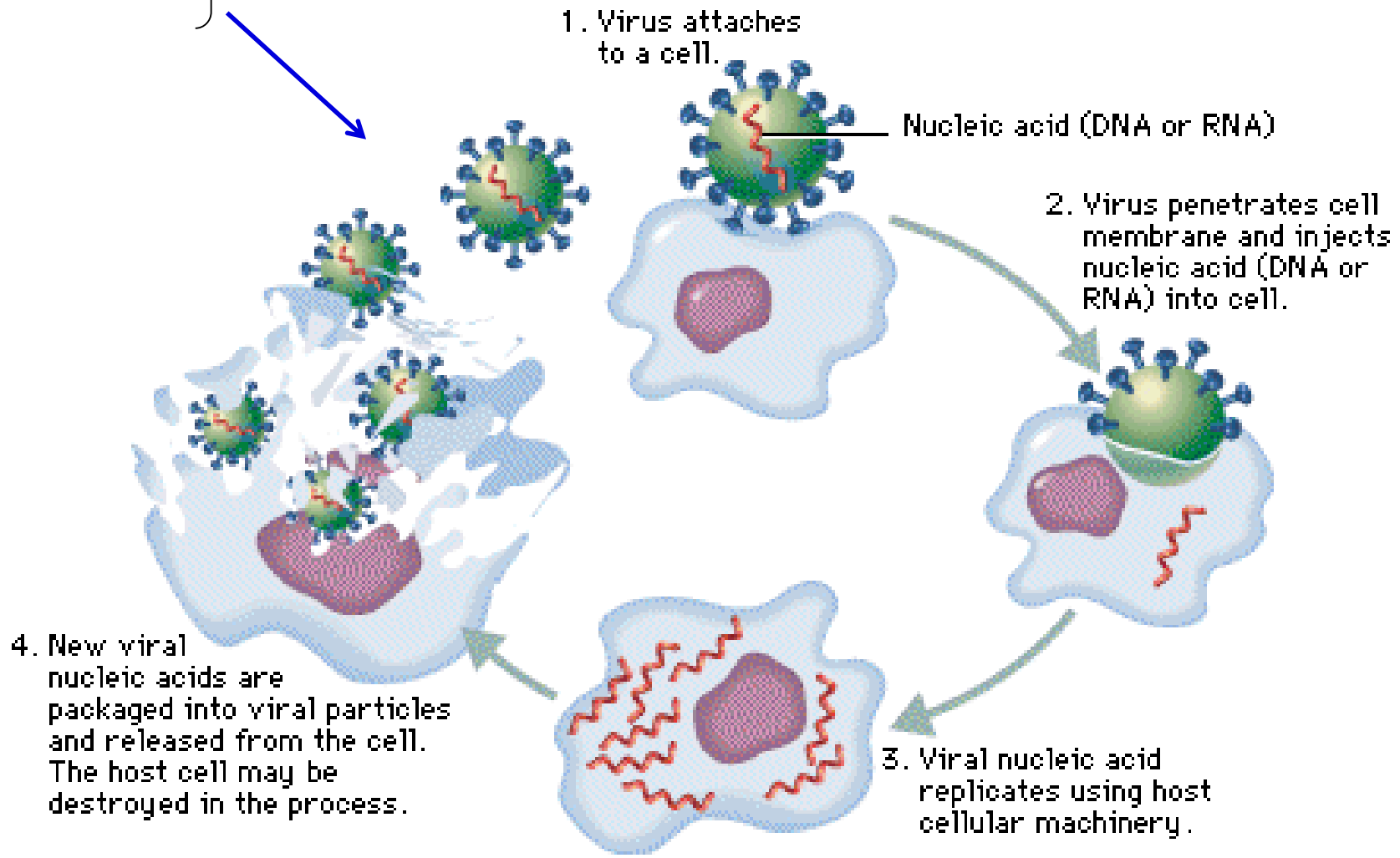
# ANTIVIRALS

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

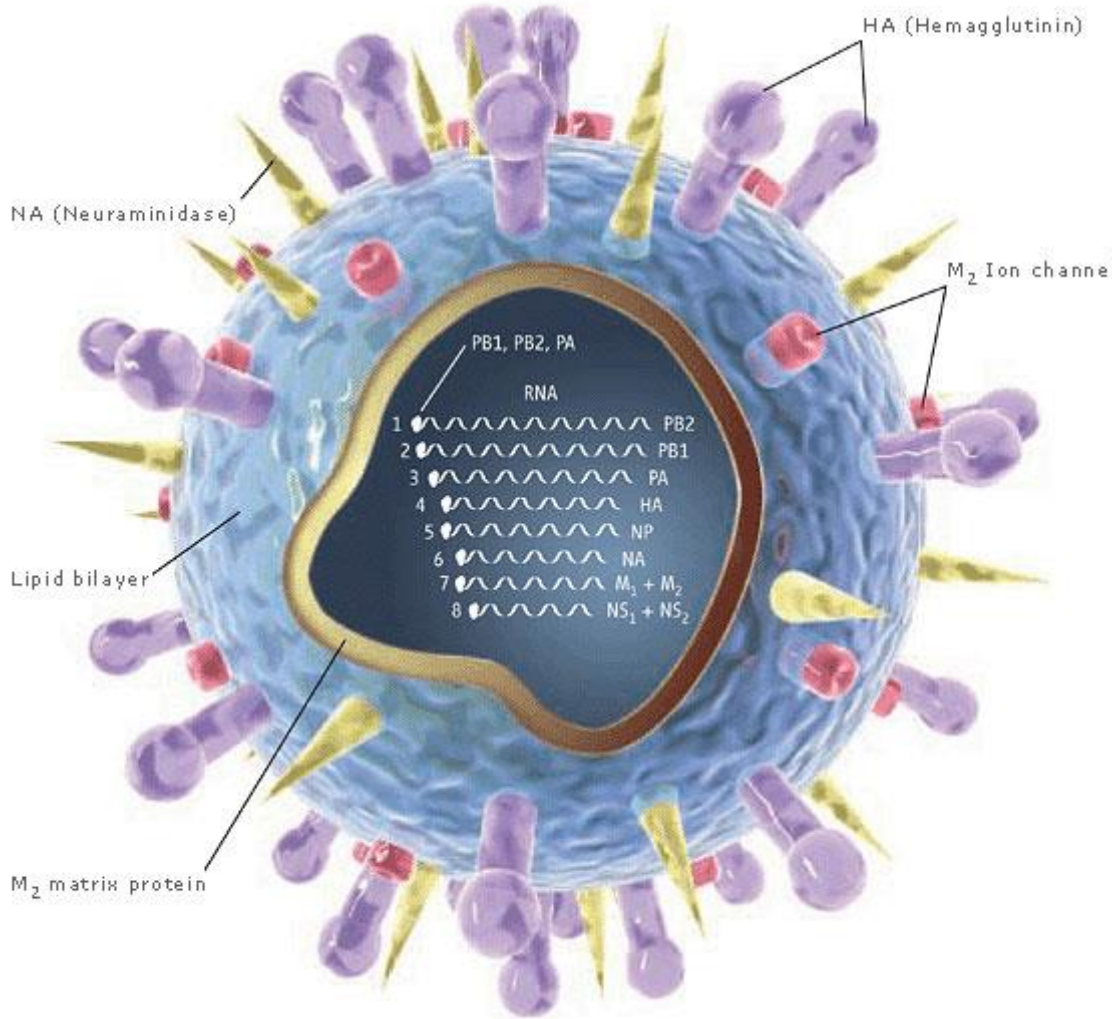


# Virus use endogeneous proteins for penetration into the cell

| Host cell structures that can function as receptors for viruses | Virus |
|---|---|
| Helper T 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)<br>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

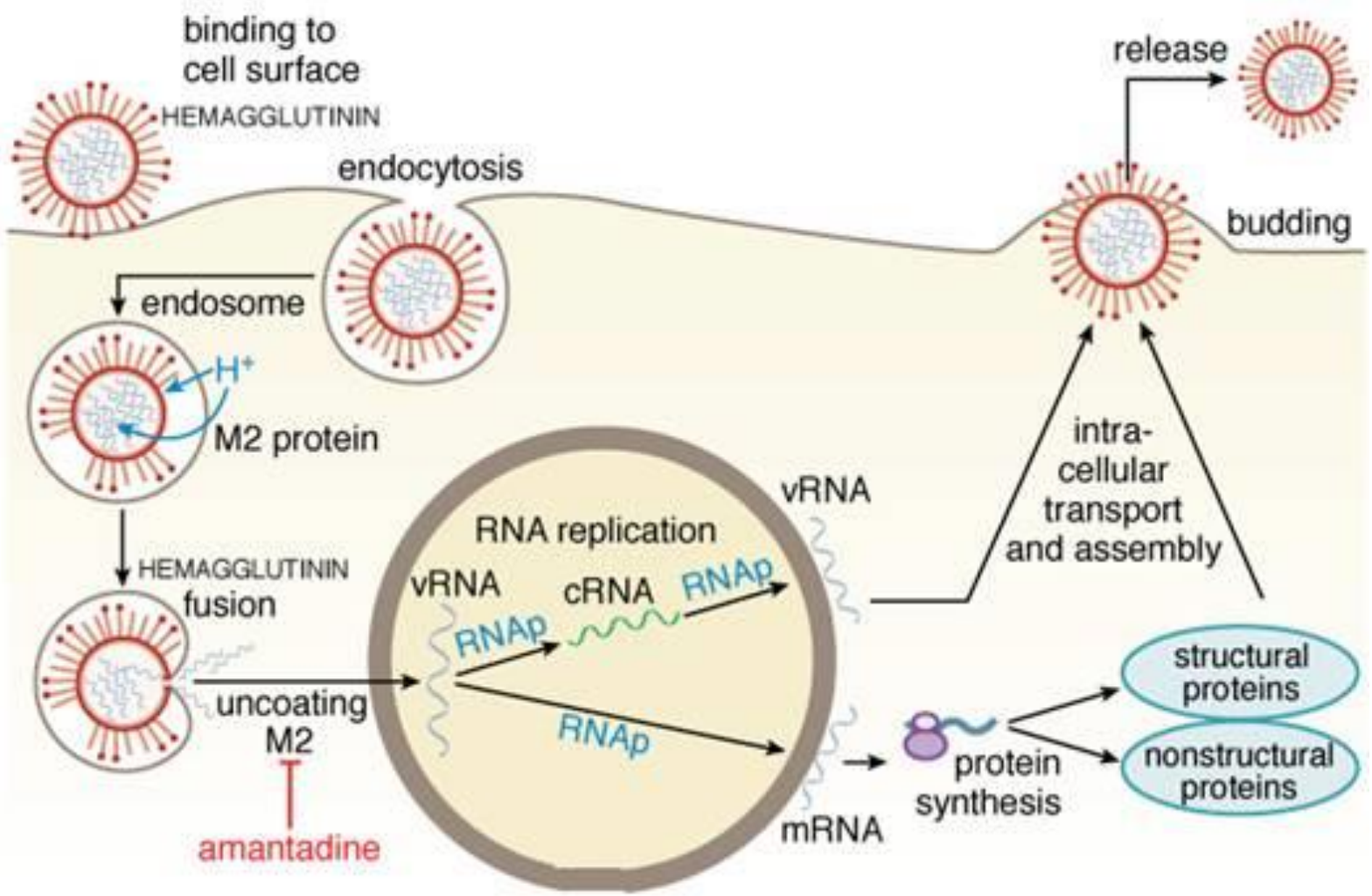
***A*** – causes epidemia, many potential hosts, quickly mutate in bird hosts

***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*

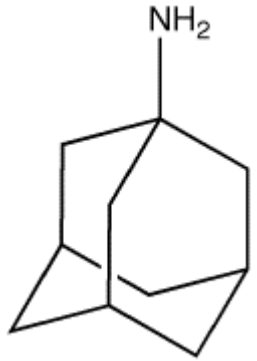


# *Amantadine*

↑ 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

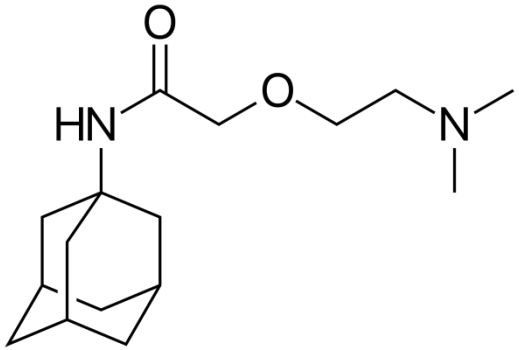
## *Rimantadine*

–structural analog of amantadine – similar effect and use

## *Tromantadine (Viru-Merz)*

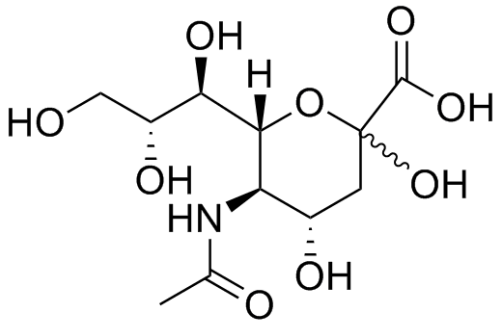
–syntetic derivate of aminoadamantane

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

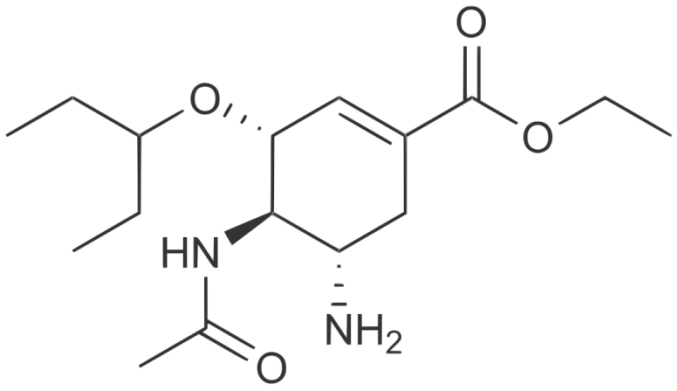


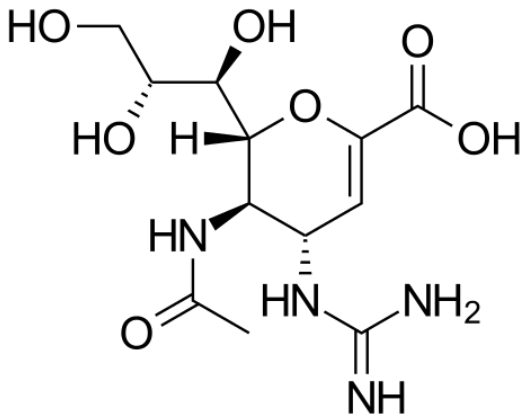
# Neuraminidase inhibitors

Sialic acid – N-acetylneuraminic acid

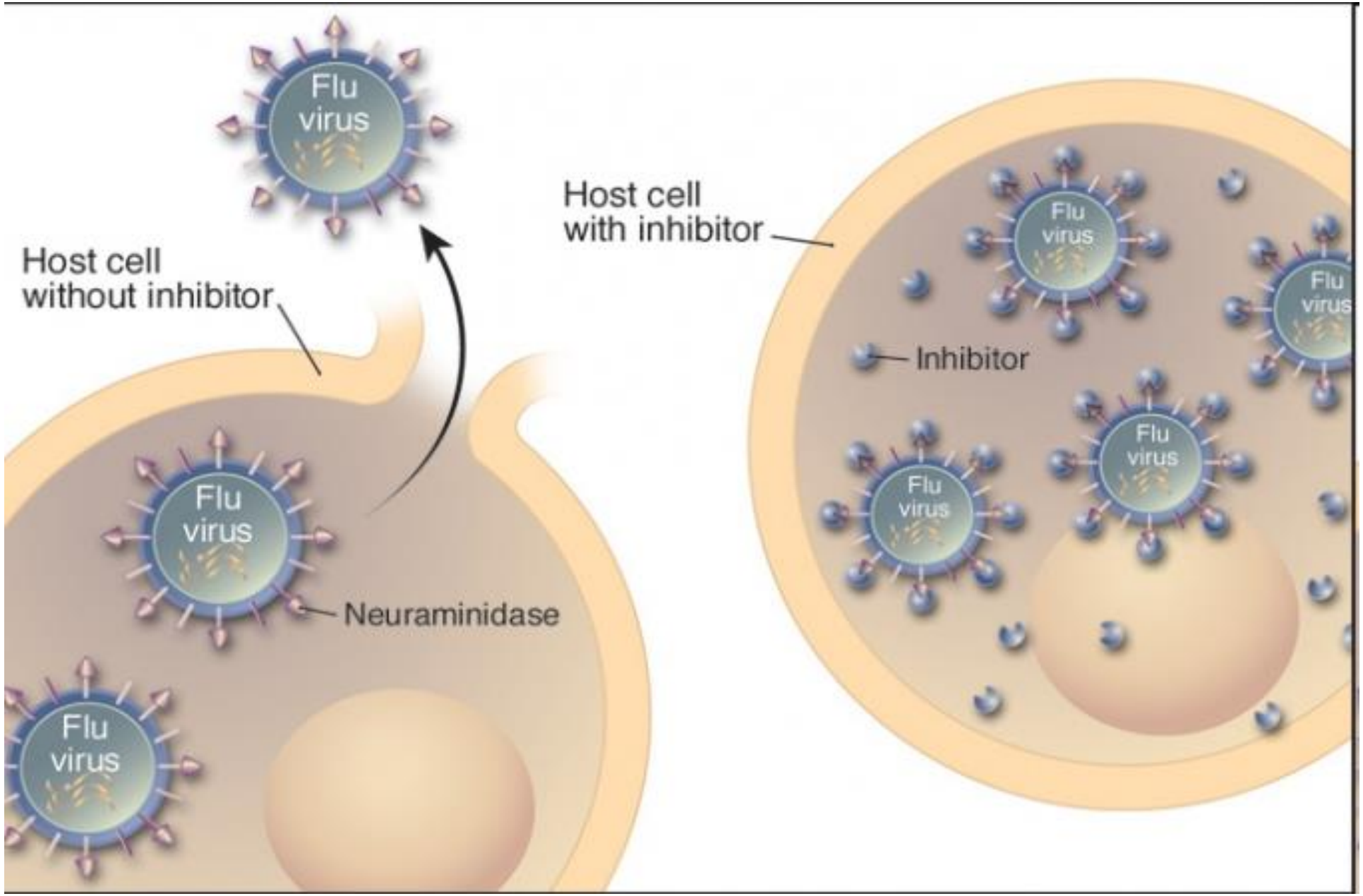


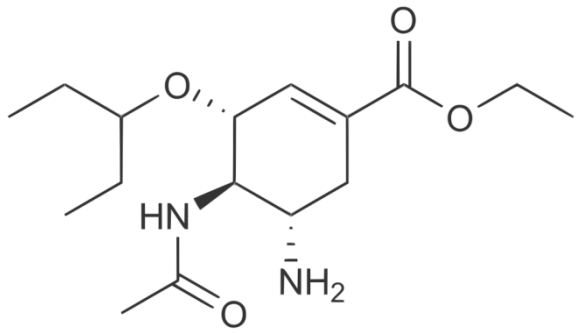

Sialic acid
(*N*-acetyl neuraminic acid)




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


Flu virus
Host cell without inhibitor
Flu virus
Neuraminidase
Flu virus
Host cell with inhibitor
Flu virus
Flu virus
Inhibitor
Flu virus
Flu virus




## 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:**

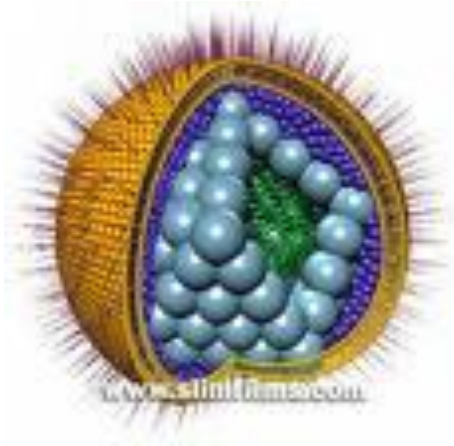
inhalation (low p.o. bioavailability)

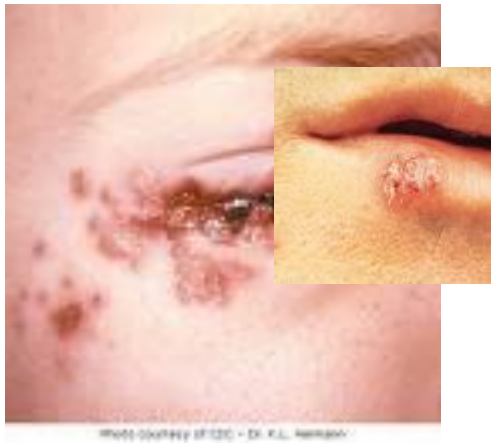
AE:

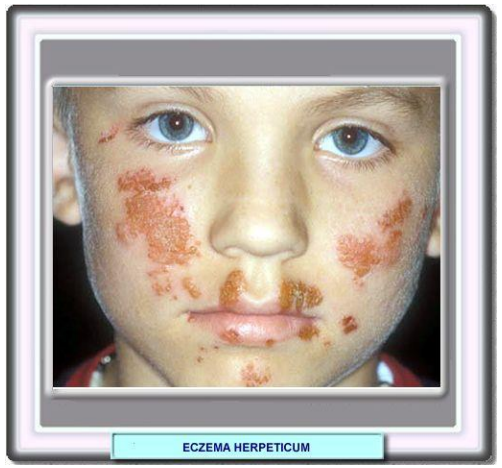
cough, bronchospasm, headache, confusion, nausea

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

# 2) Herpetic viruses







# Herpes viruses (=DNA viruses)

- HSV I
- HSV II
- VZV (Varicella-zoster virus)
- CMV
- EBV

# Anti-herpetic antivirals

**virostatic antimetabolits** *(purines, pyrimidines)*

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

**fusion inhibitors** ***- docosanol***
**antisense oligonukleotides** ***- fomivirsen***
**DNA polymerase inhibitors** ***- foscarnet***

# Anti-herpetic Drugs

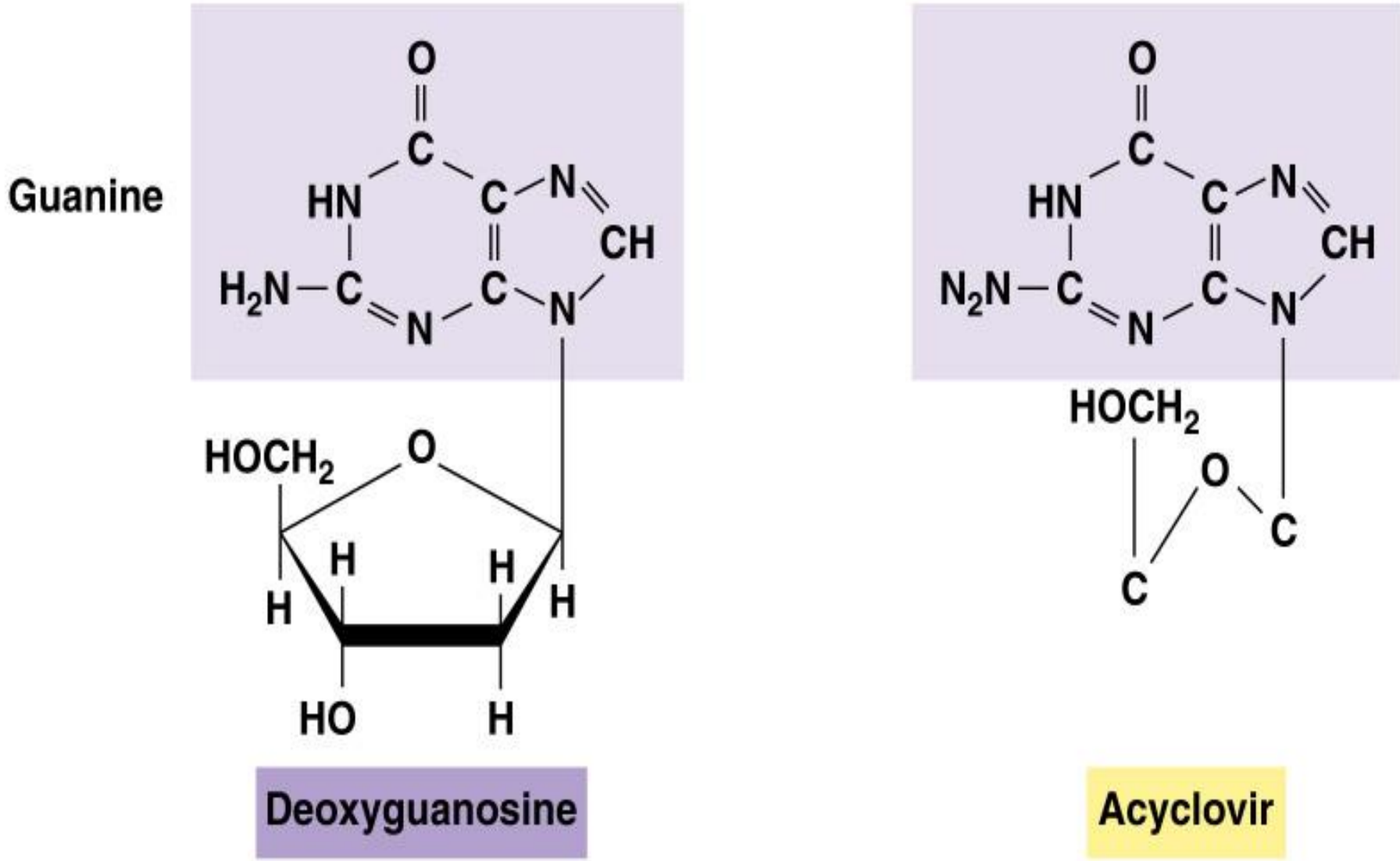
## Virostatic antimetabolites

syntetic nucleosides, so called nucleoside analogs (antimetabolites)

fosforylation → active moiety:

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

**substitution of base** → **nonfunctional DNA matrix**




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

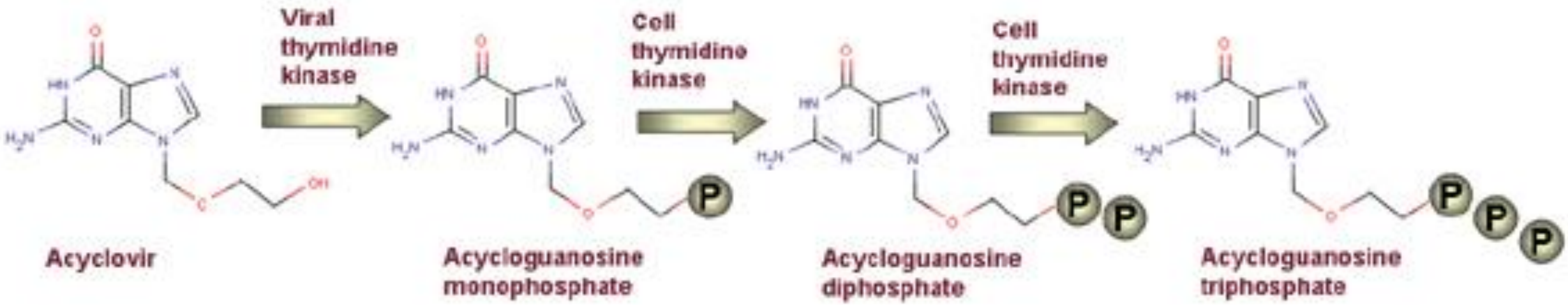
# Virostatic antimetabolites I.

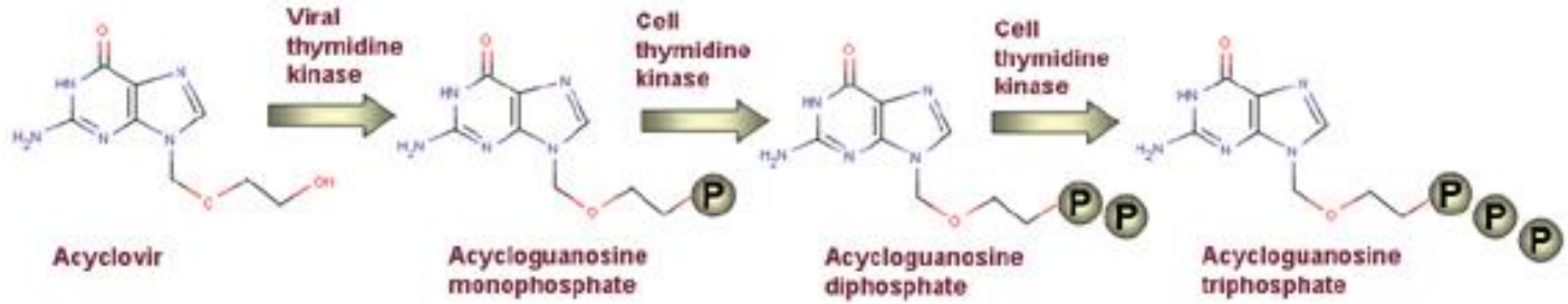
## Aciclovir

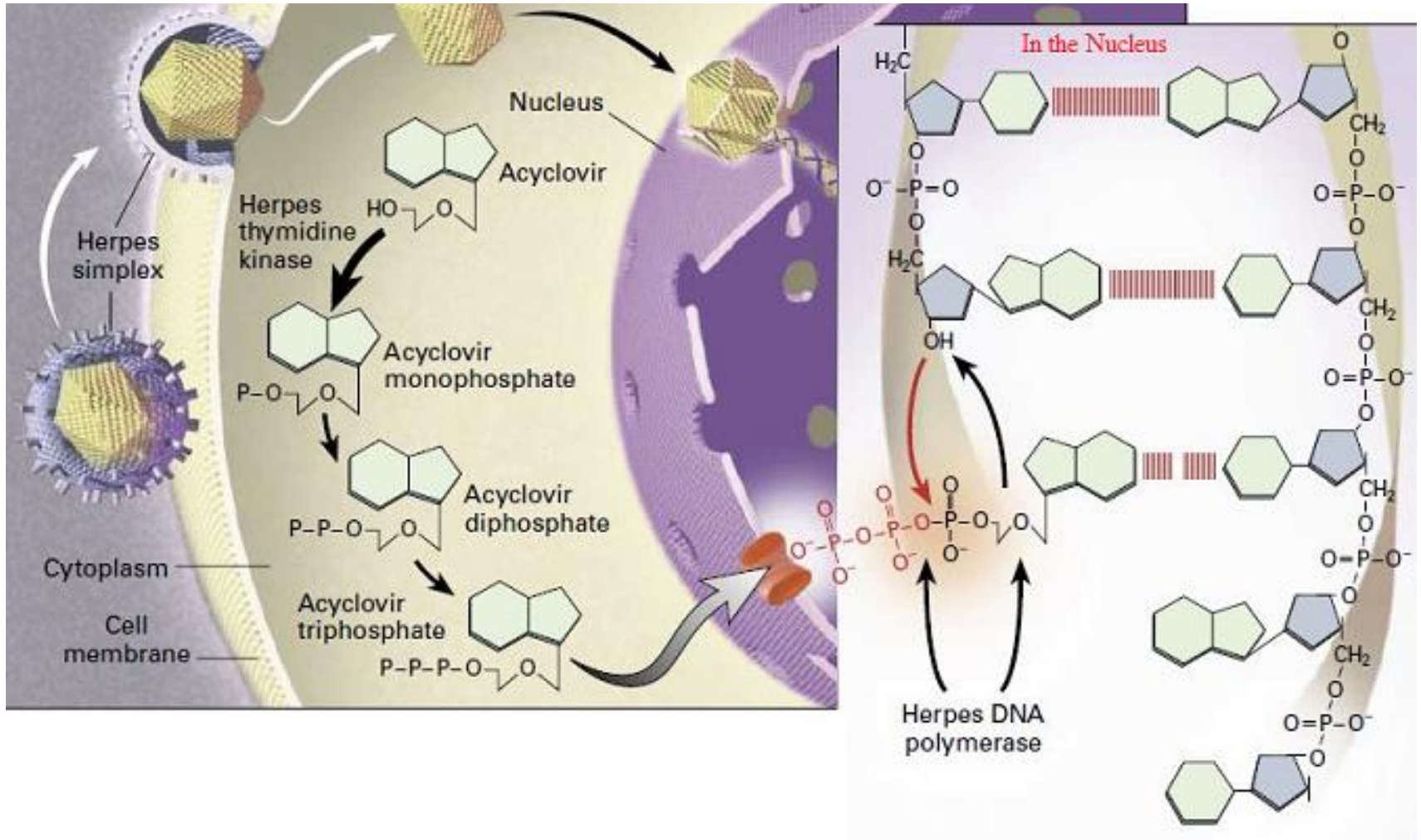
(syntetic analogue of guanosine)
specific, well tolerated antiviral

effective in form of aciclovir trifosfate

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


Viral thymidine kinase
Cell thymidine kinase
Cell thymidine kinase
Acyclovir
Acycloguanosine monophosphate
Acycloguanosine diphosphate
Acycloguanosine triphosphate


Viral thymidine kinase
Cell thymidine kinase
Cell thymidine kinase
Acyclovir
Acycloguanosine monophosphate
Acycloguanosine diphosphate
Acycloguanosine triphosphate


Herpes simplex
Nucleus
Acyclovir
Herpes thymidine kinase
Acyclovir monophosphate
Acyclovir diphosphate
Acyclovir triphosphate
Cytoplasm
Cell membrane
In the Nucleus
Herpes DNA polymerase

# Virostatic antimetabolites I.

- ***Aciclovir***

  - **anti- HSV-1,2 + VZV** >> CMV and EBV
  - i.v. herpetic encefalitis

  profylaxes of CMV infection in BMT recipient (tbl., inj.)
  in severely immunocompromised (AIDS)

–local, oral, i.v. application
–incomplete absorption from GIT (F= 10-20 %), $T_{1/2}$ 3-4h, excretion in urine

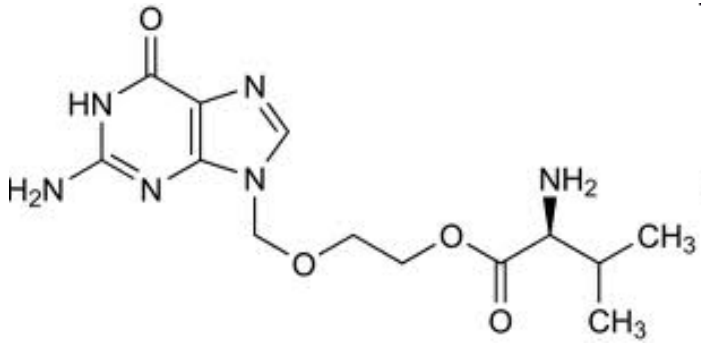
***AE:*** p.o. – GIT intolerance
i.v.: tromboflebitis (3%),
renal dysfunction, neurotoxic, mental symptoms

# Virostatic antimetabolites II.

- ***Valaciclovir***

–aciclovir prodrug (L-Valin)

–better absorption after oral application (F=77%)



- ***Famciclovir***

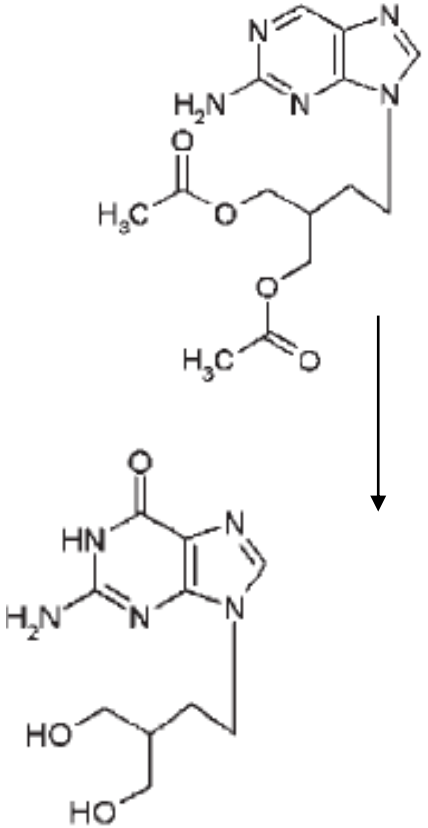
–not available in CZ

–F ~ 77 %

–prodrug – after oral application is metabolized to form: ***penciclovir*** (topical admin. – h. labialis)

–similar to aciclovir - HSV-1,2, VZV, HBV

(only for external use in CZ)



# Virostatic antimetabolites II.

- ***Aciclovir, Valaciclovir, Famciclovir/Penciclovir***

–similar efficacy
–bioavailability 10-20 % - 55 % - 77 %
–generics available

–aciclovir – better proven safety
–penciclovir (only topical drug)
–valaciclovir – less frequent dosing

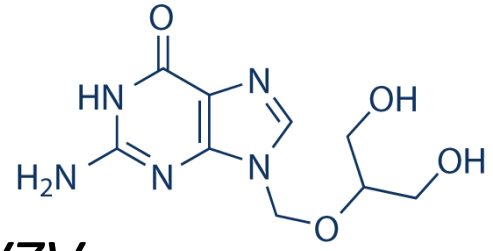
# Virostatic antimetabolites III.

## *Ganciclovir*

**I: severe CMV infections** in immunodeficiency patients (retinal inflammation, lung) in AIDS patients (CD4 + <50/µl)

–transplantation: **prevention of CMV transmission** from CMV+ donors

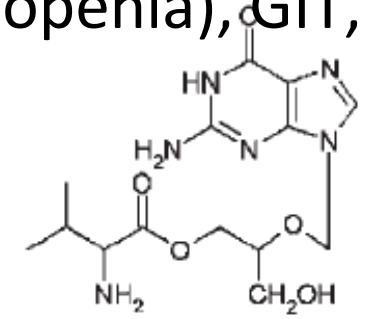
- i.v. application (oral pro-drug)
- excreted unchanged in the urine.




*! Senzitive:* ***CMV,*** *HSV-1 +HSV-2, HHV-6, HHV-7, HHV-8, EBV, VZV +HBV*

**AE: haematologic**: up to 40 % (anaemia, neutropenia, trombocytopenia), GIT, psychosis, convulsions, etc..

- teratogenic – spermatogenesis inhibition




## *Valganciclovir*

(= prodrug: valylester of gancyklovir)

# Virostatic antimetabolites IV.

## *Cidofovir*

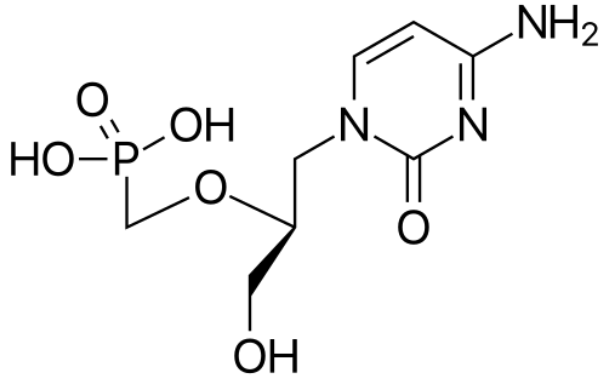
–not available in CZ

–analogue of cytidine – effective against **CMV** (also in case of ganciclovir resistence)

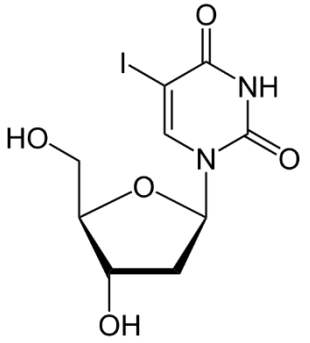
–CMV retinitis in AIDS patients

–for infusion

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



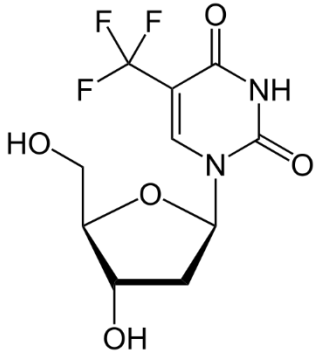
# Virostatic antimetabolites V. *(topical)*




- ***Idoxuridin*** *(not available in CZ)*
  - –uracil analogue: MA - inhibits base pairing
  - –inhibits NA synthesis in both viruses and human cells → → toxic also for host!!!
  - –corneal herpetic infections (in case of impossible systemic application)

- ***Trifluridin***

I: CRC (the only one approved indication!) locally in herpetic eye infections and chronic skin ulcerations,




AE: burning, edema, irritation, blurred vision

# Other anti-herpetic drugs

## *Fomivirsen*

antisense oligonukleotide - 21 bp nuclease resistent

5'-GCG TTT GCT CTT CTT CTT GCG-3'

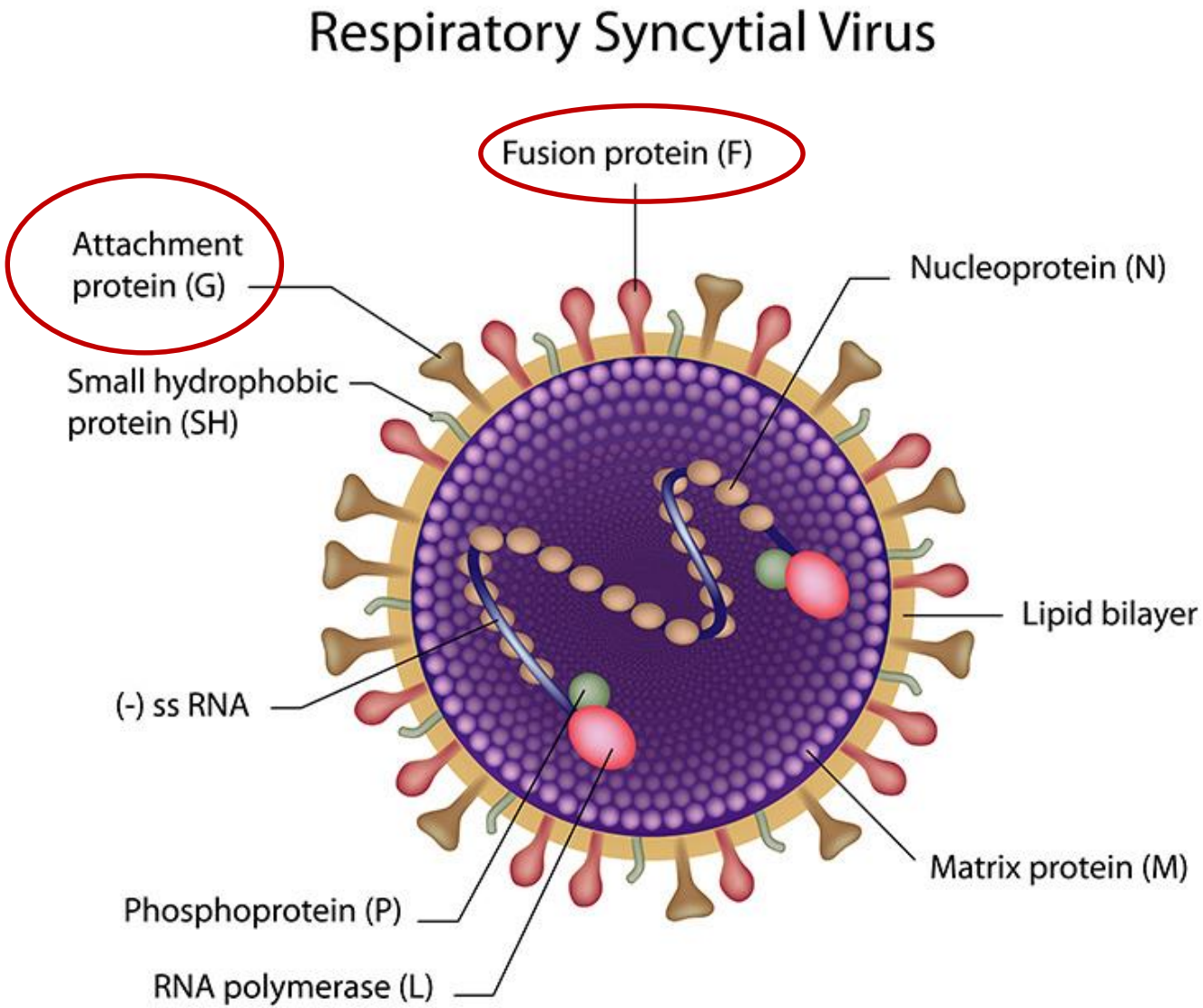
I: CMV retinitis

MA: binding to mRNA, IE2 protein synthesis inhibition

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

not available in CZ

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



# 3) 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
- the % estimate varies: (17-22 % vs 11 %) OR 2,5

*Korppi et al. 2004 vs Henderson et al 2005*

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

### *3) RSV*

## *Palivizumab (Synagis)*

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

D: 15ml/kg IM/ month, 5 doses/ season

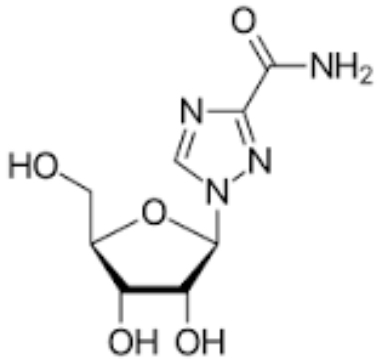
AE: local reactions, hypersensitivity, apnoae, convulsions

## *Motavizumab*

- not approved in CZ
- IgG1 MAB 2. generation
- 70x higher affinity for F protein (permits penetration into cells)
- It reduces the number of hospitalizations by 26% (x Pavilizumab) and the need for subsequent outpatient care

*3) RSV*

## Ribavirin




I: HVC

syntetic nukleoside,
off label: viral pneumonia in children and immunocompromised patients
Doubts about efficiency

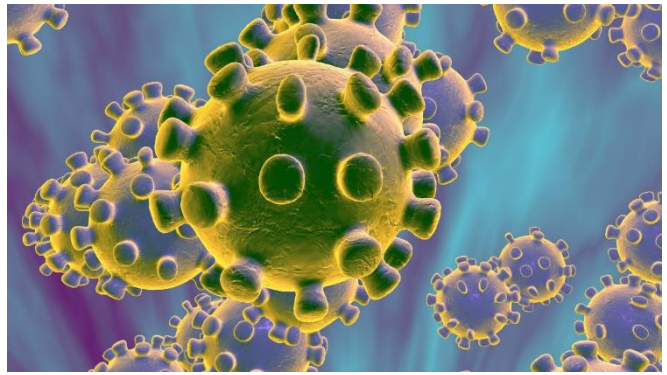
accelerates the withdrawal of clinical symptoms and improves oxygenation
KI: AZT, didanosin

AE: allergy, anemia, aminotransferase elevation, depression, pancreatitis, nephrotoxicity

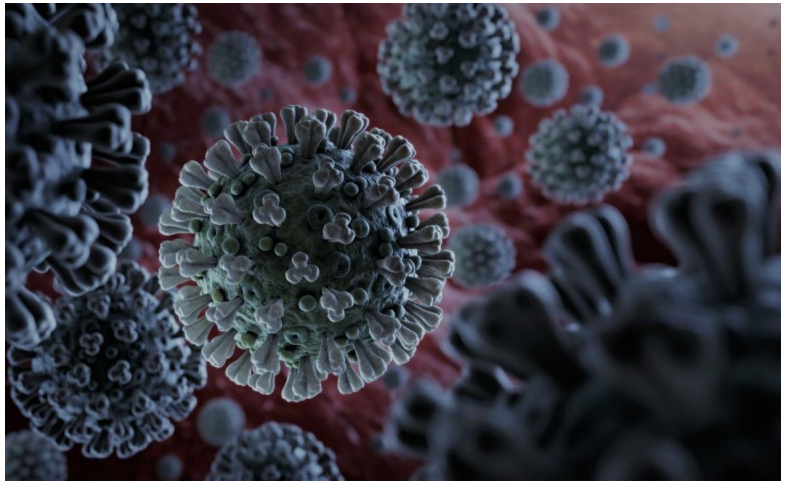
# SARS, MERS, COVID

(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



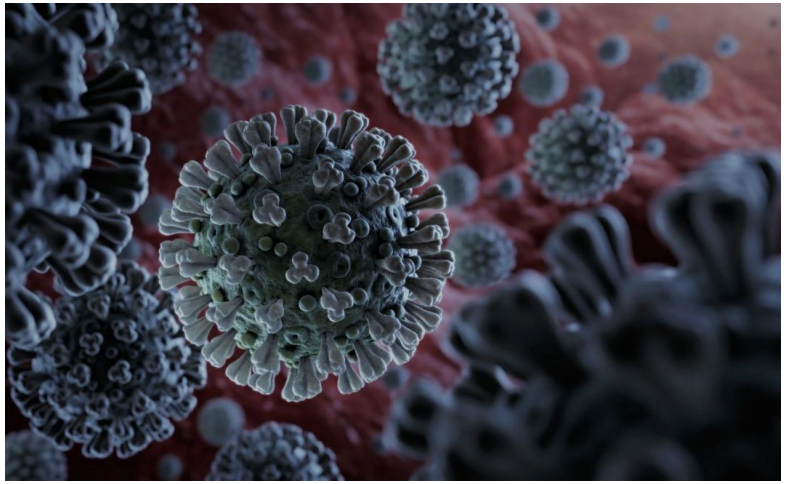
# Bamlanivimab / etesivimab



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;
**Mof A:**
recombinant human IgG1k MAb to the spike protein of SARS-CoV-2.
binds to the spike protein, blocking attachment to the human ACE2 receptor

700 mg as a single dose,
$T_{1/2}$: Bamlanivimab: 17.6 days, Etesevimab: 25.1 days.

# Casirivimab + imdevimab



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;

**Mof A:**

recombinant human IgG1κ and IgG1λ, respectively MAb to the non-overlapping epitopes of spike protein of SARS-CoV-2.

binds to the spike protein, blocking attachment to the human ACE2 receptor

Dose- single: 300 mg/1332 mg (i.v. infusion)

# Remdesivir

**Mof A:**

adenosine nucleotide prodrug metabolized to nucleoside triphosphate metabolite

incorporation into the viral RNA template

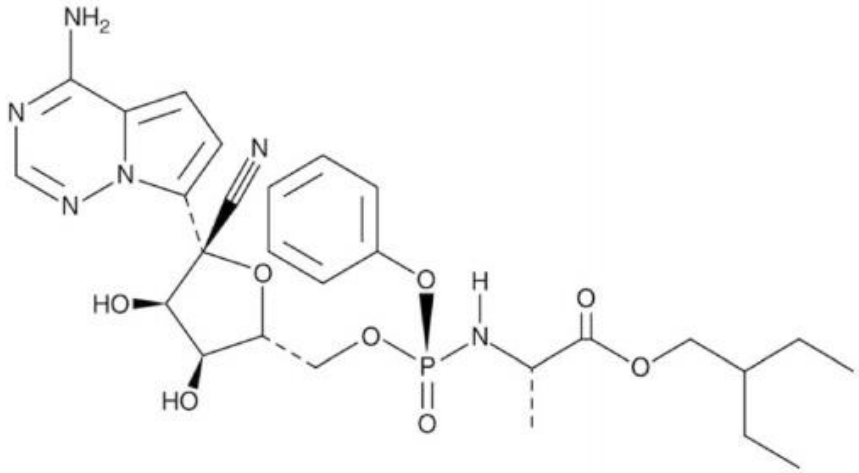
i RNA-dependent RNA polymerase (RdRp)

**PK:**

High protein binding (90 %)

T1/2 = 1h, metab. 27 hrs

Excretion – urine



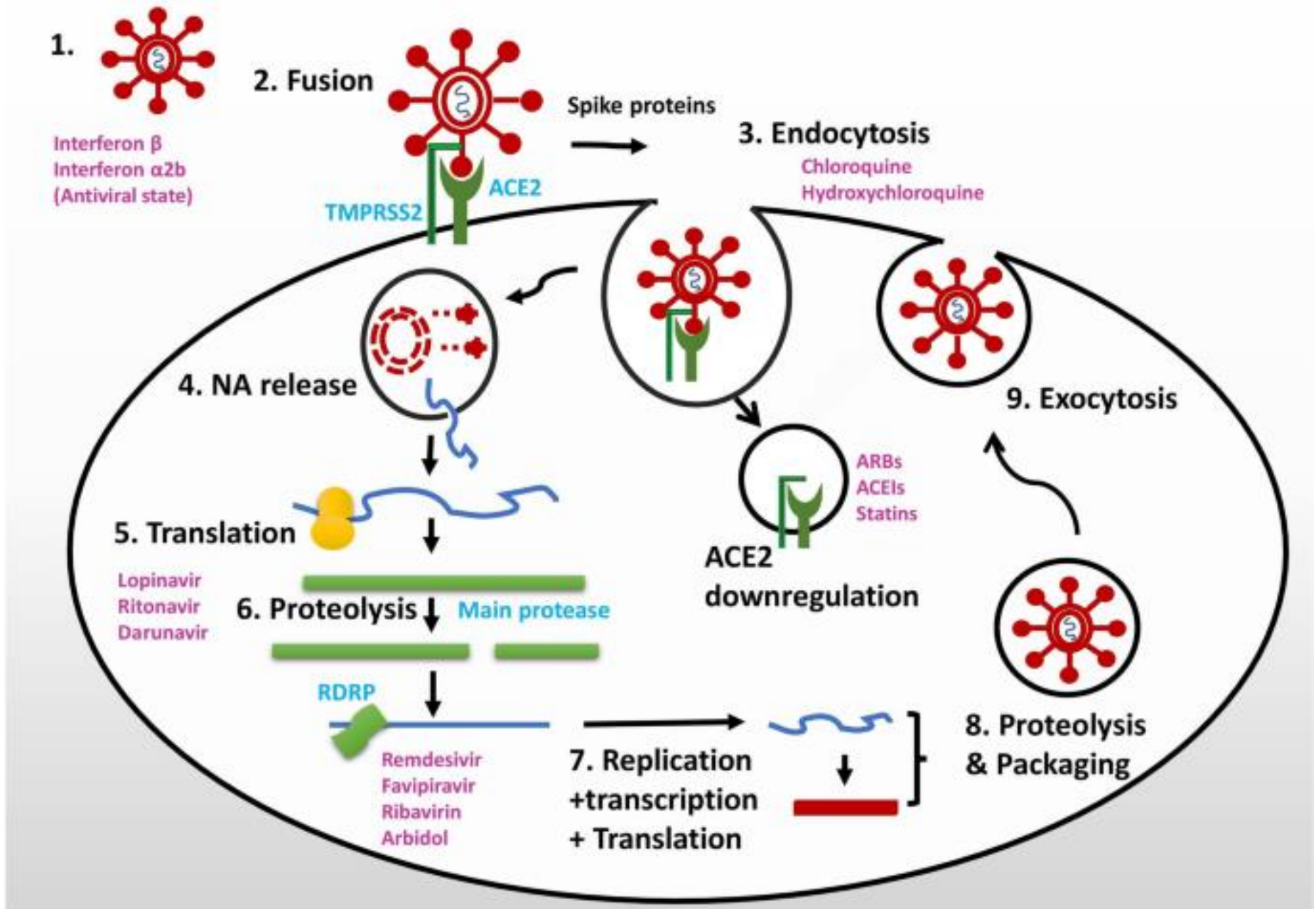
# Remdesivir

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

used with dexamethasone

if a corticosteroid cannot be used, may use remdesivir in combination with baricitinib (Jak Tki)

RCT:  most benefit in pts. on supplemental oxygen who do not require high-flow oxygen or ventilatory support


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

Article | Published: 25 March 2021

# Bispecific IgG neutralizes SARS-CoV-2 variants and prevents escape in mice

Raoul De Gasparo, Mattia Pedotti, [...] Luca Varani

*Nature* (2021) | Cite this article

**16k** Accesses | **199** Altmetric | Metrics

## Abstract

Neutralizing antibodies that target the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein are among the most promising approaches against COVID-19[1,2]. A bispecific IgG1-like molecule (CoV-X2) has been developed on the basis of C121 and C135, two antibodies derived from donors who had recovered from COVID-19[3]. Here we show that CoV-X2 simultaneously binds two independent sites on the RBD and, unlike its parental antibodies, prevents detectable spike binding to the cellular receptor of the virus, angiotensin-converting enzyme 2 (ACE2). Furthermore, CoV-X2 neutralizes wild-type SARS-CoV-2 and its variants of concern, as well as escape mutants generated by the parental monoclonal antibodies. We also found that in a mouse model of SARS-CoV-2 infection with lung inflammation, CoV-X2 protects mice from disease and suppresses viral escape. Thus, the simultaneous targeting of non-overlapping RBD epitopes by IgG-like bispecific

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Abstract
Main
Methods
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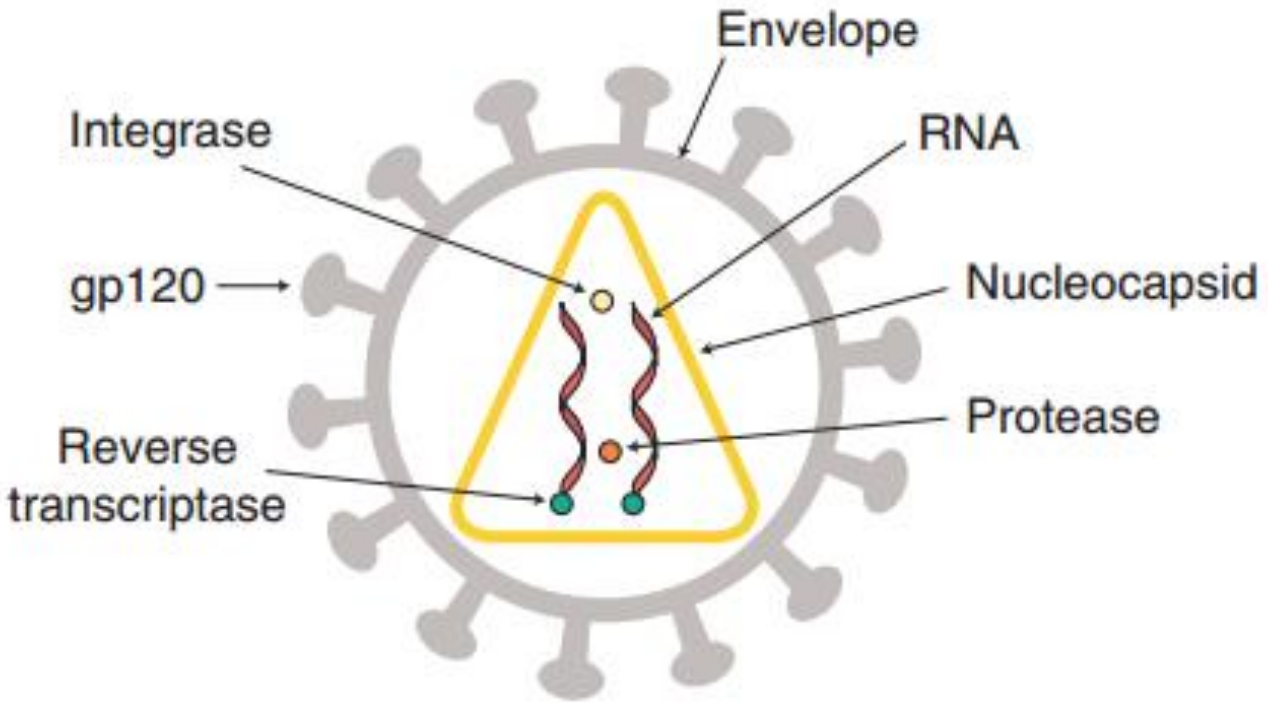
Comments

Bispecific Antibody Generation

# 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.

# 5) Antiretrovirals



# 5) Antiretrovirals

## Retroviruses

genome in RNA → reverse transcriptase (ie. DNA polymerase) → → DNA

HIV attacks the CD4 subset of Th lymphocytes

HIV-1

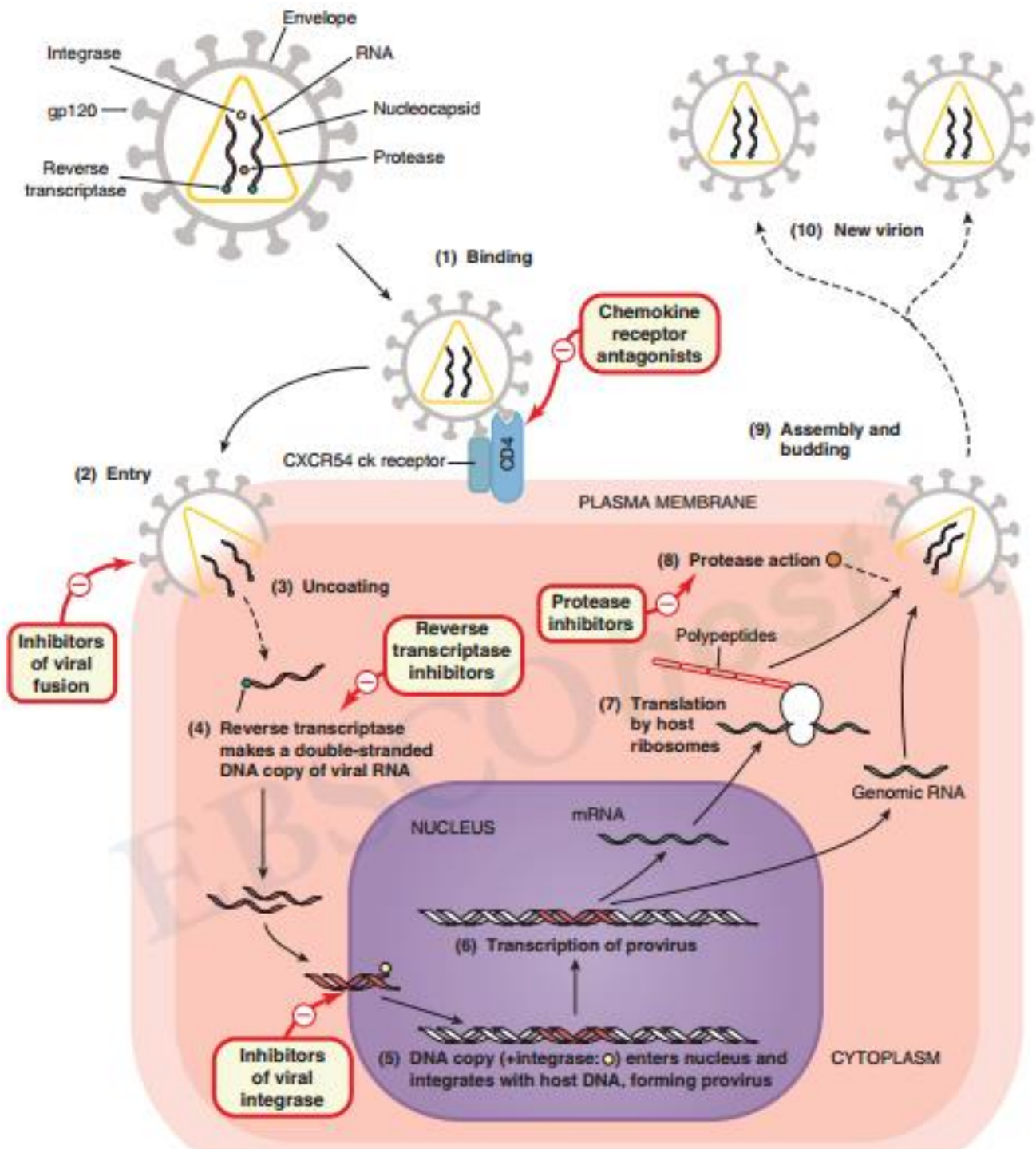
HIV-2

AIDS

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

# Antiretrovirotics

| | |
|---|---|
| **Reverse transcriptase inhibitors** | **RTI** |
| Nucleoside | NRTI |
| Nucleotide | NtRTI |
| Non-nucleoside | NNRTI |
| **retroviral Protease inhibitors** | **PI** |
| **Fusion inhibitors** | **FI** |
| **Integrase inhibitors** | **InSTI** |

**Maturation inhibitors (IFN + research)**

# NRTI

- synthetic dideoxynucleosides
- **Mechanism of action:**

  phosphorylation by viral kinases: triphosphate → → **reverse transcriptase inhibition**

→ binding as false precursors – **inhibition of DNA synthesis**

→ higher affinity for the virus enzyme than the host cell → specific effect

# 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

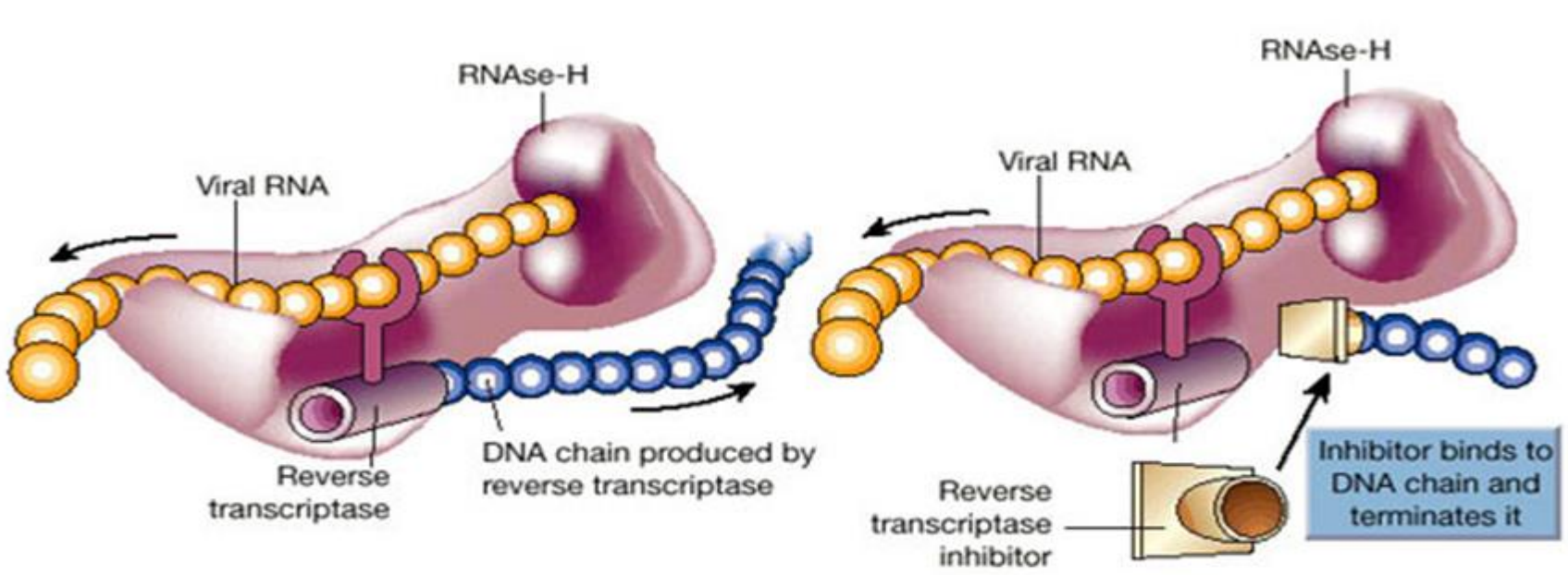
***stavudine, didanosine, lamivudine, abacavir, emtricitabine***
later introduced NRTI
**AE:** hepatomegaly with steatosis, lactic acidosis, hyperglycaemia, lipodystrophy, insulin resistance, pancreatitis, peripheral neuropathy, retinal damage, hyperuricemia

# Nucleotide Reverse Transcriptase Inhibitors (NtRTI)

**tenofovir**

part of combination therapy in patients with NRTI resistance

2015: tenofovir alafenamid: reduced nephrotoxicity, bone toxicity

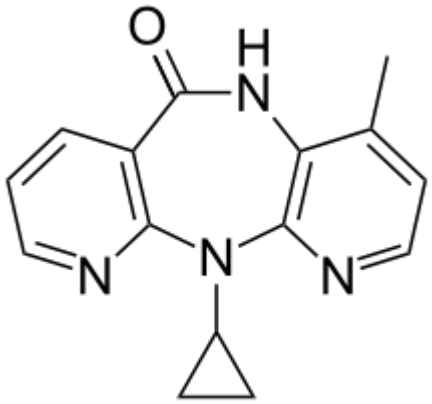


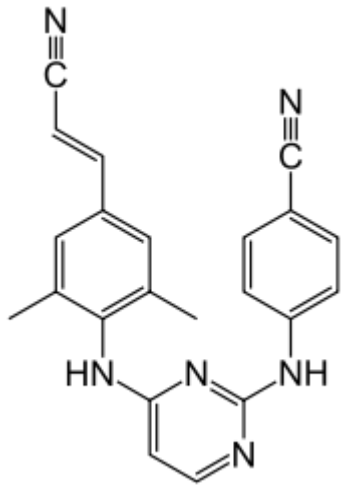
# Non-nucleoside RTI (NNRTI)

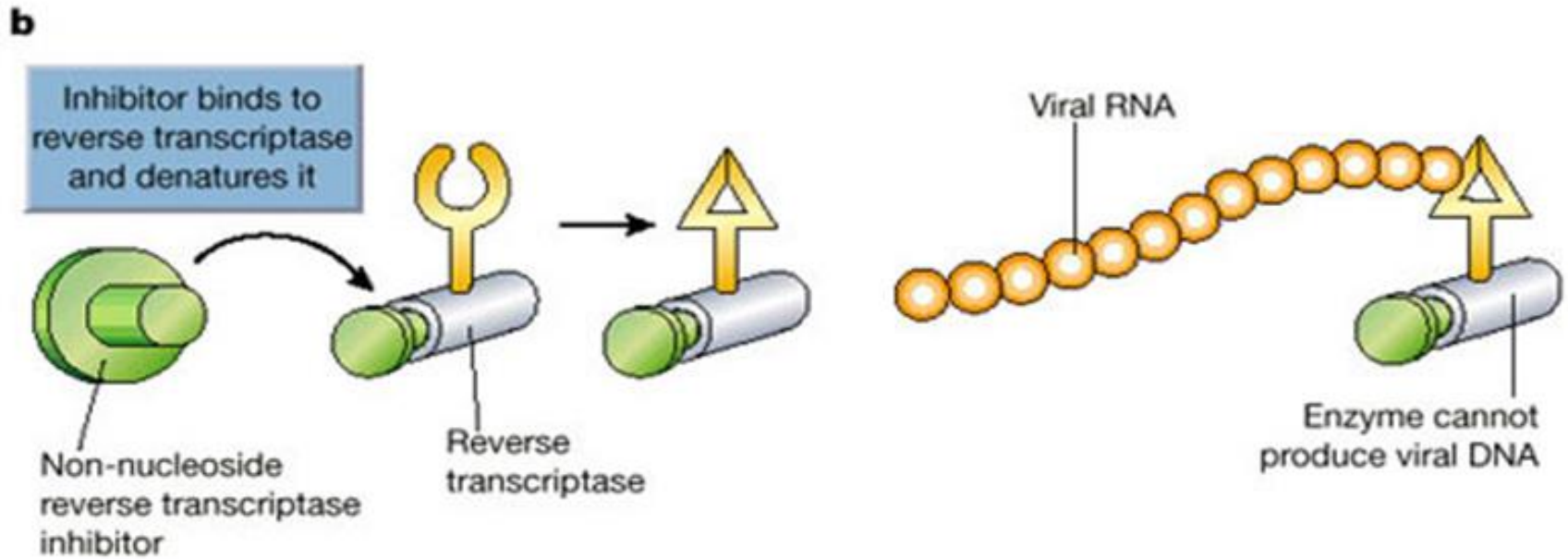
- direct effect (without intracellular phosphorylation)
- only in combination therapy

***nevirapine***
***efavirenz***
***etravirine***
***rilpivirine***
***delavirdine***

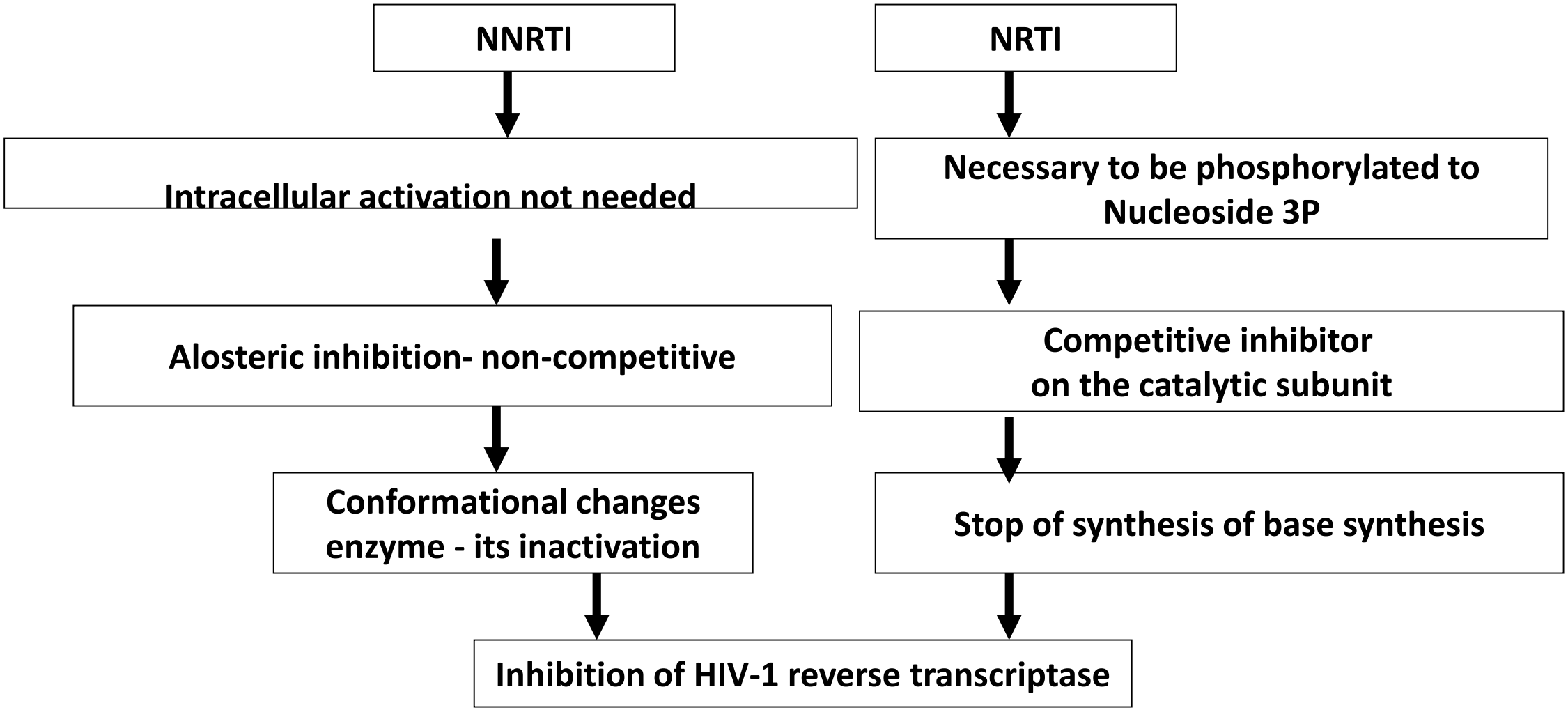
**AE:** rashes, liver failure
– frequent interactions (inducers of CYP 450)




b
Inhibitor binds to reverse transcriptase and denatures it
Non-nucleoside reverse transcriptase inhibitor
Reverse transcriptase
Viral RNA
Enzyme cannot produce viral DNA

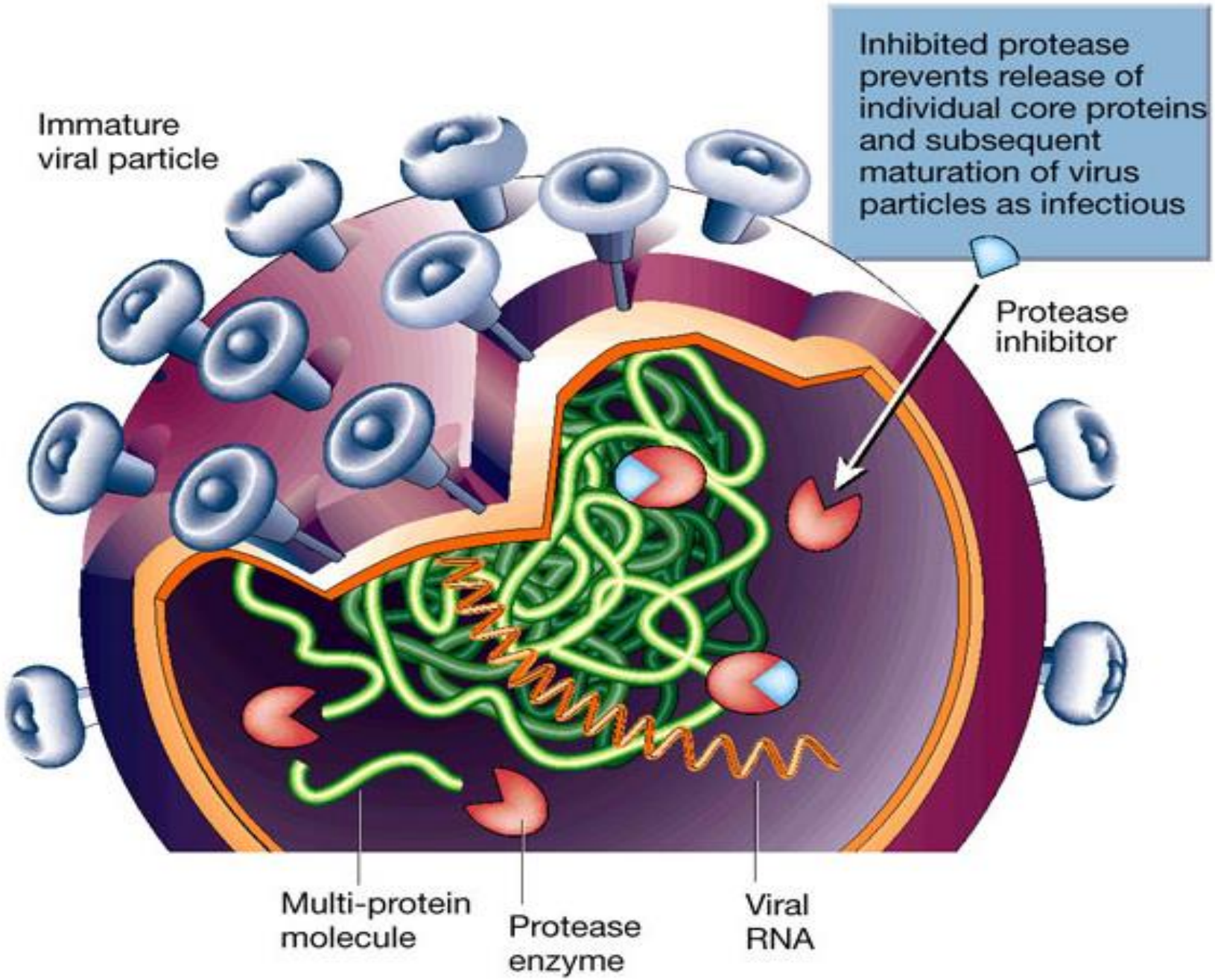
# Differences in the mechanism of action of NNRT and NRTI



# retroviral Protease inhibitors (PI)

inhibit the active protease center
prevents cleavage of viral glycoprotein precursors
***darunavir, ritonavir, atazanavir***
cross resistance
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)

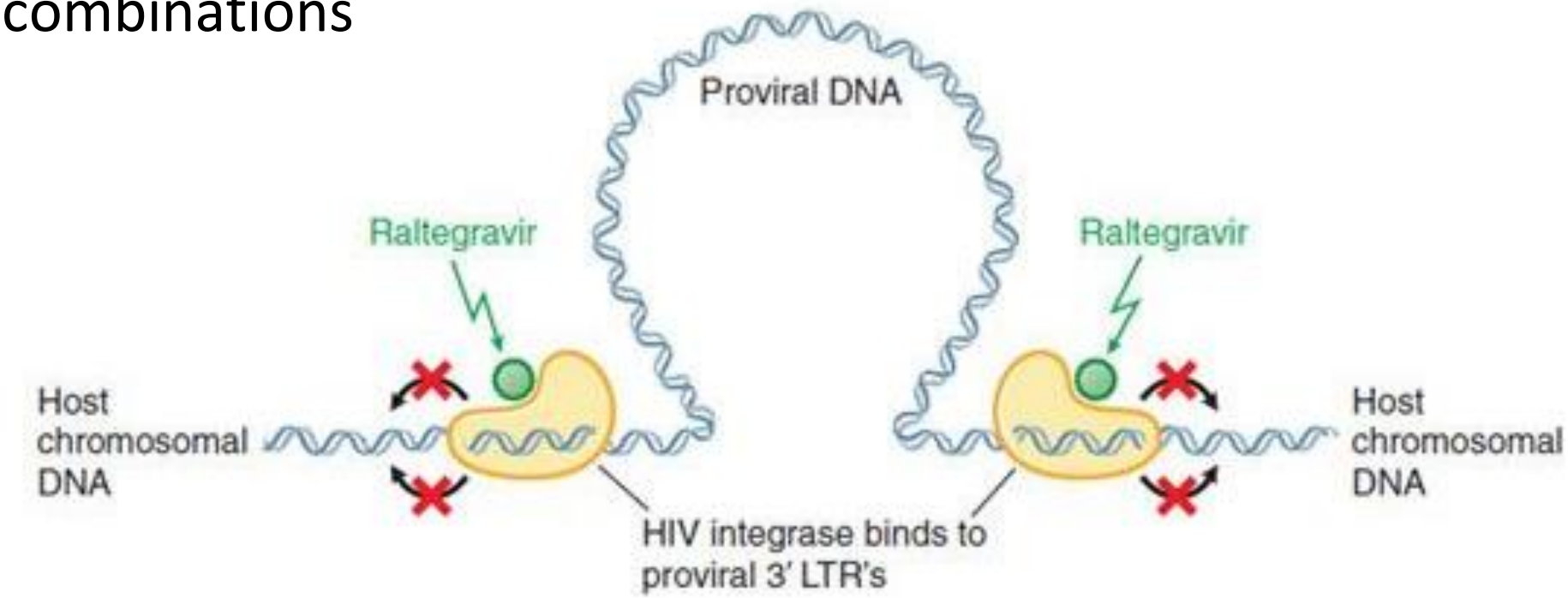

Inhibited protease prevents release of individual core proteins and subsequent maturation of virus particles as infectious
Immature viral particle
Protease inhibitor
Multi-protein molecule
Protease enzyme
Viral RNA

# Integrase inhibitors (InSTI)

inhibit covalent insertion of the HIV genome into the host cell genome
without negative metabolic effects of PI
BUT: adipogenic effect

Ideal for (fixed) combinations

**Raltegravir**
**Dolutegravir**
**Elvitegravir**

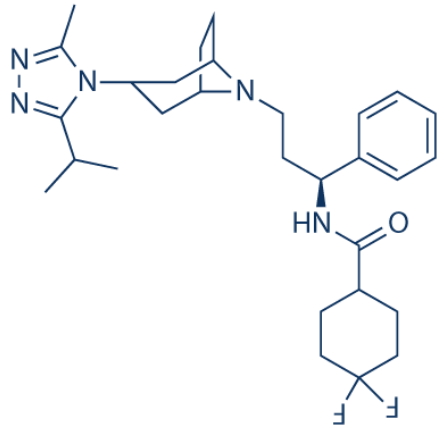


# Fusion inhibitors

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

***maraviroc***

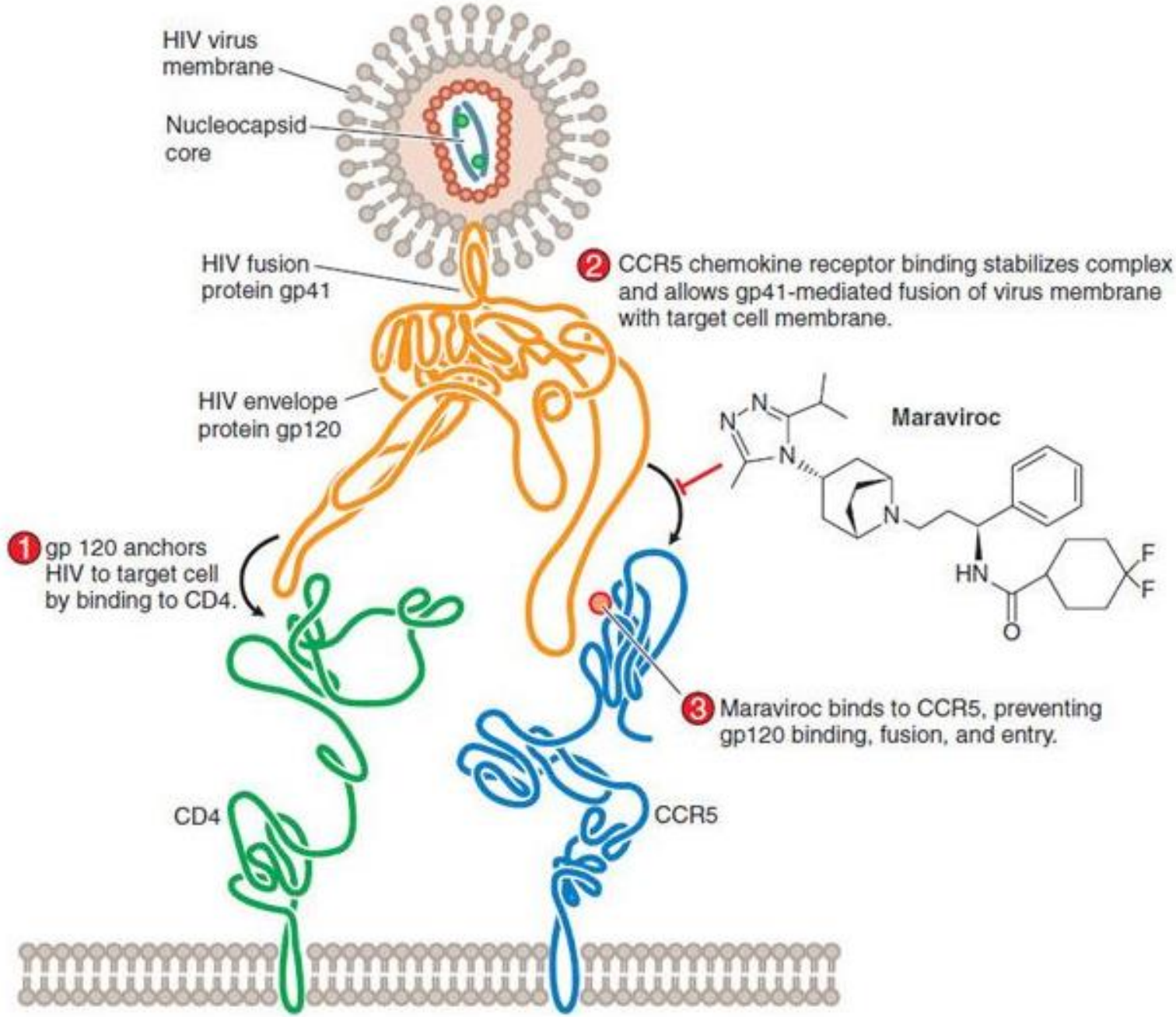
binding to human chemokine receptor CCR5, inhibiting interaction with glycoprotein 120, preventing CCR5-tropic HIV-1 from entering the cell
I: only CCR5- tropic HIV-1, not the CXCR4
CYP3A4 substate




***enfuvirtide***

peptidic structure– s.c. administration, 2x daily ($T_{1/2}$ 3.8 h)
extracellularly blocks viral membrane fusion

# Fusion inhibitors



# Strategy of ART

AIDS therapy:

**Antiretroviral therapy +**

treatment of associated diseases: opportunistic infections (pneumonia, mycobacterial and fungal infections) and tumors (lymphomas, Kaposi's sarcoma)

**Since 1996, the triple combination - HAART (Highly Active Antiretroviral Therapy)**, a fixed combination

# HAART

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

**Effect evaluation:** accordingly to viraemia – target levels:

in 3 months below 400 copies HIV1 RNA/ml

in 6months below detection level

**Change in the combination**: prevents accumulation of resistant mutants

- treatment outcome is better if in the time of swithch is lower viraemia. and higher CD4+

# PEP

High / low risk injury
- range, quantity, nature, status of infectious

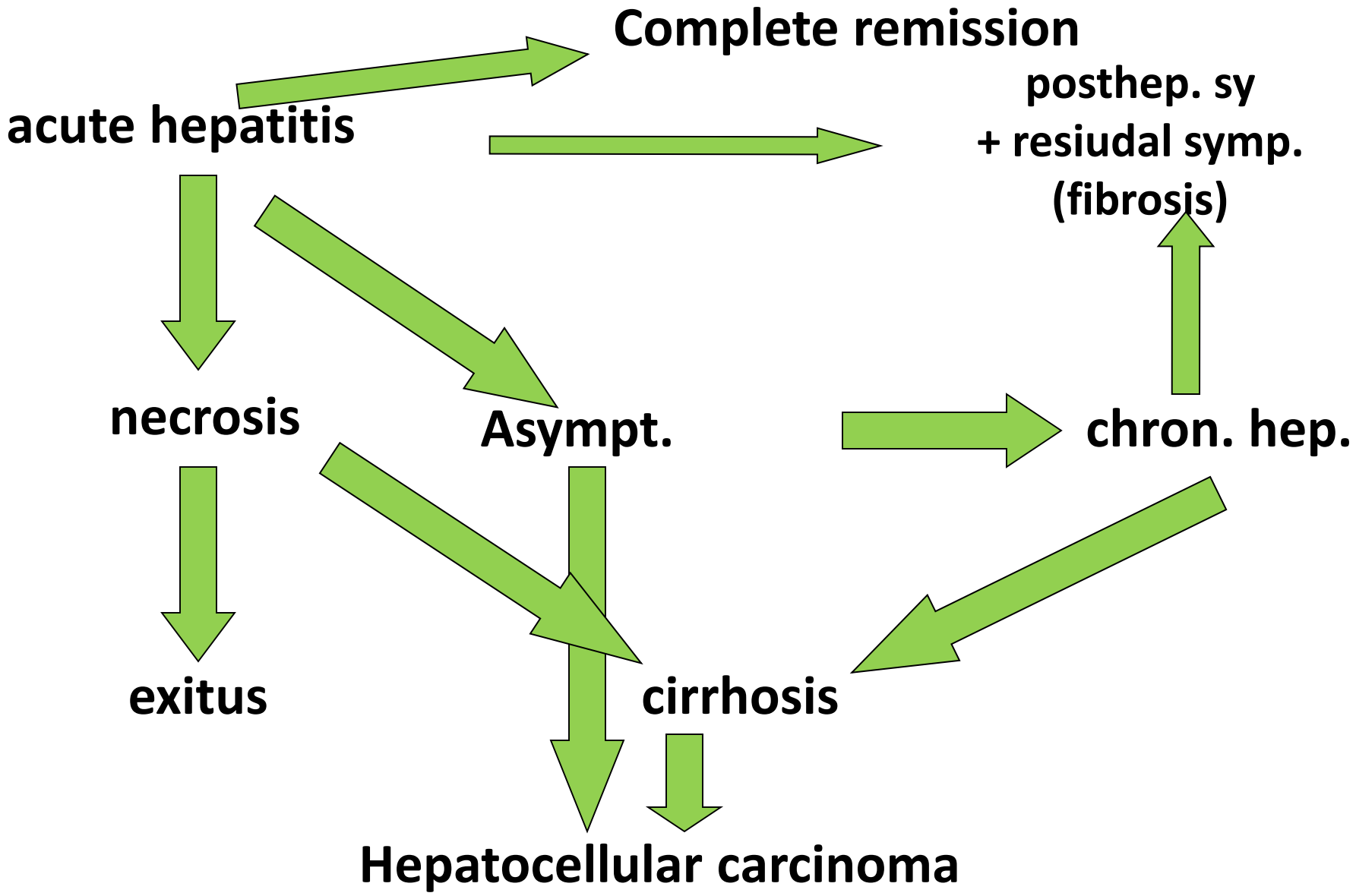
Up to 24-36 h
4 weeks: tenofovir + emtricitabine + raltegravir
(= NtRTI + NRTI + iNSTI)

# Antivirals in hepatitis

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

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

# Course and possible consequences of acute hepatitis



# Drugs used in HBV infection

- Pegylated interferon alpha-2a (PEG-IFN)
- interferon alfa (IFN) tzv. conventional
- lamivudin (LAM) (NRTI)
- adefovir dipivoxil (ADV)
- entecavir (ETV)
- tenofovir (TDV)
- telbivudin (TBV)

# Adefovir-dipivoxyl (inhibition rt *HBV*)

- Prodrug of adefovir (analogue of adenosin MP)

In mammalian cells converted to adefovir diphosphate

- Inhibition of viral polymerase

- Selective inhibition of HBV DNA polymerase

# Entecavir and Telbivudin (inhibition rt HBV)

## Entecavir

Guanosine Analogue (G)

Phosphorylation by kinases to the active triphosphate GTP competitor, DNA chain termination

## Telbivudin

Thymidine Analogue (T)

Phosphorylation by kinases to telbivudine 5'-triphosphate

TTP competitor, DNA chain termination

# Drugs in the treatment of HCV

- **sofosbuvir**
- **simeprevir**
- **daclatasvir**
- **dasabuvir**
- **ritonavir**

- Preferentially regimes without IFN

# Boceprevir, Telaprevir, Simeprevir (HCV)

**Non-structural HCV NS3 / 4A protease inhibitors.**
Binding to active site of protease NS3 - serine (Ser139)
inhibition of replication in infected bb.
CYP3A4 / 5 inhibition - Beware of combinations with other CYP3A4 / 5 inhibitors or inducers
**Chronic HC genotype 1 with peg-IFN alpha and ribavirin (adults)**

*Simeprevir also works on other genotypes*

# Ribavirin (HCV)

- **Wide-spectrum antiviral, Essential drug WHO**

The mechanism of action is unknown

**RNA viruses-** Imitates adenosine or guanosine (by rotation)

Incorporated into RNA may cause lethal virus mutations

**DNA viruses**

Inhibition of Inosine Monophosphate Dehydrogenase

- **HCV**

The mechanism of action by which ribavirin with IFNα-2b + Peg-IFNα-2b works is unknown so far

# New Antiviral against Hepatitis C Virus
# „Directly acting antivirals DAA“

**inhihitor protease NS3 / 4A** Paritaprevir + Ritonavir - improves the pharmacokinetics of ABT450

**"replicase" inhibitor NS5A:** Daclatasvir, Ledipasvir

**NS5B nucleoside inhibitor:** Sofosbuvir does not require combination therapy with ribavirin and interferons.

**non-nucleoside inhibitor of NS5B polymerase:** Tegobuvir

# Interferons – Immunomodulatory cytokines

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

# IFN- MofA

**Antiproliferative**

slowing the transition from G1 to S phase

**Immunomodulatory**

increased expression of cytotoxic lymphocytes, macrophages and NK-cells,

increasing the MHC expression required to induce a cytotoxic response

**Inhibition of viral replication**

**Anticancer**

reduction of c-myc, v-myc oncogenes expression

# Interferons – AE

- Restricted thrombopoiesis and granulopoiesis - limiting dosing
- Flu-like syndrome (2-4 hours after application, lasts 4-8 hours)

- Hypotension, fluctuating pressure, rhythm disorders
- Interferon pneumonia
- Manifestations of autoimmune diseases
- Proteinuria