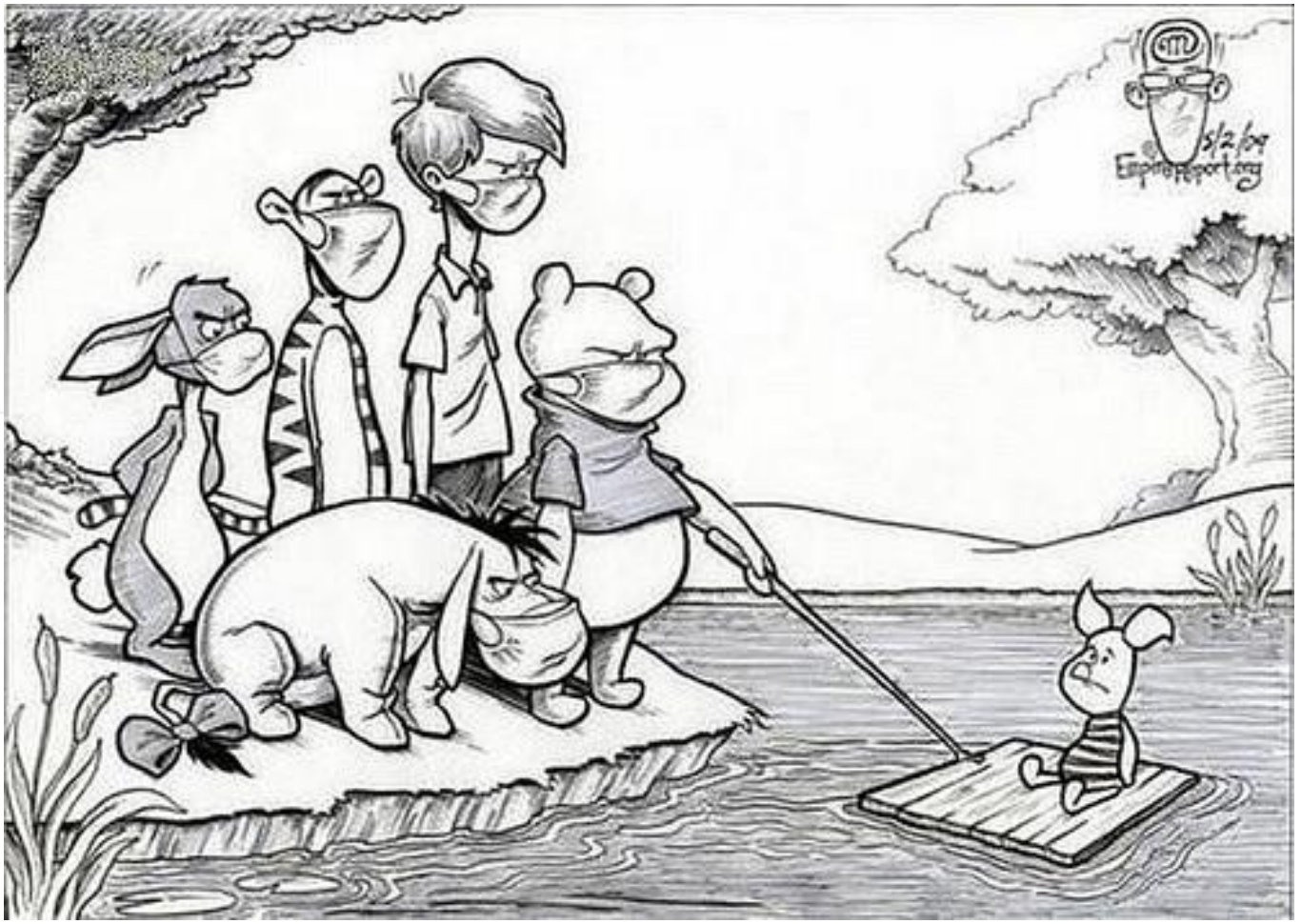
Antivirotics

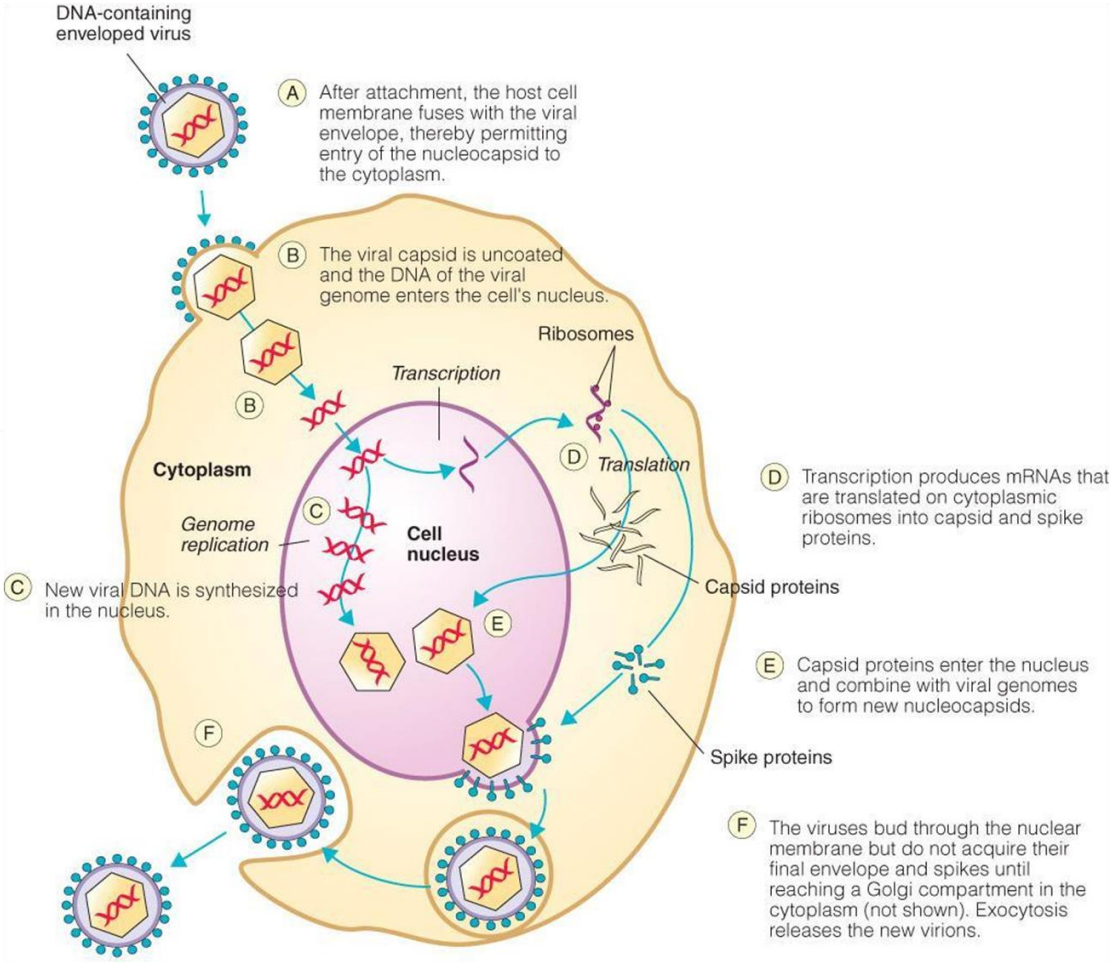
Scary predictions – swine flu :)



Viral diseases

- common diseases (rhinitis, cold, flu) – **symptomatic**
- against several there is **vaccination**: flu, hepatitis, child infections
- **antivirotics**: immunodeficiency
  - herpetic infections
  - flu viruses
  - HIV viruses
- many AE – viruses “take over”

Herpes simplex virus cycle



Defense mechanisms

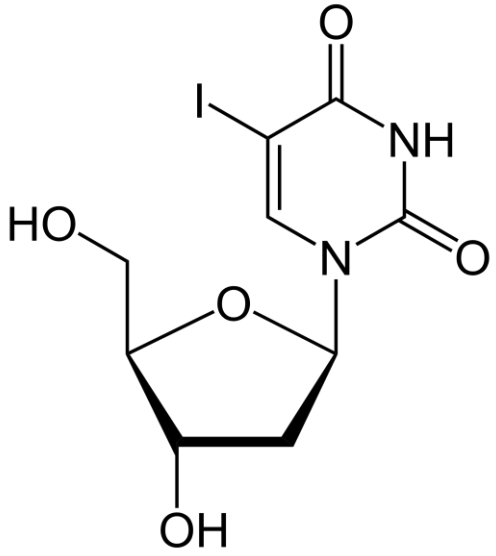
Interferons (IFN):

- glykoproteins released by cells infected with viruses – inhibition of viral protein synthesis
- innate imunity
- IFN-α (leucocytes), IFN-β (fibroblasts), IFN-γ (lymphocytes)
- e.g.: IFN-β for th. of severe herpetic infections
- INF-α therapy of hepatitis C

Virostatic antimetabolites

false base (T) – **idoxuridine**:

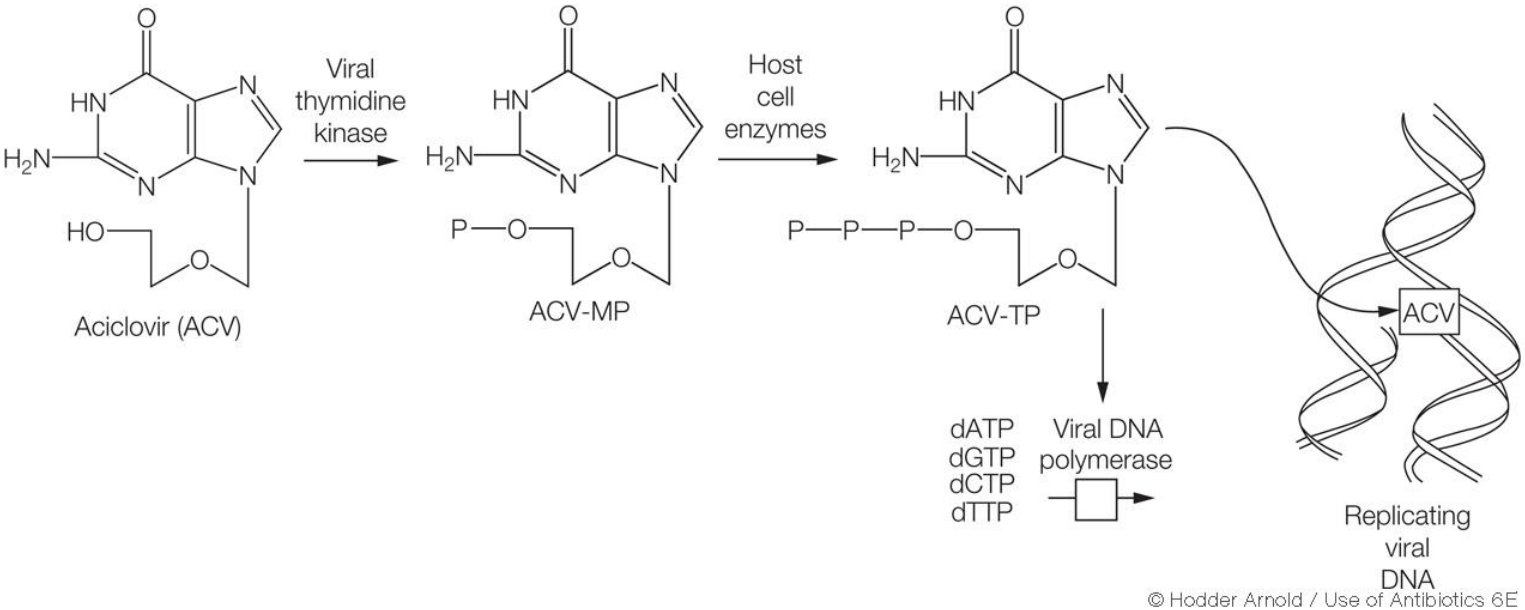
- incorporates into DNA and damages – affects also human DNA
- suitable only for local administration (ceratitis caused by Herpes simplex)



Virostatic antimetabolites

false sugar – **aciclovir**:

- very specific, well tolerated, activated only in infected cells
- 1st rxn catalyzed by viral tymidinkinase



Virostatic antimetabolites

false sugar – **aciclovir**:

- indicated for therapy of severe Herpes simplex virus infections – encephalitis, generalized infection; Varicella zoster (severe shingles) – i.v. infusion
- after p.o. dose resorption incomplete
- local form - cream
- synthesis of human DNA is not affected

Virostatic antimetabolites

false sugar – other examples:

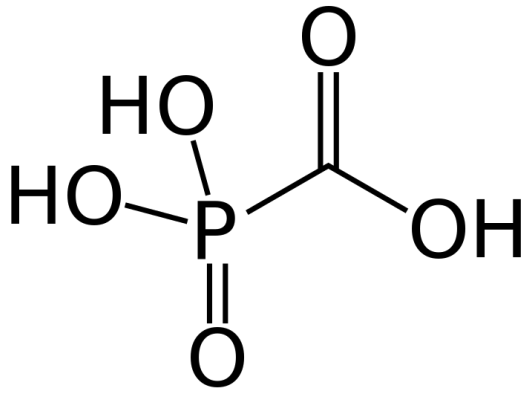
- **valaciclovir**: esterified with AA – enteral resorption 2× effective

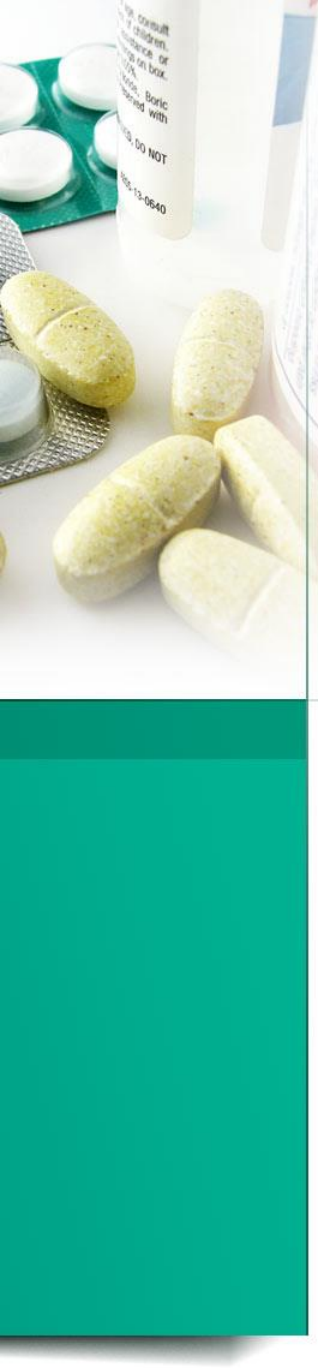
- **ganciclovir**: therapy of severe cytomegaloviral (CMV) infections – not very well tolerated (AE: leucopenia, trombocytopenia)

Virostatic antimetabolites

foscarnet:

- diphosphate analog
- inhibits DNA-polymerase – interaction with bonding site of diphosphate
- I: sever CMV in AIDS patients, local therapy of inf. Herpes simplex





Virostatic antimetabolites

Herpes simplex - labialis:

Tingling, itching, or burning beneath the skin (usually around the mouth or nose) may begin. **The first sensation is the ideal time to begin treatment.**

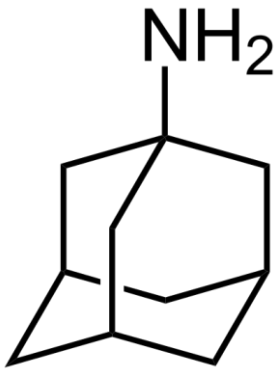
Small red bumps begin to blister.

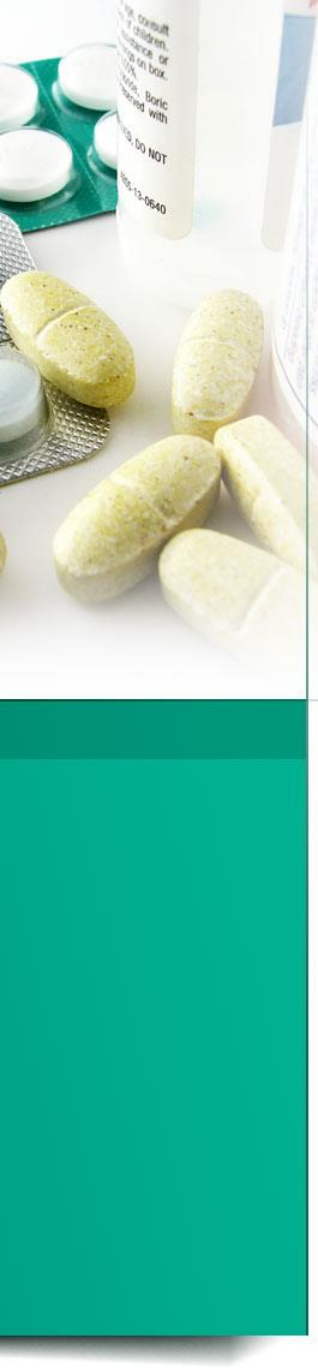
The blisters fill with fluid, forming a full-scale cold sore.

Flu therapy

amantadine:

- flu virus A (RNA virus) – inhibits release of viral NA – uncoating (blocks pump for H^+ in virus)
- used rarely, mainly in prophylaxis; also for Parkinson's disease

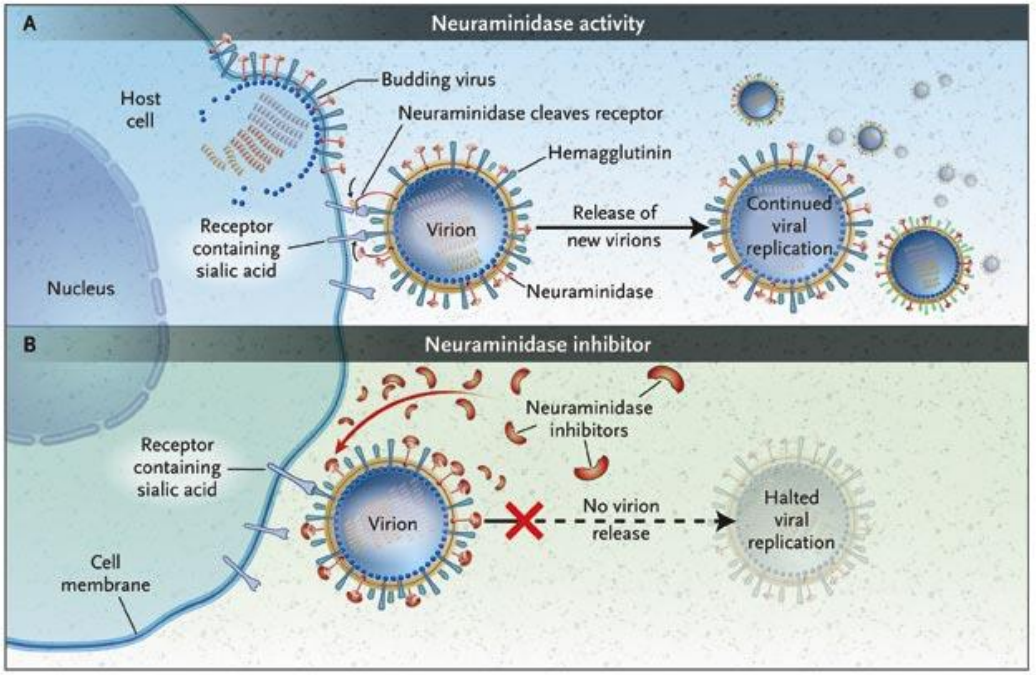




Flu therapy

neuraminidase inhibitors:

- inhibit release of flu viruses A and B
- **zanamivir** (inhalation), **oseltamivir** (p.o.)
- therapy and prophylaxis of flu infection



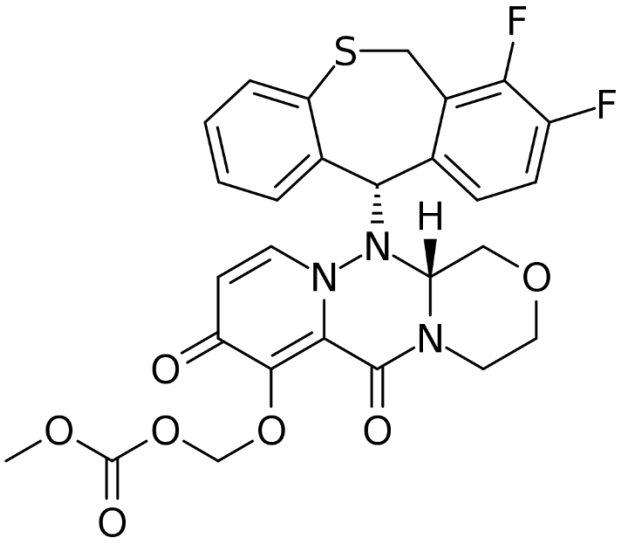
Flu therapy

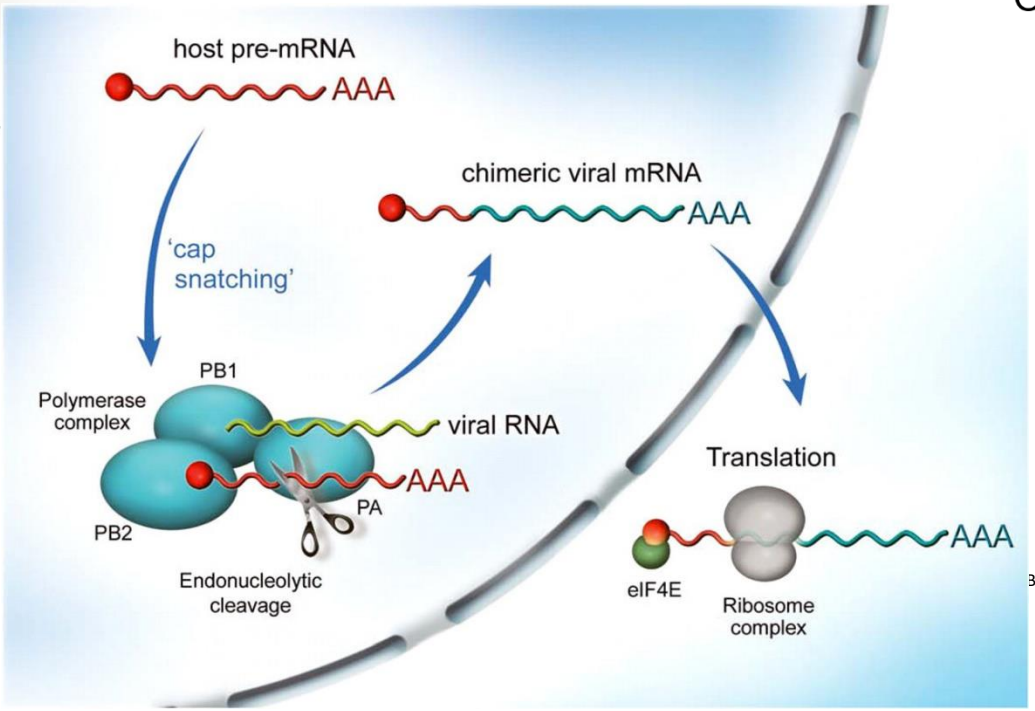
baloxavir marboxil

- in 2018 reg. in USA, EMA: 2021
- prodrug: metabolisation to active from
- child. > 12 y and adults – first 48h
- peroral treatment
- AE: diarrhea, vomiting, sinusitis, headaches
- MoA: inhibition of cap-dependent endonuclease („cap snatching“)

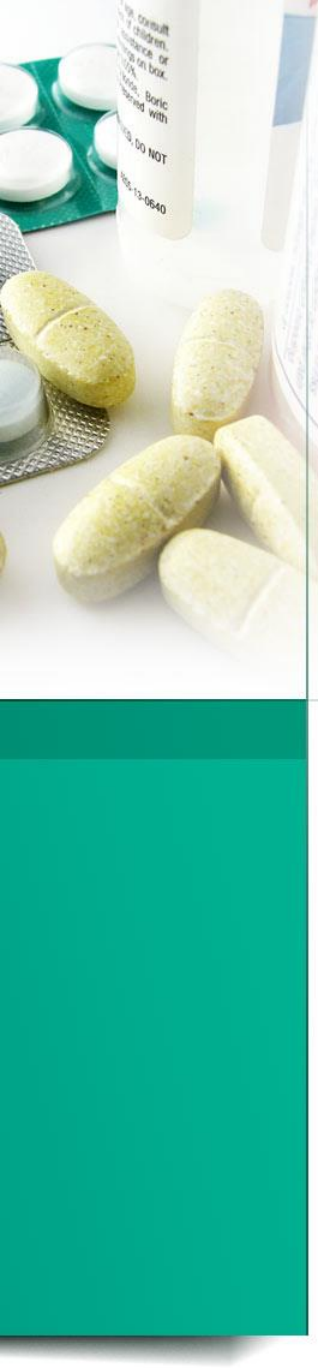
Flu therapy

baloxavir marboxil



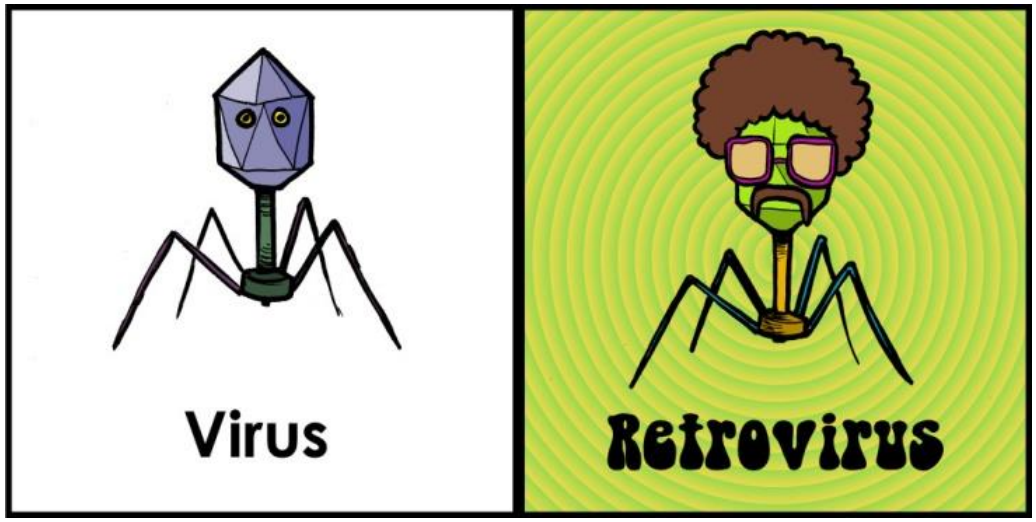


Influenza A Virus Polymerase: Structural Insights into Replication and Host Adaptation Mechanisms
Boivin, Stéphane et al.
Biological Chemistry, Volume 285, Issue 37, 28411 – 28417, 2010

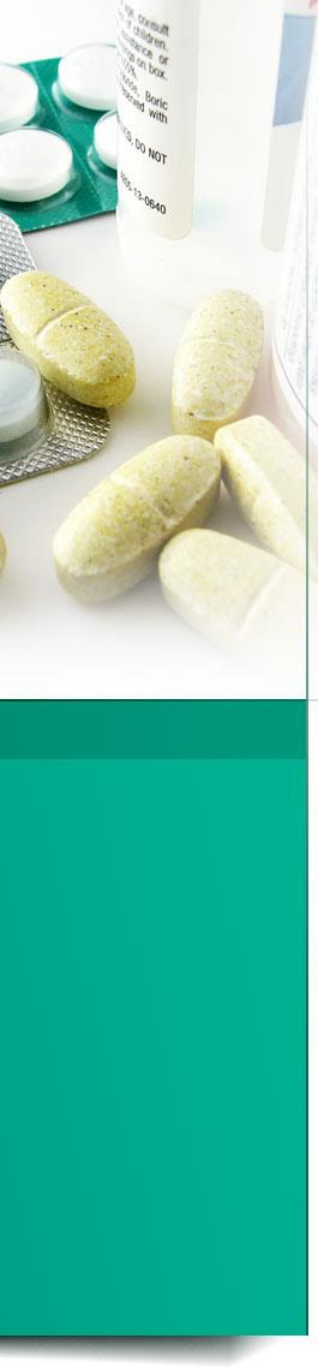


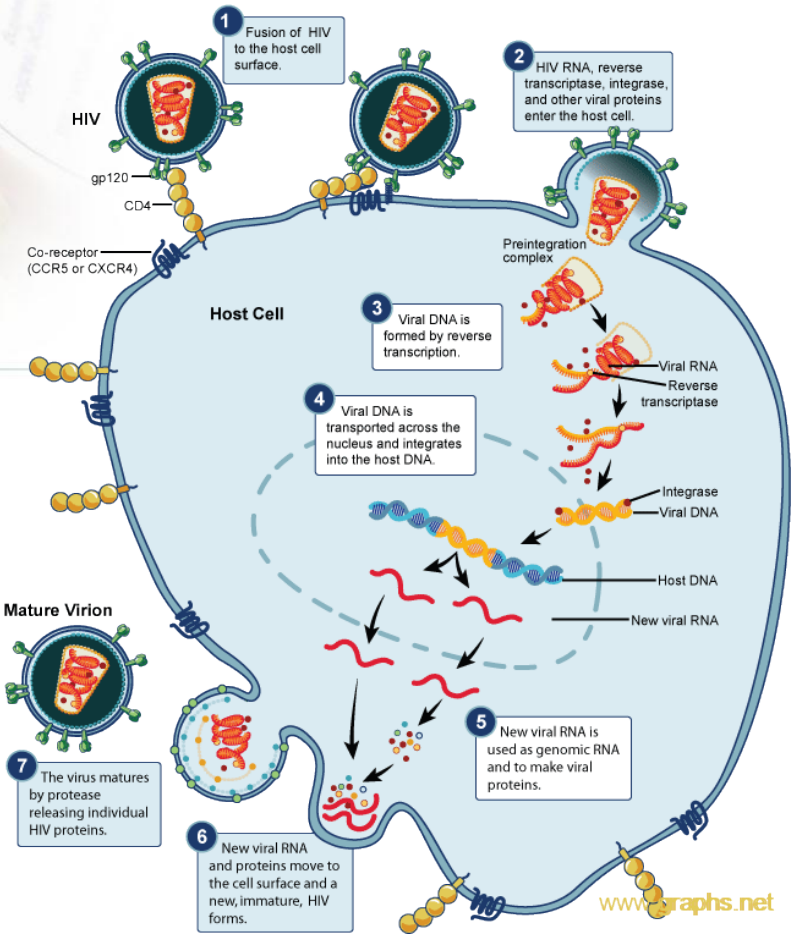
AIDS therapy – HIV virus infection

- targeted inhibiton of specific processes (retrovirus)
- virus binds to CD4-receptor at helper T-lymphocytes
- 1981 - Kaposi sarcoma; pneumonia in gays
- 1983 – HIV virus discovered as the cause



AIDS therapy – HIV virus infection





1. fusion inhibitors

3. reverse transcriptase inhibitors (N; NN)

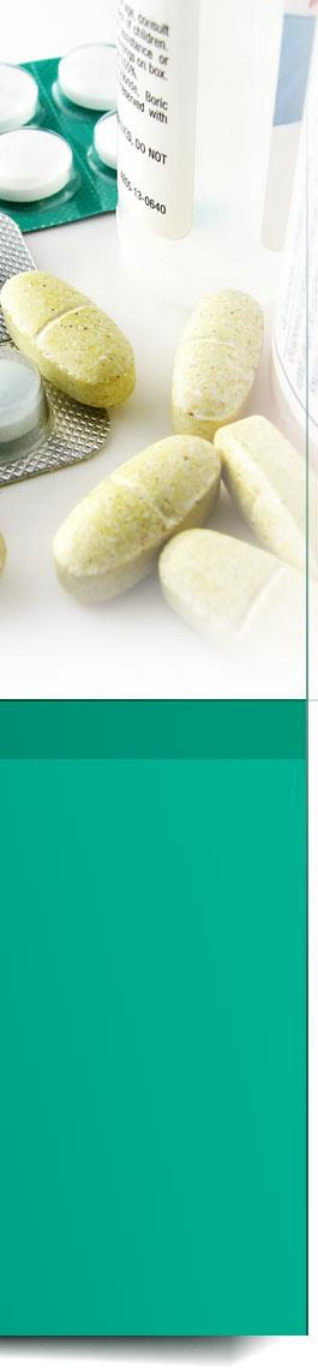
4. integrase inhibitors

7. protease inhibitors

Fusion inhibitors

enfuvirtide:

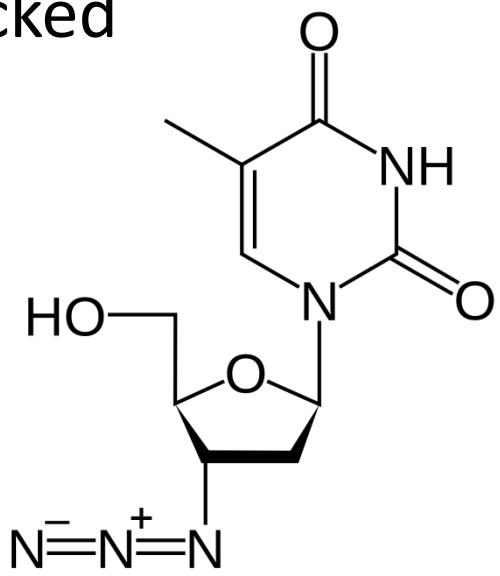
- peptide, s.c. administration
- because of AE only as salvage therapy in patients with multidrug-resistant HIV
- binds to viral fusion protein and inhibits the conformation change



RT inhibitors – nucleoside (NRTI)

- 1987 – **zidovudine**: 1. approved drug (*in vitro* results in 1985!!!)
- nucleosides with abnormal sugar – activation by phosphorylation
- RT inhibition – synthesis blocked
- p.o. administration
- AE: leucopenia
- others (dideoxyderivatives):

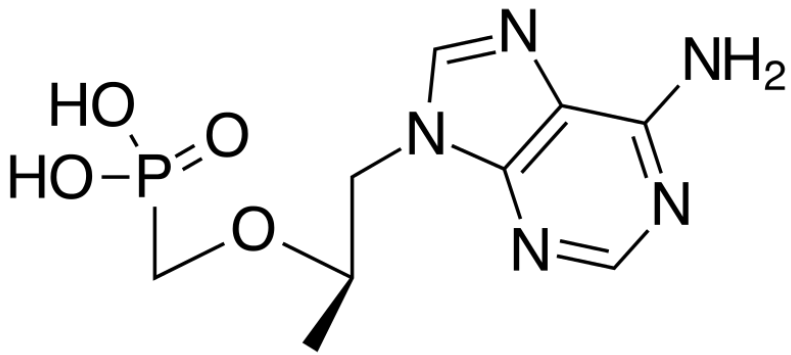
  lamivudine



RT inhibitors – nucleoside (NRTI)

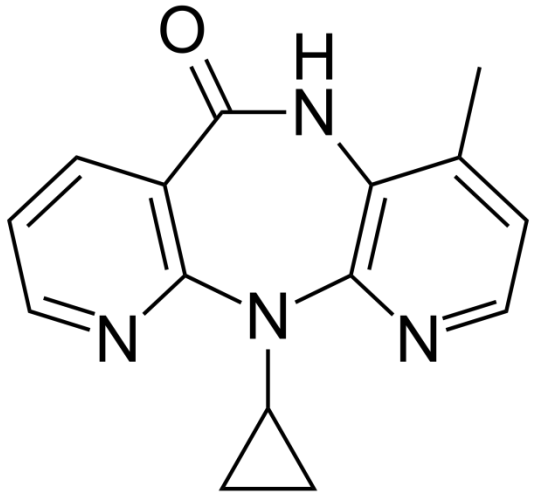
nucleotide inhibitor (NtRTI) – **tenofovir**:

- phosphorylation of phosphonomethyl group
- RT inhibition – synthesis blocked
- syntetized by prof. Holý (ÚOCHB) 1984 – Gilead Sciences



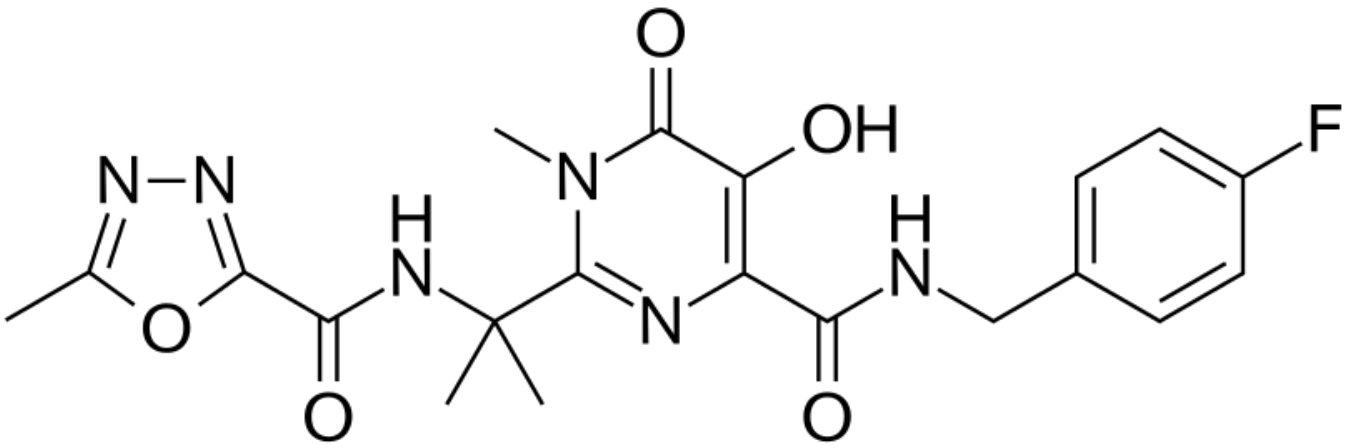
RT inhibitors – non-nucleoside (NNRTI)

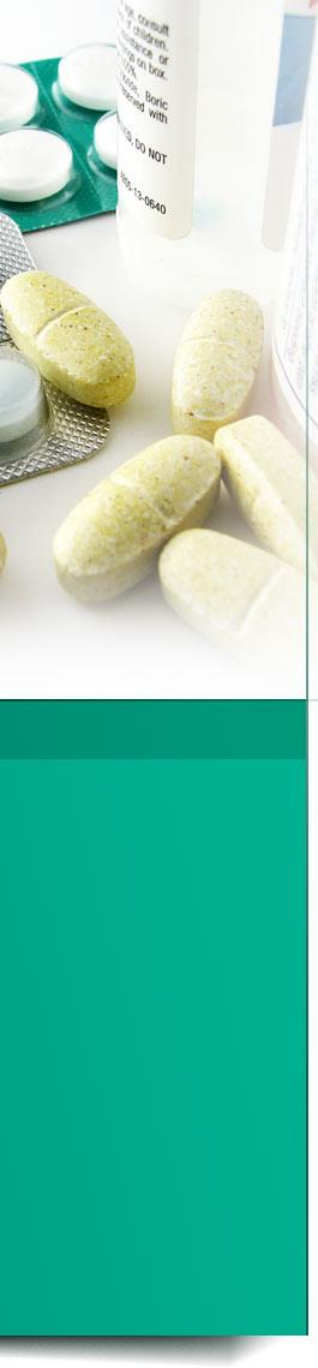
- various heterocyklic structures – no phosphorylation – active inhibition of RT
- AE: exanthema, interaction with cytochrom P450
- **nevirapine**, **efavirenz**



Integrase inhibitors

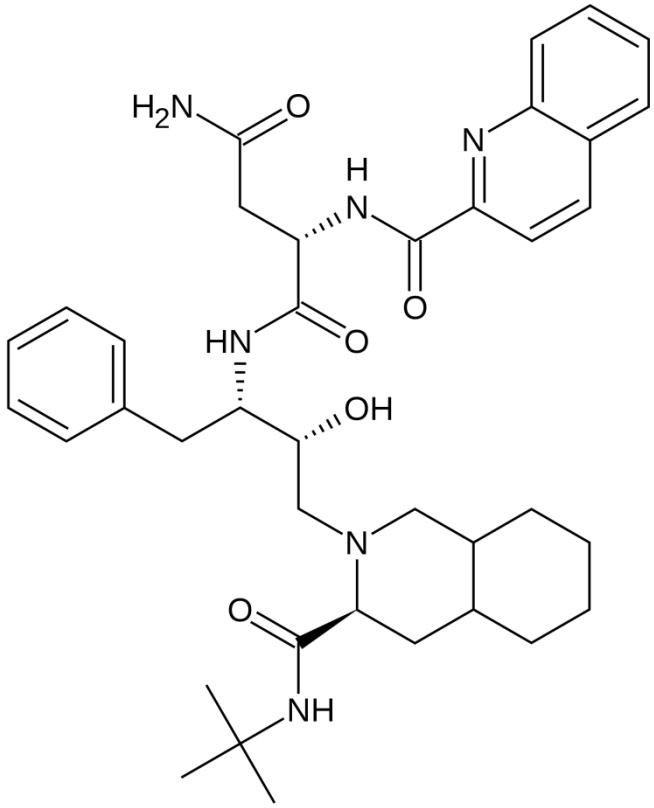
- inhibit intgration of viral DNA into human in the form of provirus
- p.o. dosage; post exposure prophylaxis
- **raltegravir**: AE fatigue and allergies





HIV-protease inhibitors (PI)

- stop viruses from maturation by hindering of polypeptide cleavage
- p.o. administration; interactions; hyperlipidaemia
- **saquinavir**: abnormal peptide, low bioavailability -> **ritonavir**, **indinavir**



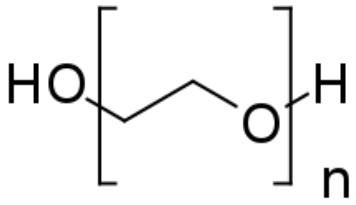
Combination antiretroviral therapy (cART)

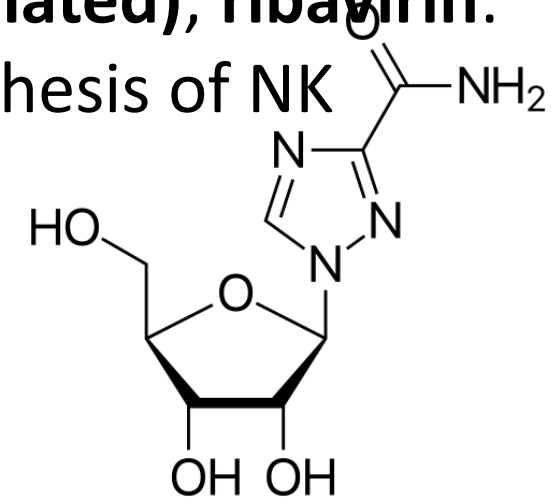
- most often 2 NRTI + PI or 2 NRTI + NNRTI
- improvement of patient's prognosis – decrease of viraemia under detectable level, increase of $CD4^{+}$Th and reducing of opportunistic infections and tumors
- total eradication impossible (retrovirus)

Therapy of viral hepatitis

- **HBV** – not retrovirus, but uses RT and thus the inhibitors are effective: **lamivudin** and **tenofovir**

- **HCV** – **interferon α (PEGylated)**; **ribavirin**: analogue of G, inhib. synthesis of NK



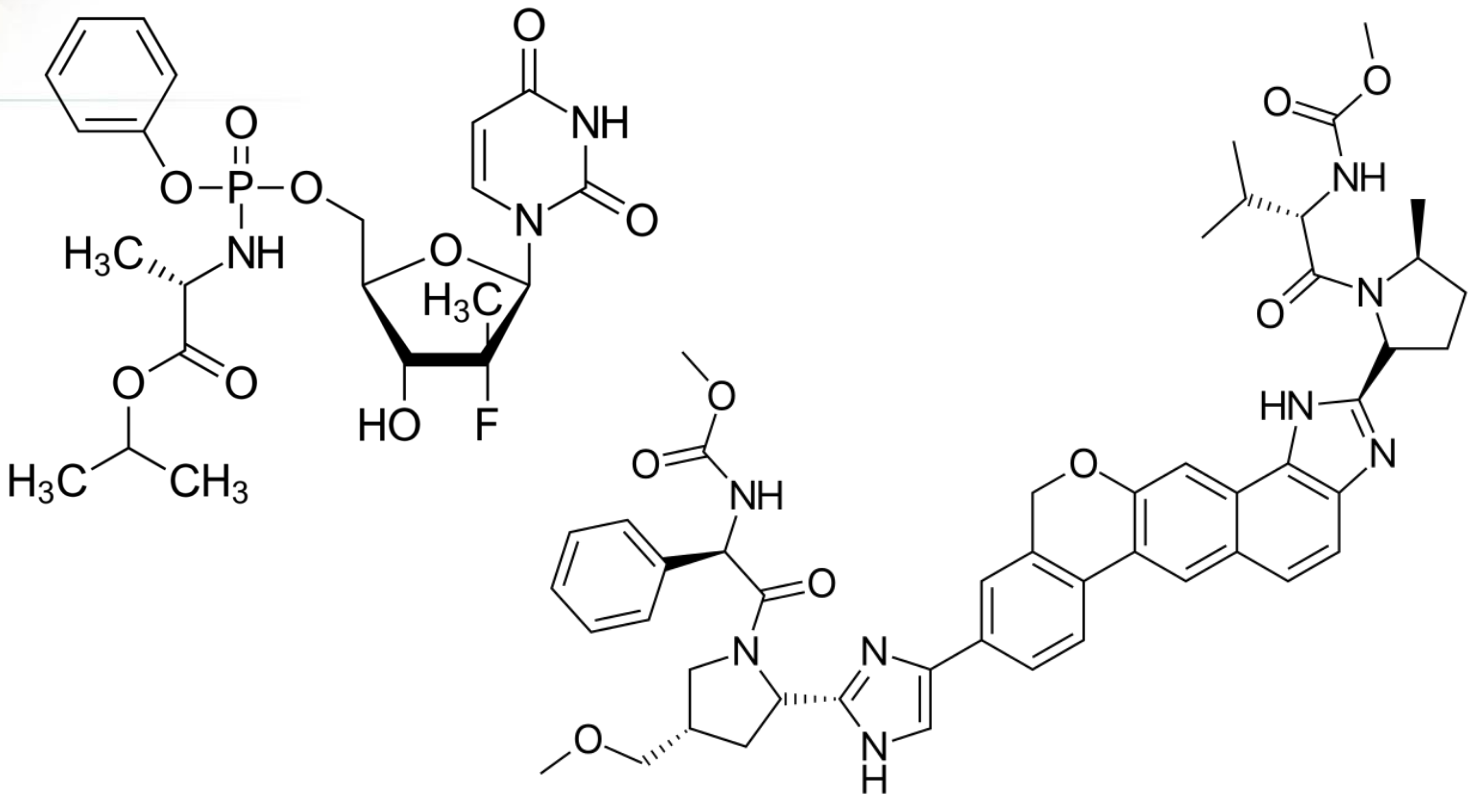


Therapy of HCV

- because of AE (half of patients; flu-like) new **direct acting antivirals** (**DAA**):
- genotypization needed, less AE; up to 100% efficacy; p.o. 8 – 12 weeks; combinations
- e.g. **sofosbuvir/velpatasvir** (2016; MoA: inhibition of enzyme **NS5B** – RNA-dep RNA polymerase and enzyme **NS5A** – inhibition of domain I, decreased binding to RNA and thus the RNA replication is halted)

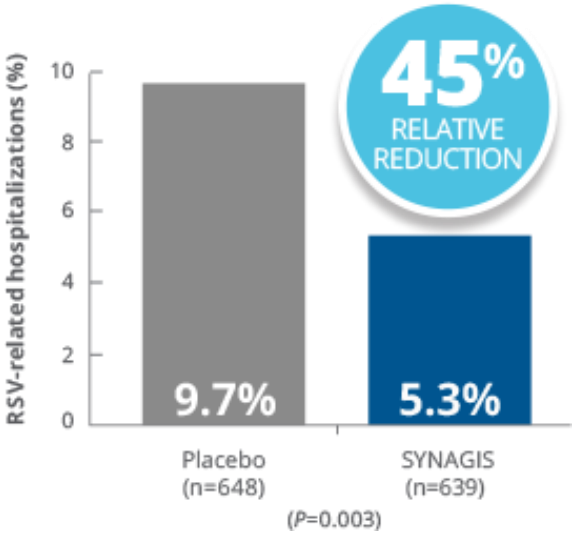
Therapy of HCV

- **sofosbuvir/velpatasvir** (S: analog U; Protide prodrug; rychlá bun. metabolizace na trif.; V: určitá symetrie)



Therapy of RSV

- apart from ribavirin, **palivizumab** is used
- mab against F protein – stops fusion and viral entry into the cells
- once a month i.m. in severe cases of small children



Zmapp – Ebola virus

- bleeding fever Ebola – largest epidemic 2013/14 – west Afrika (fever, muscle ache, vomiting, diarrhea, bleeding; lethality upto 90%)
- exp. therapy – 3 chimeric mab – neutralisation (pasive immunity)
- in 2014: 7 pac., 2 died; then run out.. (controversion – why not given to Africans?)
- 2015: <200 subjects – 40% lower risk of death

Zmapp – Ebola virus

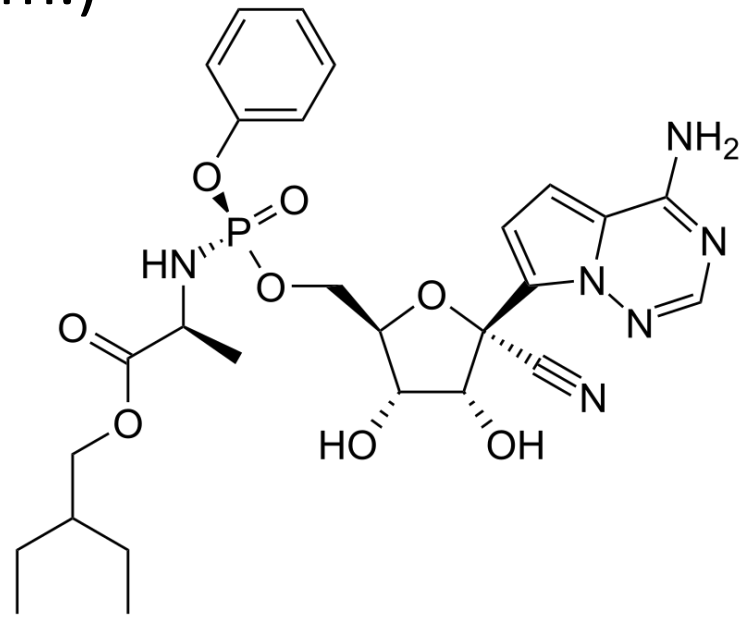
Nicotiana benthamiana – viral vector

Therapy of Covid-19

- in non-compl. **symptomatic**; compl. with risc factors **breathing support** + therapy:
- **favipiravir** (broadspectrum antivirotic, inh. RdRP)
- **hydroxychlorochin** (alleviation of cytokine storm; antimal., antireum.; quest.?; AE)
- **ivermectin** (FNUSA asked for CT; inh. 3CL pro; useful?)
- **dexametasone** (glucocort.; questionable)

Therapy of Covid-19

- **remdesivir** (Gilead; previously Ebola and Marburg; authorized in EU for severe cases of pneumonia with necessity of O_2; analogue of A, inh. RdRP; accord. to WHO Nov 2020 not recom.)



Therapy of Covid-19

- **bamlanivimab/etesevimab:** monoclonal antib. against surface spike-protein – in cases without addition of oxygen, but with risk of severe case – under review
- **tocilizumab** (non-effective; mab against Il-6)
- **molnupiravir** (under review; FDA red.; inh. RdRP)

Antiparasitics

Antiparasitics

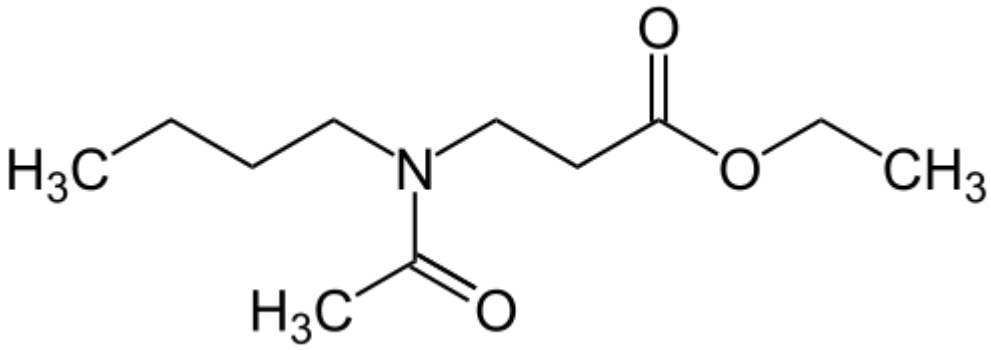
- **ectoparasites**: head louse, flea, scabies
  - insecticides

- **endoparasites**: tapeworms, roundworms, pinworm, trichinella
  - anthelmintics

- tropical diseases: **malaria**

Insecticides

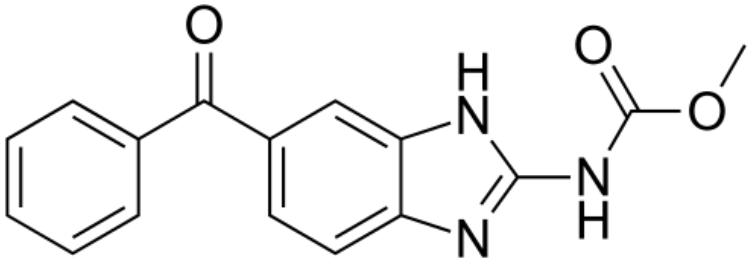
- remove the cause (flea, head louse)
- for pediculosis (head louse) and scabies (*Sarcoptes scabiei*) insecticides are necessary – shampoo or solutions
- **lindane** (hexachlorocyclohexane) – scabies
- **ethyl butylacetylaminopropionate** (IR3535)



Anthelmintics

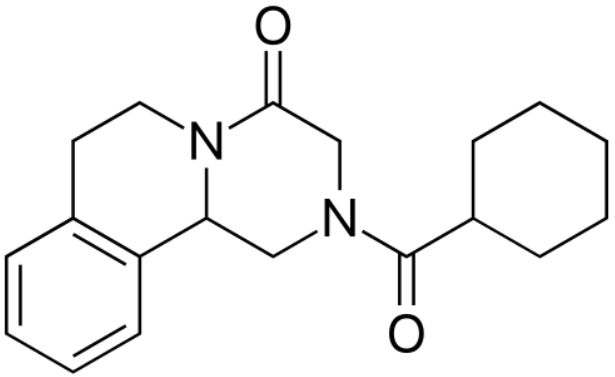
mebendazole:

- against worms (round- and pin-) and trichinella
- inhibition of microtubule synthesis – immobilization



praziquantel:

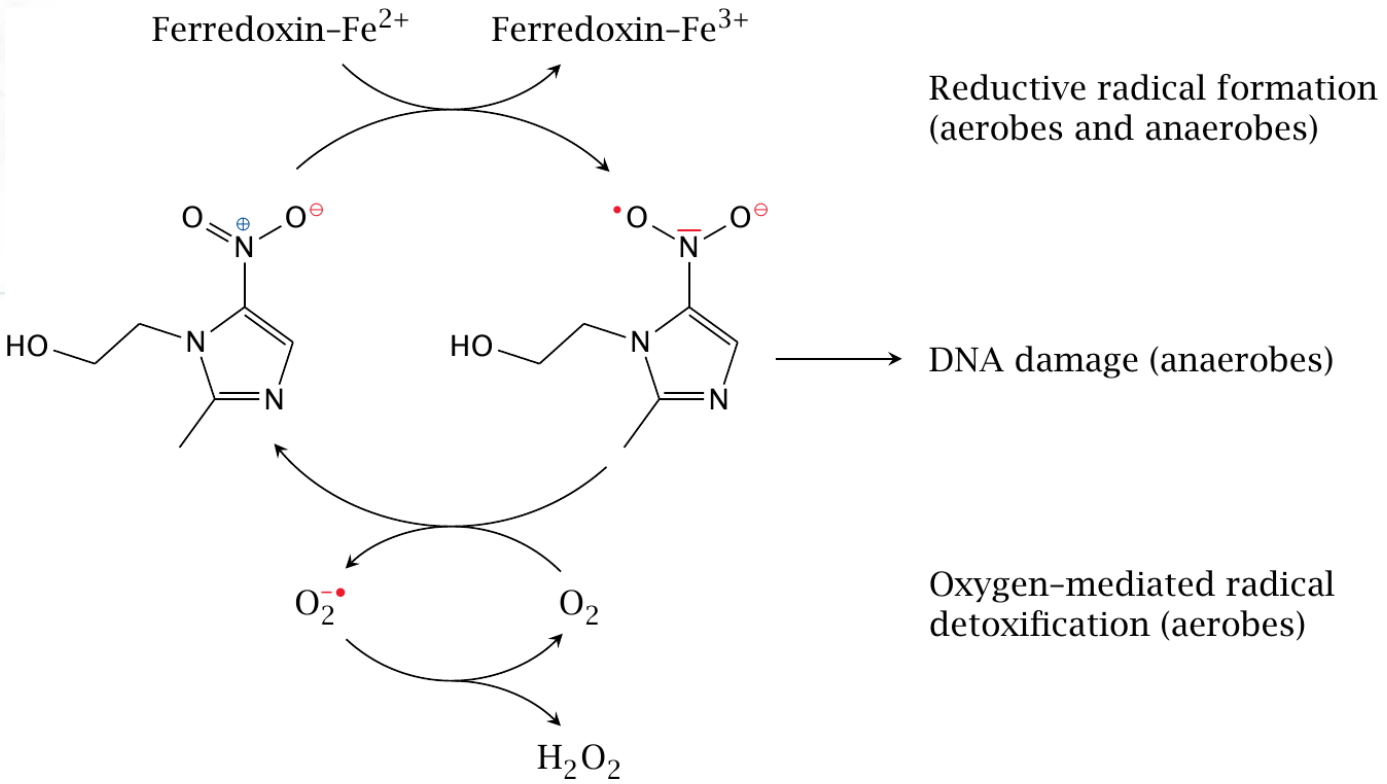
- against tapeworms and schisostomosis
- paralysis, cramps



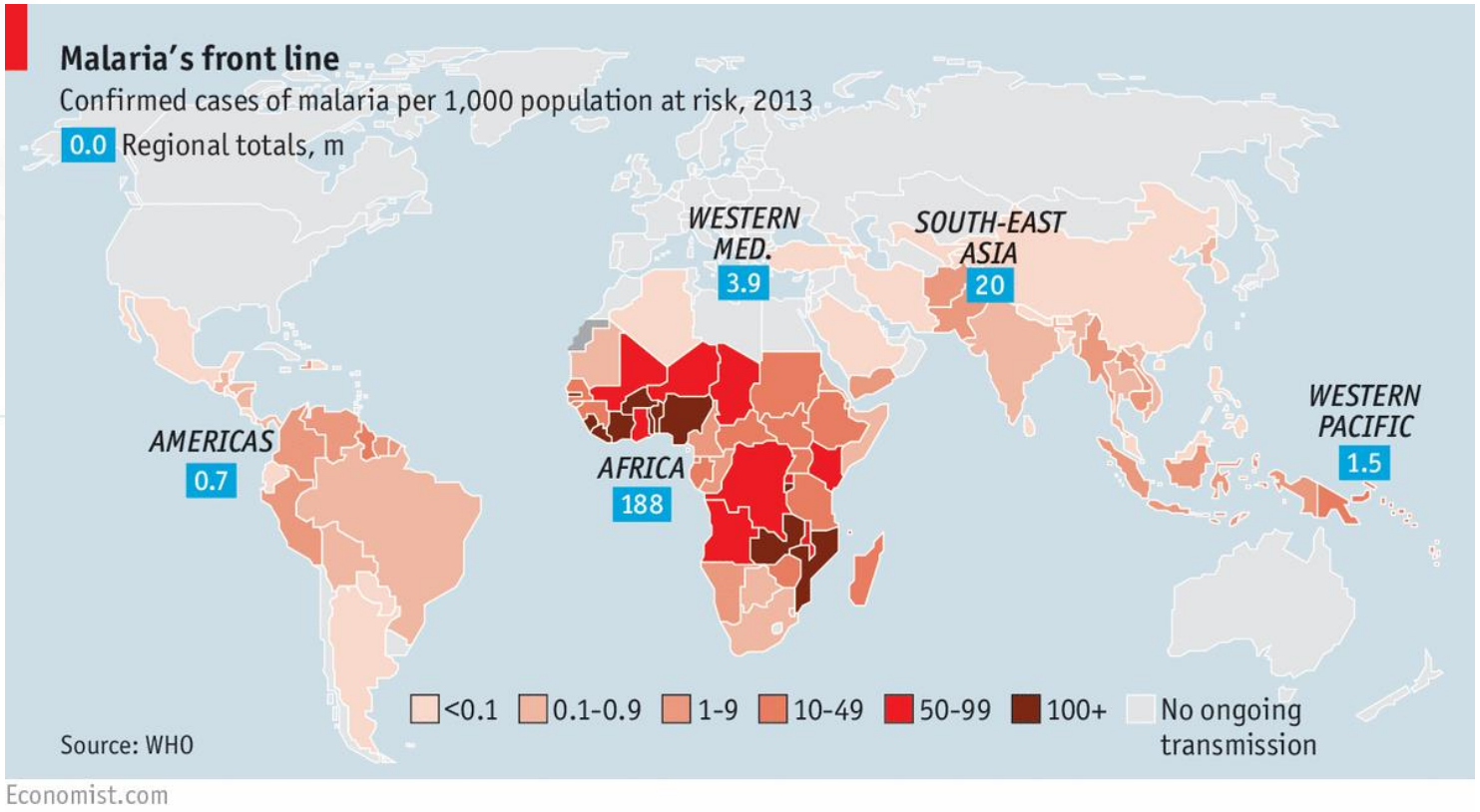
Derivatives of nitroimidazole

- damage to DNA by forming complexes and strand breaks (reactive metabolites)
- bactericidal (usual anerobes) + protozoa *(Trichomonas vaginalis*; *Entamoeba histolytica)*
- **metronidazole**: p.o., vag. tbl.
- CI: pregnant, breastfeeding women

Derivatives of nitroimidazole



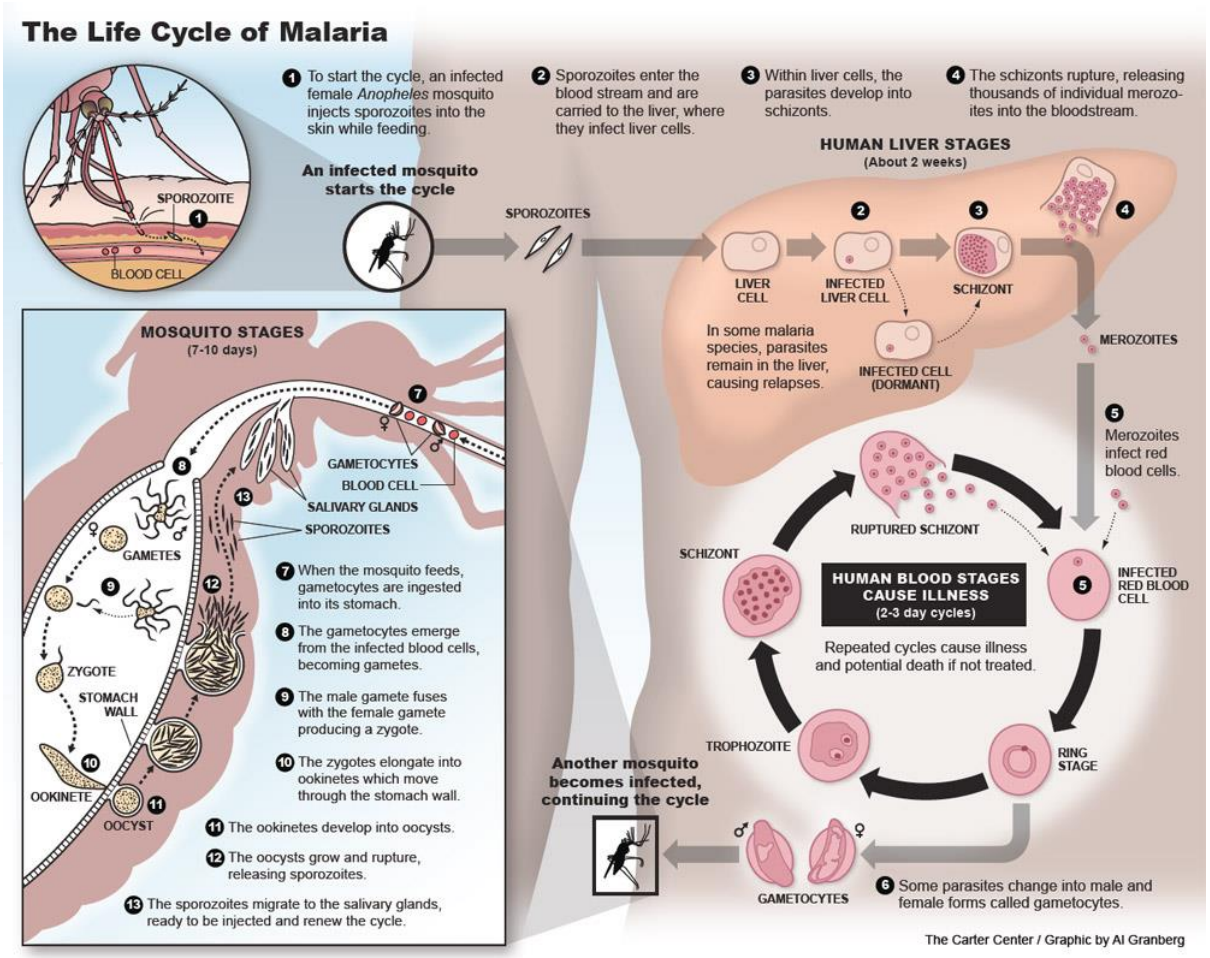
Malaria



45 N – 30 S (latitude)

worldwide: 1,5–3 mil deaths/year, incidence: 300–500 mil/year

Malaria

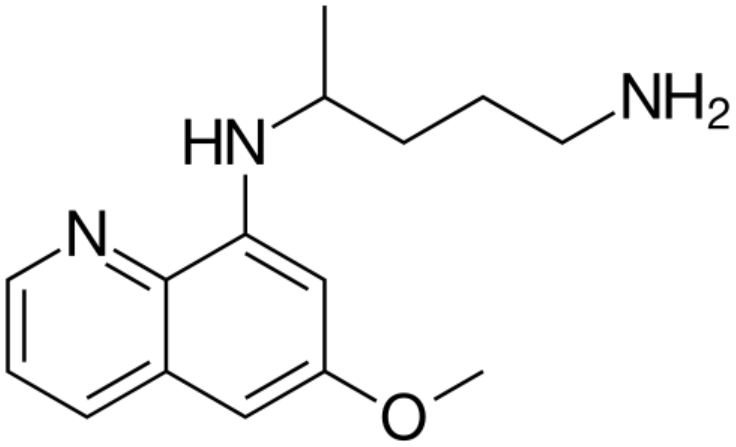


causes: *Plasmodium malariae, vivax, falciparum*

Antimalarials

primaquine:

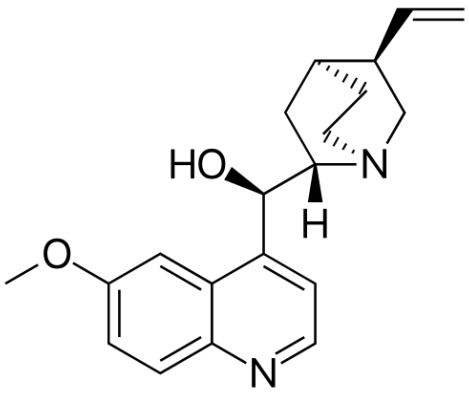
- mainly against liver schizonts and hypnozoits (!)
- not prophylaxis – because of resistance and worse toleration



Antimalarials – blood schizonts

quinine:

- only for chloroqine-resistant *P. falciparum*
- cumulation in vacuoles – inhibition of heme polymerization (toxic for parasite)
- *Cinchona* sp. – 1600s – jesuit's bark
- 1820: isolation – Pelletier, Caventou

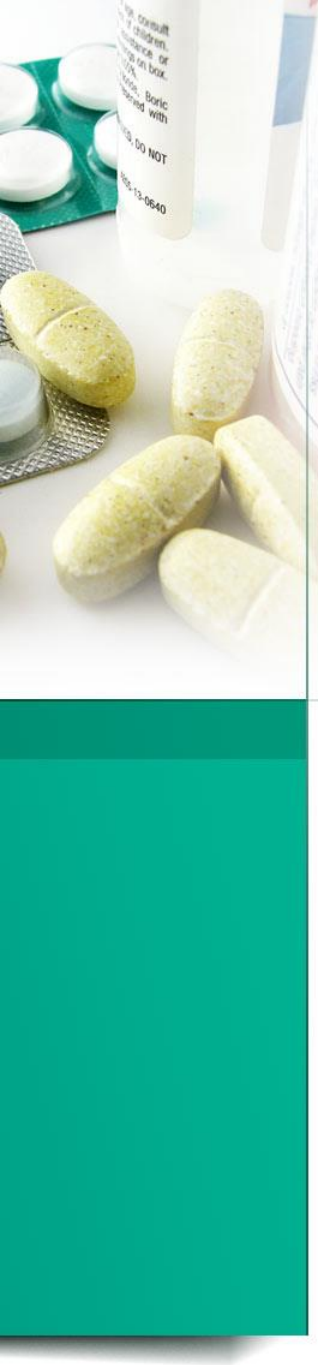


Antimalarials – blood schizonts

chloroquine:

- effective, but many are resistant

proguanil, **atovaquone**, **pyrimethamine** (inhibition of dihydrofolate reductase), **sulfadoxine** (sulfonamide)

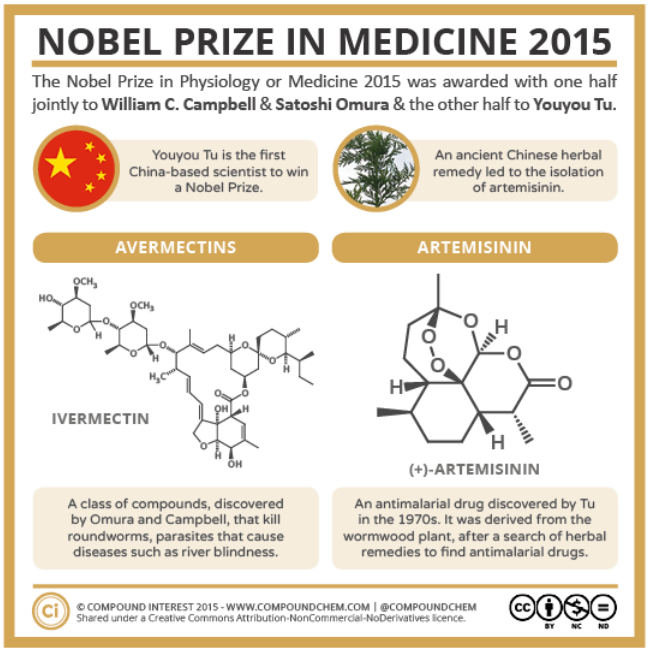


Antimalarials – blood schizonts

artemisinin:

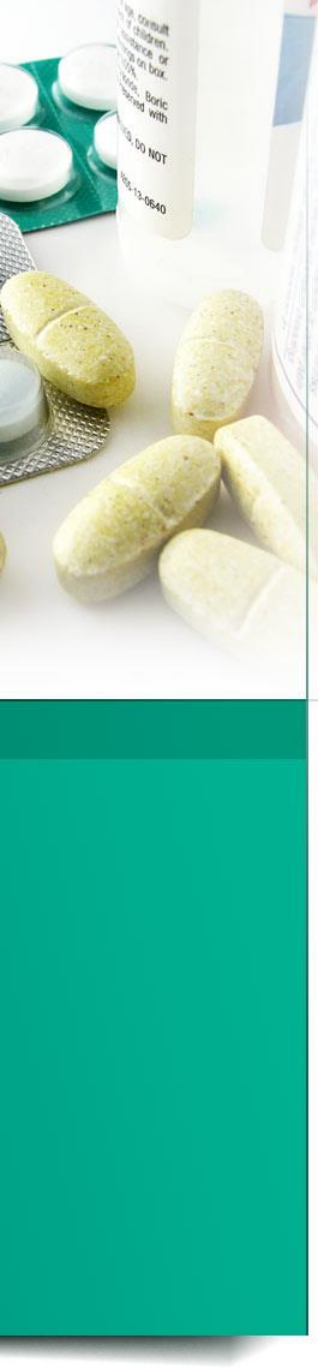
- isolated from *Artemisia annua* – TCM
- chinese: ***qinghao su*** 青蒿素
- MoA: ROS formation
- ACT: combinations
- semisynthetic derivatives:

artemether, **artesunate**



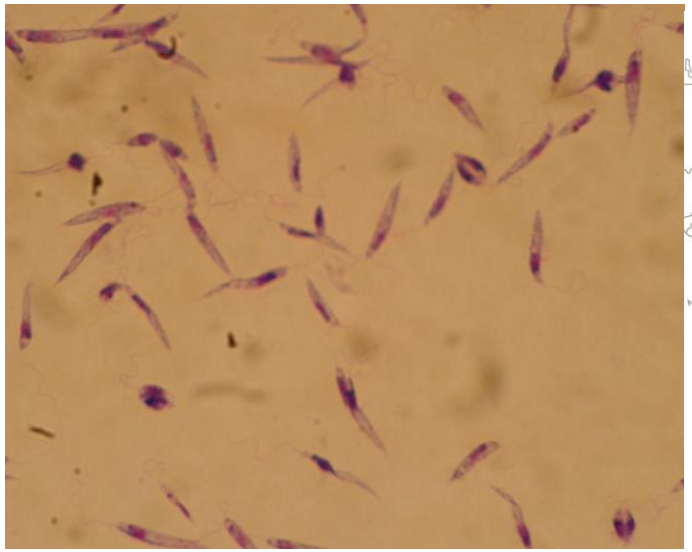
Prevention

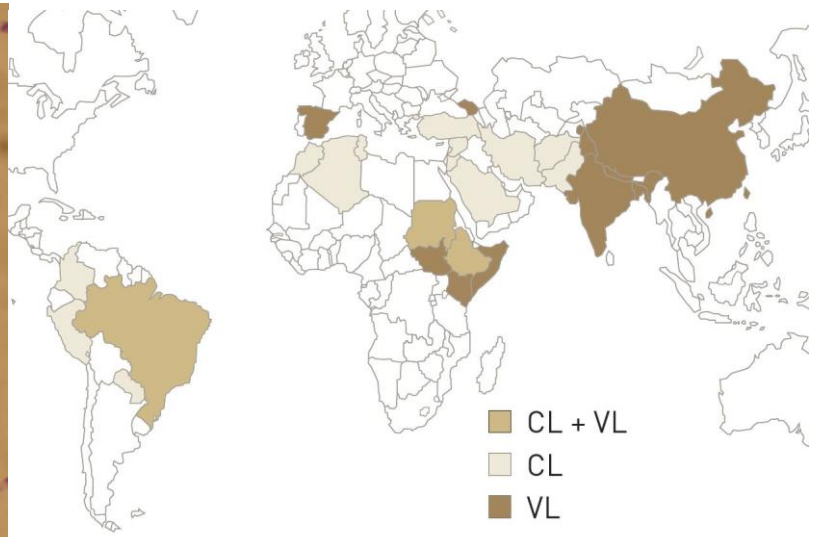
1. **Exposure prophylaxis:** repellents, insecticides, mosquito nets in windows and doors, white clothes with long sleeves and legs.
2. **Chemical prophylaxis:** antimalarials before, during and after staying in endemic region: meflochin, chlorochin, proguanil, atovaquon, doxycyklin.
3. **„Stand-by“ therapy:** regions with low risk of malaria or long stay in endemic regions – take with you antimalarials for **„emergency treatment“** (in case of symptoms; substitute for AD2).

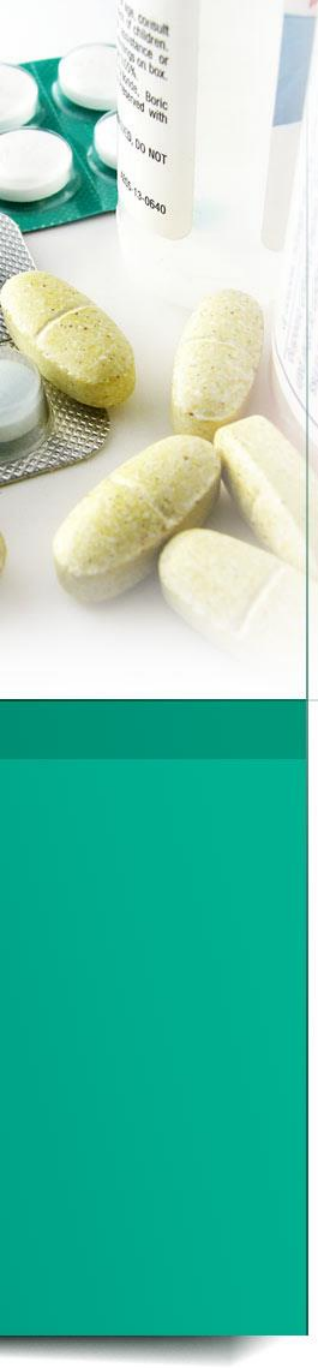


Leishmaniasis (DNDi)

- cause: g. *Leishmania* – IC parasites; flagellates
- spread by: blood sucking insect *Phlebotomus*, etc.
- 2 main froms: **visceral (VL**; AKA kala-azar) fatal without treatment; **cutsneous (CL)**: ulcers on exposed areas (hands, feet, face)
- cca 1,5 mil. new patients; 20 – 40 tho. dead (VL)

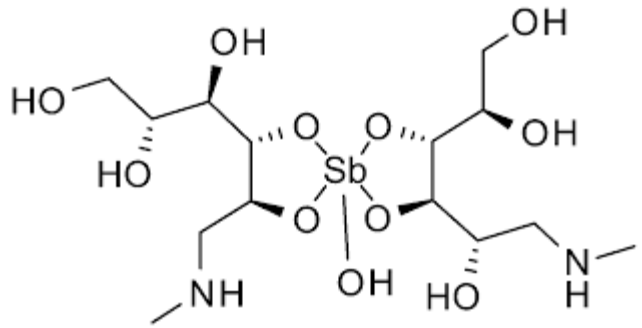




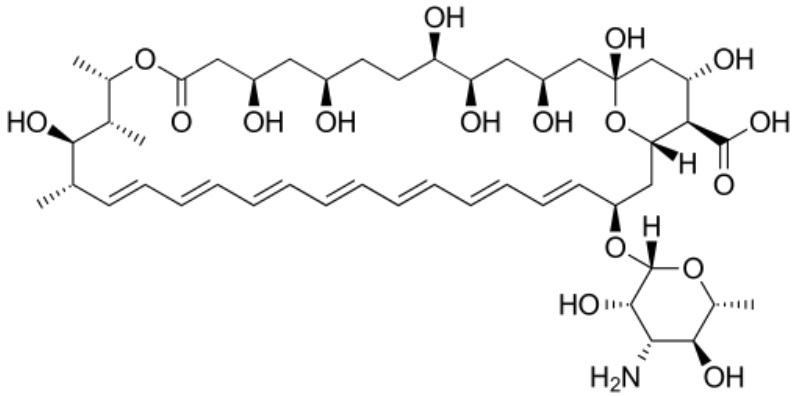


Leishmaniasis (DNDi) – therapy:

- **pentavalent antimonials**: 60 years used, now not so much; injection, cardiotoxicity; e.g. **meglumine antimoniate**

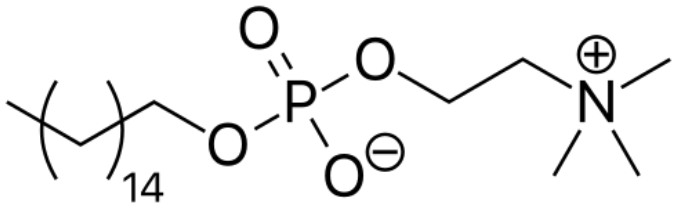


- **amphotericin B**:
  as liposomal infusion
  (increase in safety and efficiency)
  dose 10 mg/kg can treat 96 % VL cases; cold chain!

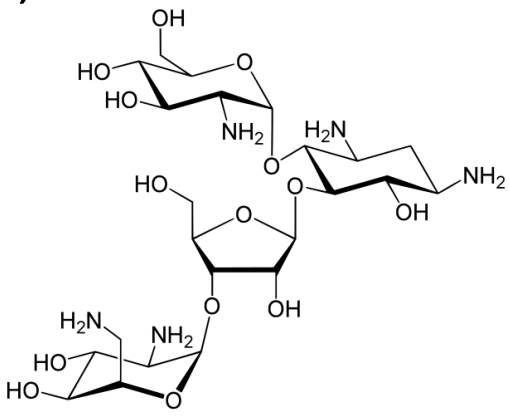


Leishmaniasis (DNDi) – therapy:

- **miltefosine**: p.o. dose 2× a day, bad compliance; simultaneously contraception; MoA: interaction with lipids, inh. cytochrom C oxidase, apoptosis

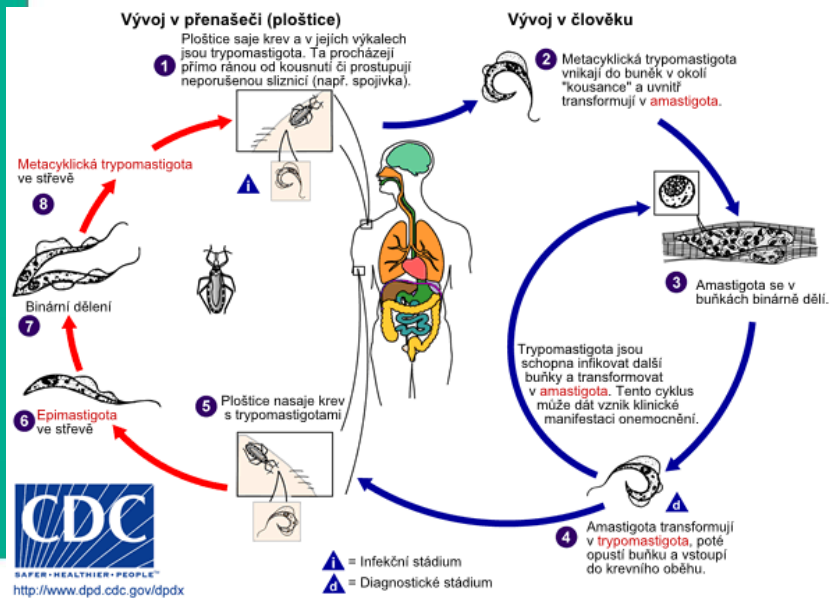


- **paromomycine:** ATB for parasitosis and amebosis; similar MoA as aminoglycosides; i.m.



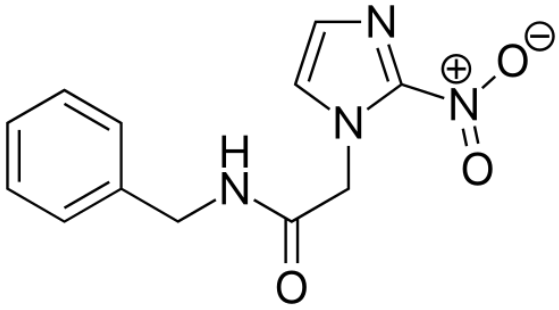
Chagas disease (DNDi)

- cause: *Trypanosoma cruzi* – protist, IC parasite
- spread by: blood sucking „kissing bugs“
- **acute** (5 % children die) – fever, 4 months – latent – **chronic** (even whole life) – heart and GIT disease
- 6 – 8 mil. infected; 12 tho. dead per yr.; <1% treated



Chagas disease (DNDi) – therapy:

- **benznidazole**:
  production of ROS, damage to DNA; effect in acute phase, later less effective



- **nifurtimox**: 60 day treatment; MoA: binding to DNA, damage