Pharmacolological treatment of viral infections

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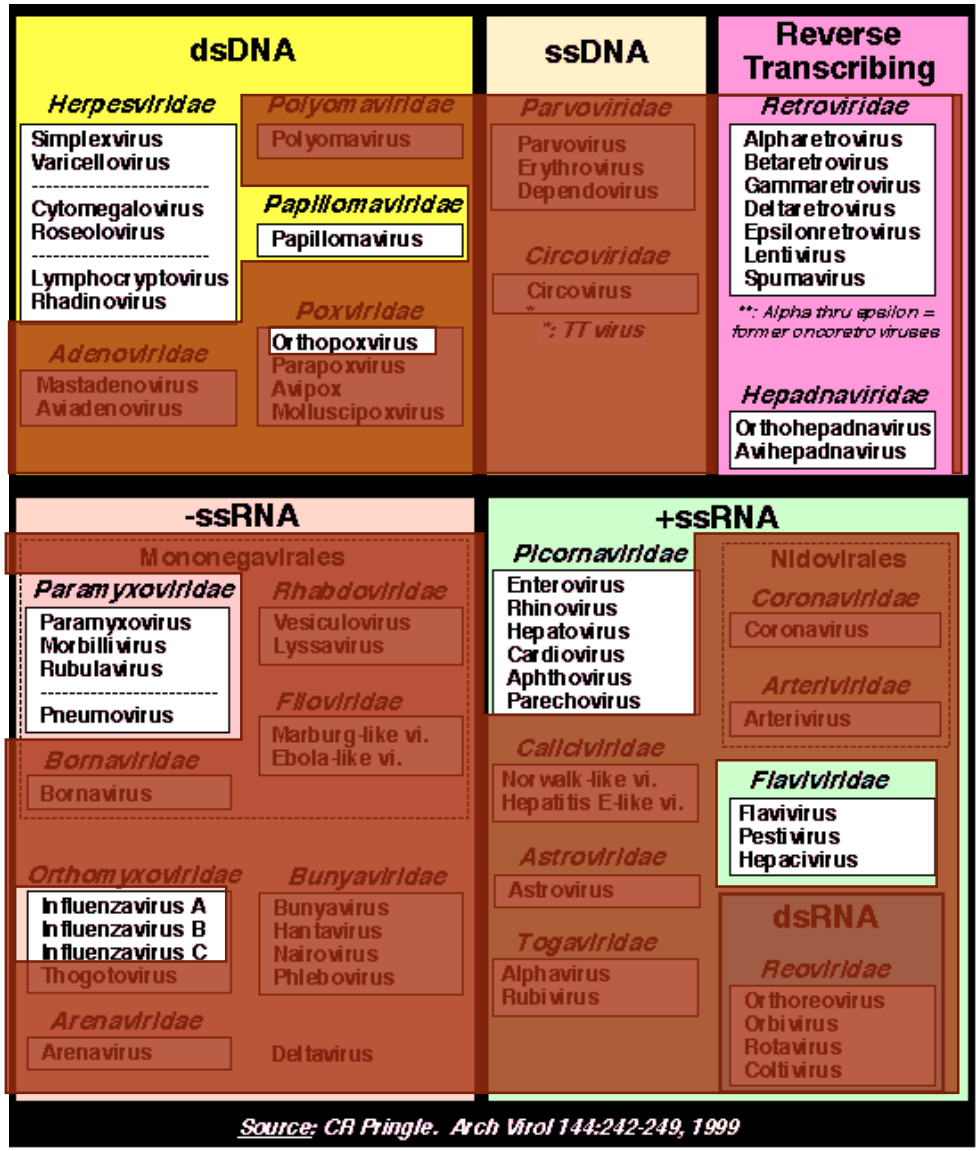
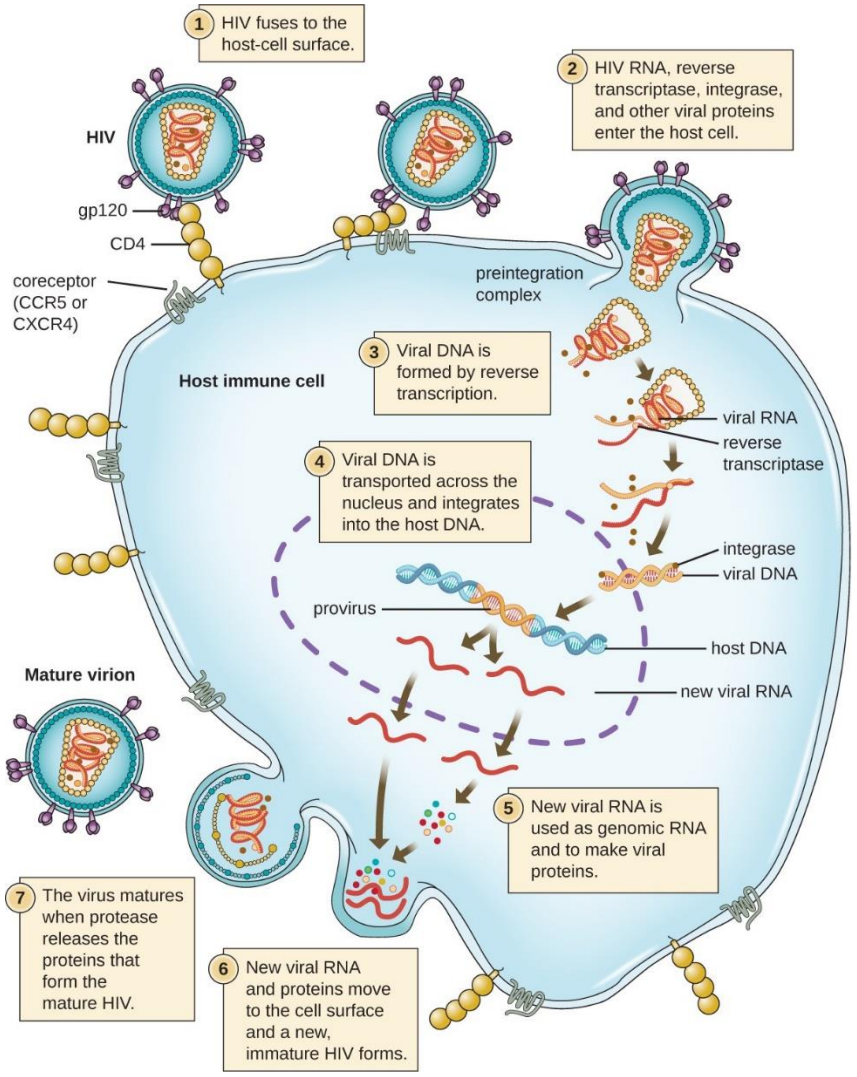
Dec. 13, 2019.

Classification of viruses – treatment modalities

- preventive measures
  - vaccines
  - tonics
  - hygiene
- specific treatment
  - pharmacological
  - natural products
- symptomatic, adjuvant treatment
  - hydration, volume supplementation
  - anti-inflammatories
  - pain management
  - GI: probiotics
  - respiratory support
  - prevention of secondary infection
- management of secondary diseases



Targets of antiviral agents

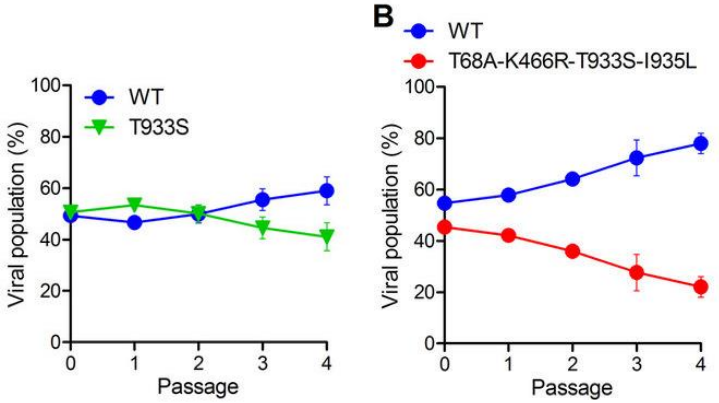


- Entry inhibitors (maraviroc, enfuvirtid)
- Uncoating inhibitor (amantadin)
- DNA/RNA synthesis inhibition
  - Nucleoside/nucleotide analogs
  - Non-competitive inhibitors (NNRTI, foscarnet, HCV)
- Other viral enzyme inhibitors
  - Kinase inhibitor (DNA synthesis, CMV)
  - Terminase inhibitor (DNA maturation, CMV)
  - Protease inhibitors (protein processing, HIV, HCV)
  - Integrase inhibitors (HIV)
  - Neuraminidase inhibitors (release, Influenza)
- Immunological agents
  - Interferon α
  - Imiquimod
  - Palivizumab

https://opentextbc.ca/microbiologyopenstax/chapter/the-viral-life-cycle/

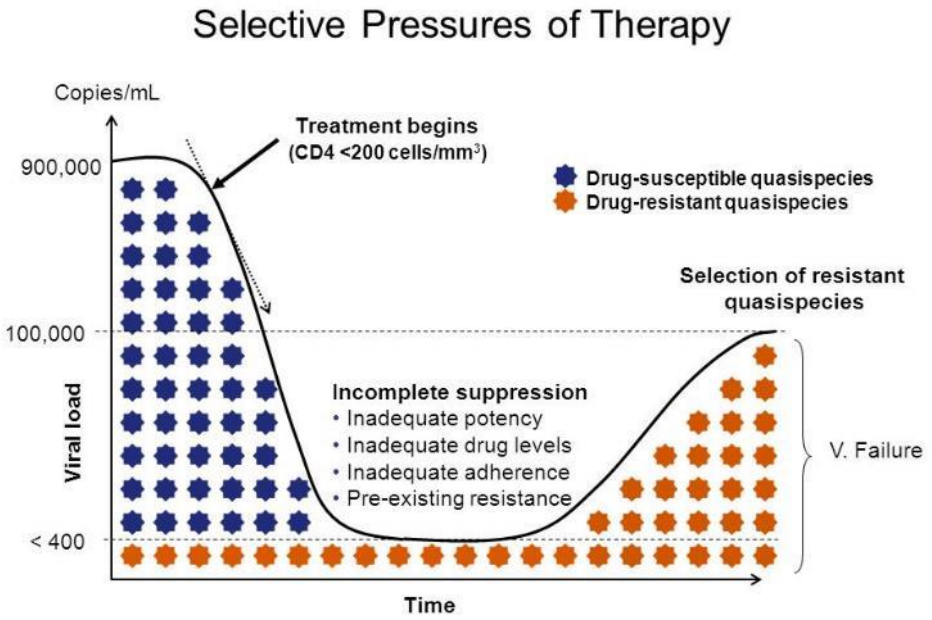
Resistance to antiviral agents

- Mutations are frequent
- „Viral fitness”
  - Most mutant viruses can replicate slower then wild type
  - The agent can select the mutant
  - Another mutation can restore fitness



DOI: 10.1128/JVI.02082-16

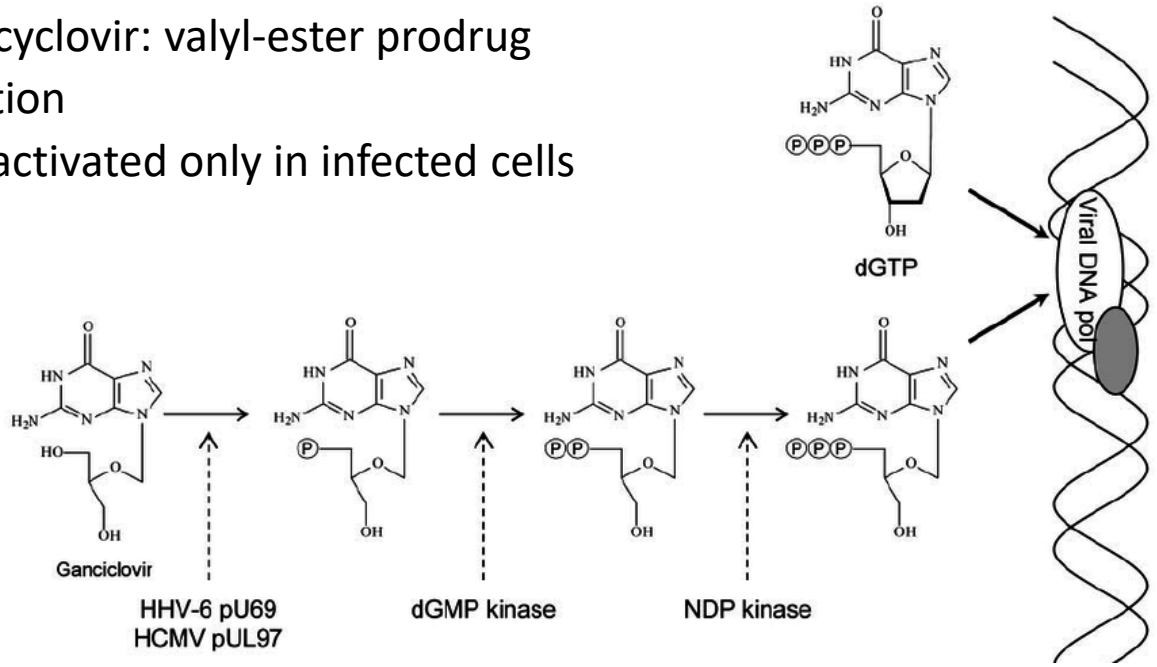
- „Antiviral Potency”
  - Low potency agent: minimal pressure, no resistance
  - High potency agent: blocks multiplication, no mutations, resistance
  - Modest potency: problematic



- „Genetic barrier”: how many mutations needed for resistance

Agents against herpes viruses I.
Herpes simplex 1, 2, Varicella zoster viruses

- Aciclovir (iv., po., local), Valaciclovir (po.)
  - Guanosine analogs, valacyclovir: valyl-ester prodrug
  - Need triple-phosphorylation
  - Viral thymidine kinase – activated only in infected cells



Clinical Microbiology Reviews 18(1):217-45

- Penciclovir (local), Famciclovir (po.)
  - Penciclovir: ACV analogue, but does not cause DNA termination
  - Famciclovir: diacethyl-prodrug of penciclovir

Agents against herpes viruses - guanosine analogs II

- Indications:
  - HSV and VZV infection in immunosuppressed patient,
  - herpes encephalitis, neonatal herpes (iv.),
  - genital herpes,
  - disseminated and ophtalmic zoster,
  - prophylaxis during immune suppression: val(ACV)

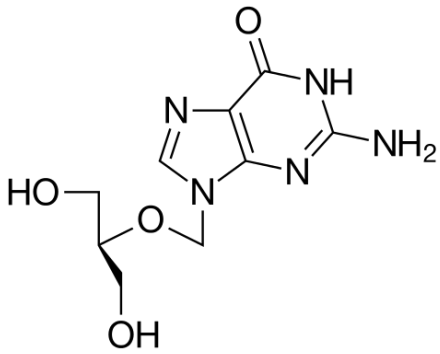
- ACV does not eradicate latent viral colonization
- Kinetics:
  - Penetrates into secretum, CNS
  - Eliminated via urine (filtration and secretion)
  - $T_{1/2}$ 2,5-3h
- Adverse effects:
  - well-tolerated
  - hydration important to prevent crystalluria

Agents against herpes viruses - guanosine analogs III, miscellaneous

- Aciclovir resistance:
  - viral TK or DNA polymerase mutations
  - 1% prevalence in normal state,
  - 3.5-10% in immunocompromised patients
- Latent, mutated viruses can be present in sensory ganglia
  - Mostly total cross-resistance with penciclovir
  - Can also be resistant to foscarnet
  - No known cross-resistance with cidofovir

- Docosanol
  - 22 carbon atom alcohol derivative
  - Inhibits the membrane penetration of HSV
  - 10% cream for labial herpes

Agents against herpes viruses IV. - CMV

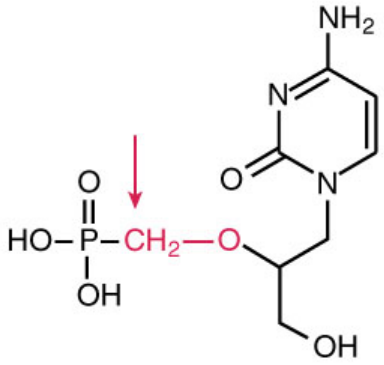


- Ganciclovir (iv.), Valganciclovir (po.)
  - deoxy-guanosine analogs
  - not as specific as ACV, broader spectrum
  - Indications
    - CMV retinitis, CMV pneumonia, oesophagitis, colitis in immunocompromised patients
  - higher toxicity than ACV
  - Same resistance methods as ACV
    - prevalence: 5-12% after transplantation, HIV patients up to 20%
  - Adverse effects: neutropenia, teratogenic.
  - Kinetics
    - Ganciclovir: poorly absorbed (3-7%)
    - Valganciclovir: absorbed well (60-70%) from GI
    - Good penetration in tissues and CNS
    - Renal elimination

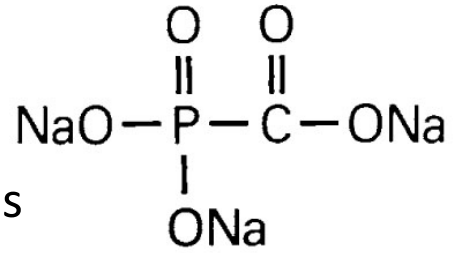
- Passive immunization
  - Hyperimmune globulin (HIG) products: prophylaxis in pregnancy

Agents against herpes viruses V. - CMV

- Cidofovir
  - dCMP analogue
  - broad spectrum:
    - herpes viruses,
    - adeno-, polioma-, pox- and papilloma viruses
    - effective on ACV and GCV resistants
  - Indications:
    - CMV retinitis of HIV patients,
    - resistant HSV or CMV infections
  - Kinetics:
    - iv.
    - does not penetrate CNS well
    - excreted in urine
  - Adverse effects: nephrotoxic, neutropenia, teratogenic

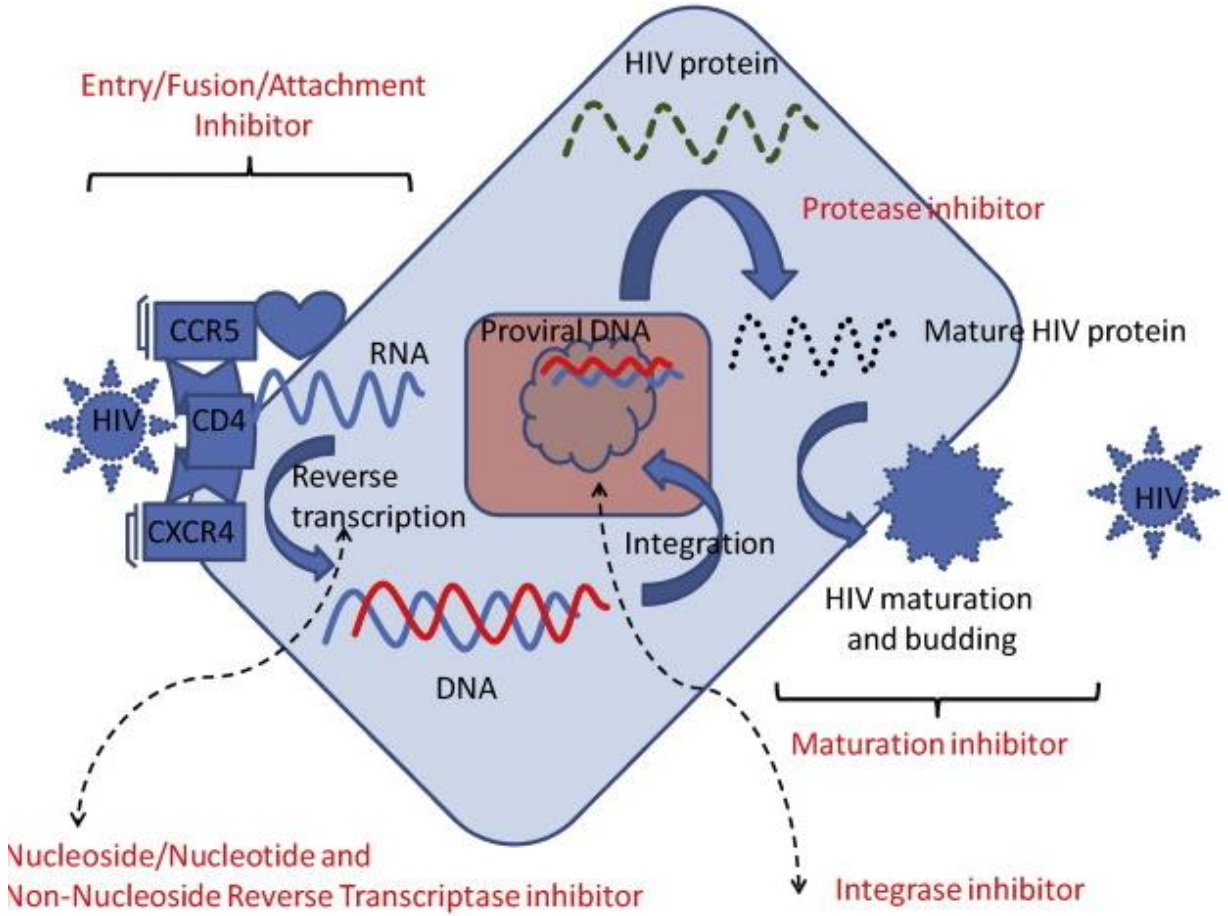


Agents against herpes viruses VI. - CMV



- Foscarnet
  - Pyrophosphate analogue
  - non-competitive inhibitor of DNA polymerase enzymes
  - Indications:
    - CMV Retinitis
    - Mucocutaneous Acyclovir Resistant HSV Infections
  - Active against human herpes viruses (HBV, HIV)
  - Synergistic with ganciclovir
  - Kinetics:
    - iv.
    - CNS penetration,
    - accumulates in bone,
    - excreted in urine
  - Adverse effects: nephrotoxicity, bone alterations

Antiretroviral agents I.

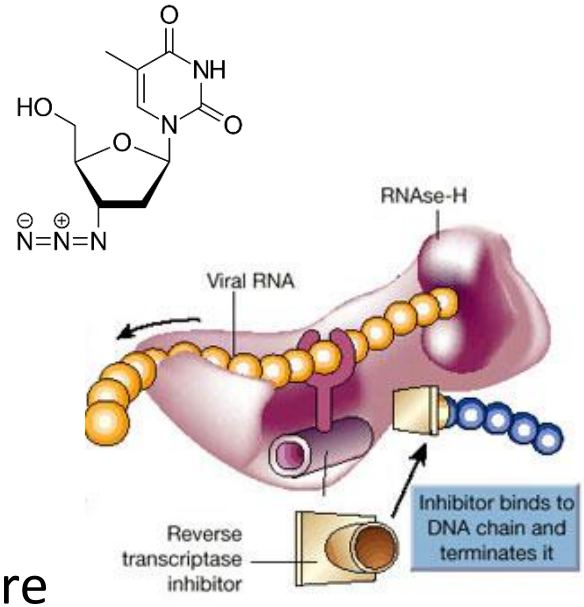


S. Bhattacharya, H. Osman: Novel targets for anti-retroviral therapy; J. of Infection (2009)59, 377-386

Antiretroviral agents -NRTIs

- Nucleoside / nucleotide RT inhibitors: NRTI
  - Thymidine analogues: zidovudine
  - Cytidine analogues : lamivudine, emtricitabine
  - Purine analogues: abacavir, tenofovir, didanosine

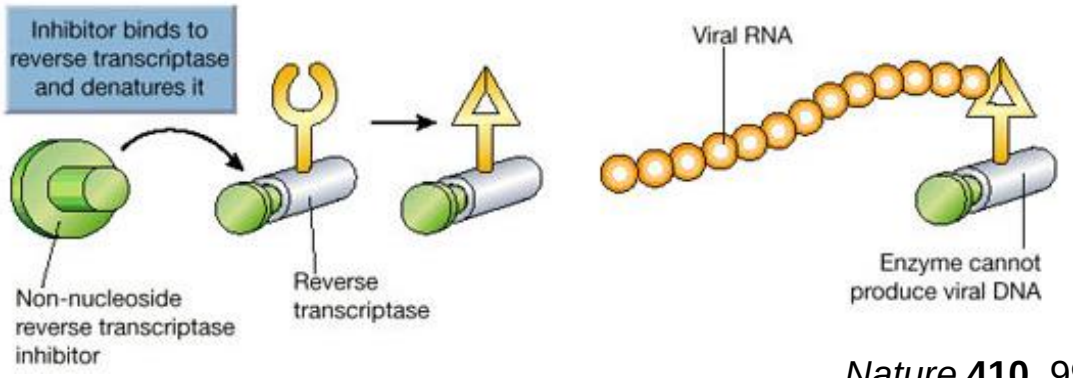
  - HIV-1 and HIV-2
  - Lamivudine, emtricitabine and tenofovir: for HBV as well
  - High genetic barrier: for complete resistance more mutations are needed
  - no cross-resistance
  - different kinetics
  - side effects:
    - All: GI problems, lactacidosis, hepatitis (mitochondrial toxicity)
    - Some: pancreatitis, neuropathy



Nature **410**, 995-1001

Antiretroviral agents - NNRTIs

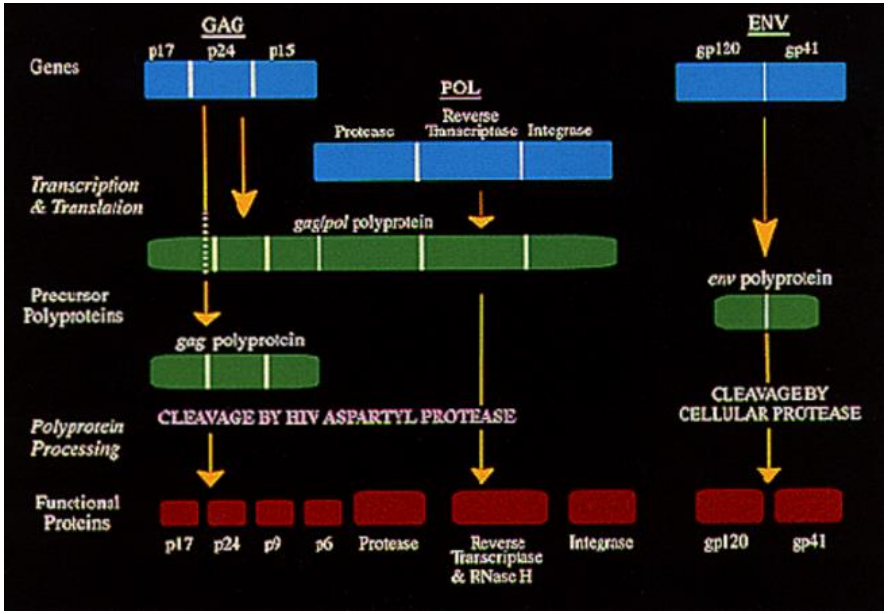
- Non nucleoside RT inhibitors: Nevirapine, Efavirenz, 2nd gen: Etravirine, Rilpivirine
  - HIV-1 only
  - g1: A single point-mutation causes total cross-resistance
  - g2: higher potency, longer half-life, less side effects
  - metabolized in the liver, nevirapin penetrates well in the CNS
  - General adverse effects:
    - liver and GI disorders
    - skin reactions, even Stevens-Johnson syndrome



Nature **410**, 995-1001

Antiretroviral agents Protease inhibitors

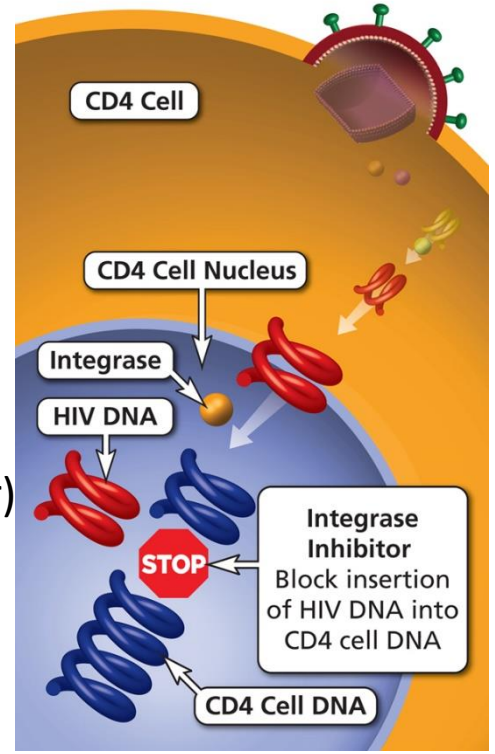
- Ritonavir, Lopinavir, Fosamprenavir, Atazanavir, Darunavir, Tipranavir, Asunavir, etc.
  - HIV protease: viral maturation
  - Adverse effects:
    - insulin-resistance (5%)
    - hyperlipidemia
    - peripheral lipodystrophy
    - transaminase elevation
    - GI and neurological disorders
    - allergic reactions
  - No general cross-resistance between PI-s
  - Kinetics:
    - various oral availability
    - no CNS penetration
    - metabolized in liver CYP3A4 (exception nelfinavir is primary CYP2C19 to also active metabolite).
    - Ritonavir blocks CYP3A4 (induces CYP1A2) and P-glycoprotein: increased oral availability, elevated plasma levels of other PIs: "booster"
    - Half-life: variable



June 1996 *HIV Newsline*

Antiretroviral agents – integrase inhibitors

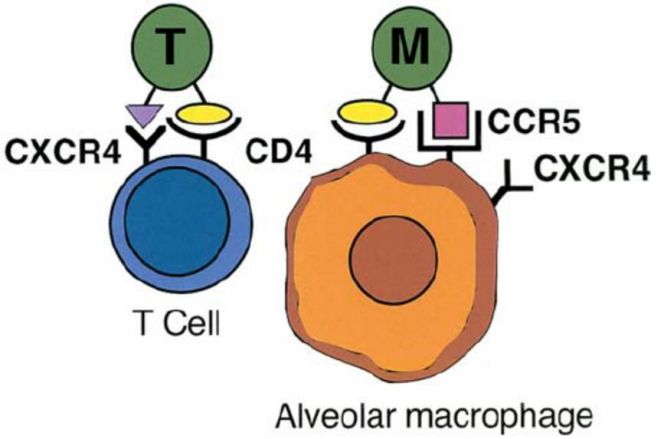
- Raltegravir
  - Inhibits integration of vDNA into human DNA.
  - PO
  - well tolerated
  - Resistance develops relatively fast
- Elvitegravir
  - PO QD with „booster” cobicistat (CYP3A inhibitor: ritonavir)
  - Cross-resistance with raltegravir
- Dolutegravir
  - Low cross-resistance, higher genetic barrier
  - Side effect: Severe hypersensitivity reactions



aidsinfo.nih.gov

Antiretroviral agents - entry inhibitors

- Enfuvirtid
  - Binds to Gp41 of HIV
  - Polypeptide (36AA) structure, sc
  - well tolerated
- Maraviroc
  - CCR5 coreceptor antagonist
  - CCR5 coreceptor:
    - mainly macrophage-infecting viruses
    - mainly present in earlier stage of the disease
  - only after tropism testing of HIV
  - Entry inhibitor
  - Adverse effects: allergic liver disorder, increased prevalence of malignancies
  - PO, metabolized in liver (CYP3A4 – interactions)



The American review of respiratory disease
142(3):516-22

Treatment strategies for HIV infection

- cART: combined AntiRetroviral Therapy
  - Emtricitabine/tenofovir
  - With different mechanisms, e.g., Lamivudine (thymidine NRTI), abacavir (purine NRTI), dolutegravir (integrase inhibitor) with sofosbuvir (NS5B inhibitor), velpatasvir (NS5A inhibitor), voxilaprevir (NS3/4A protease inhibitor)
  - ritonavir or cobicistat as a booster
  - HAART: Highly Active Antiretroviral Therapy
- long-term treatment, controlling viral load

- vaccine is under development: phase 3 trials completed

Treatment of viral hepatitis I.

- HAV: no specific treatment, vaccination
- HBV infection: INFα derivative or a nucleoside/nucleotide derivative
  - Goals:
    - total suppression of virus replication
    - normalizing enzyme levels and tissue presentation.
    - Total eradication is not yet possible
- HCV: INFα derivative + ribavirin. More combination therapies: genotypes.
  - Aviremia often achieved

- Interferon α (INFα2a, INFα2b) - recombinant
  - Complex antiviral activity (induces more than 20 antiviral proteins)
  - SC; PEGylation: once a week administration possible
  - Adverse effects: Flue-like symptoms (fever, fatigue myalgia etc.), suppression of the heamatopoesis, etc.
  - HBV: faster and longer effect than of nucleoside analogues, but less tolerated

Treatment of viral hepatitis II. HBV

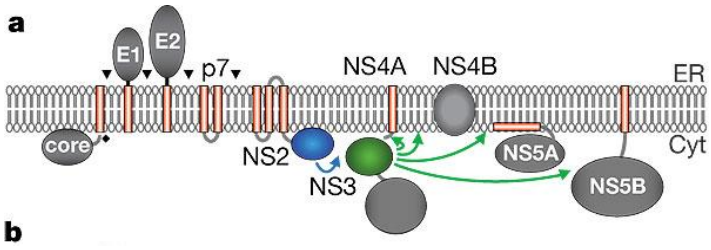
- Nucleoside / nucleotide analogues for Hepatitis B
  - Lamivudine, Emtricitabine
  - Entecavir
    - Guanosine analogue. Well tolerated
    - almost no primary resistance
  - Telbivudine
    - Thymidine analogue. Well tolerated, no cross-resistance with cytidine analogues
    - fast primer resistance development.
  - Adefovir (dipivoxil)
    - AMP analogue. Can be nephrotoxic, no cross-resistance,
    - more primary resistance

Treatment of viral hepatitis III. - HCV

- Ribavirin
  - Guanosine analogue
  - Broad spectrum – HCV and RSV. (Lassa, Hanta, Krim-Kongo fever)
  - PO, IV. For RSV: aerosol.
  - Adverse effects:
    - anemia, bone marrow suppression
    - possibly carcinogenic and teratogenic
  - HCV: 12 to 48 week PO.

Treatment of viral hepatitis IV. HCV

- NS3(/4A) Protease inhibitors:
  Simeprevir, Boceprevir, Paritaprevir, Glecaprevir
  - PO, metabolized by CYP3A, 2C8
  - Adverse effects:
    - Anemia (Boceprevir)
    - Skin reaction (can be severe: Telaprevir)
    - Photosensitivity (Simeprevir)
  - Resistance develops in short time

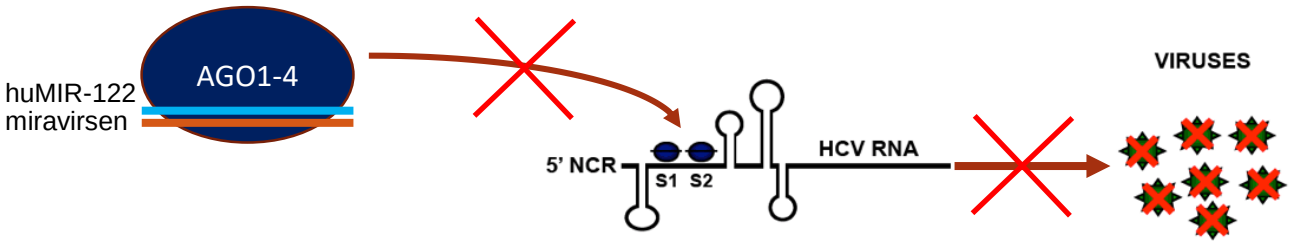


Nature **442**, 831-835

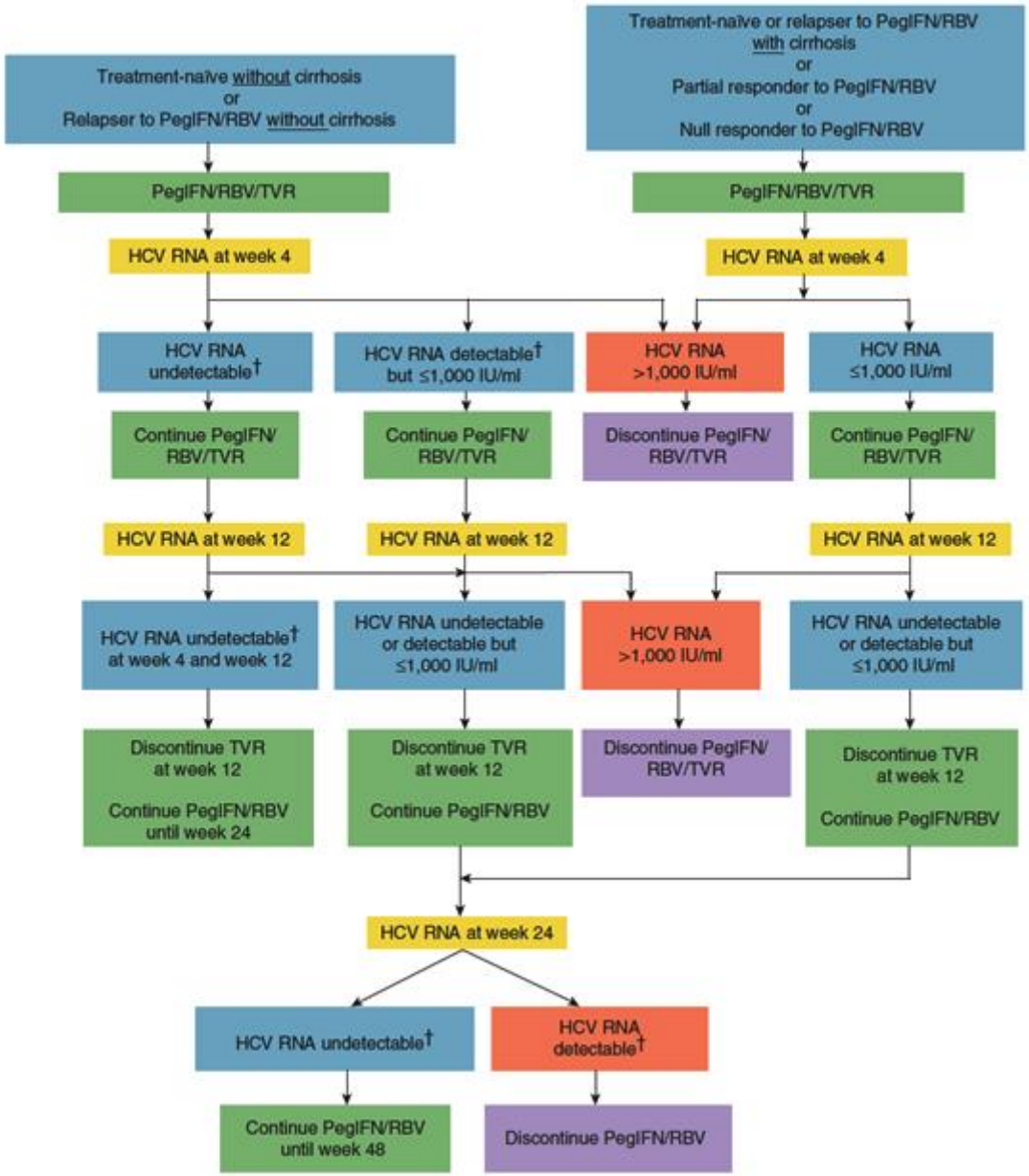
- NS5a inhibitors: Elbasvir, Daclatasvir, Velpatasvir, Pibrentasvir
  - most effective treatment of HCV: sofosbuvir + velpatasvir
- NS5B polymerase inhibitor Sofosbuvir
  - TMP analogue, causes chain termination
  - No resistance
  - Low toxicity
- Non-nucleoside NS5B polymearase inhibitor Dasabuvir
  - used as a part of a combination for Type1 HCV with Paritaprevir (+ ritonavir)

Treatment of viral hepatitis – a novel therapeutic approach

- microRNA-122 inhibitor Miravirsen
  - locked-nucleic acid microRNA analogue
  - INF-resistant HCV, Phase 2 clinical studies finished
  - in combination with telaprevir, interferon α
  - microRNA targeting: miRNAs have a broad spectrum of targets: unwanted effects?



62th Annual Meeting of the American Association for the Study of Liver Diseases San Francisco 2011 Nov 6-9



http://www.hepatitis.va.gov/provider/guidelines/2012HCV-figure2-algorithm.asp

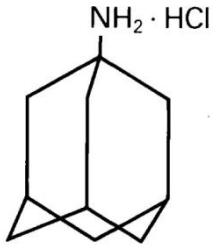
European Association for the Study of the Liver: Recommendations on Treatment of Hepatitis C 2018: interactions

Table 4A. Drug-drug interactions between HCV DAAs and antiretroviral drugs.

		SOF	SOF/ LDV	SOF/ VEL	OBV/ PTV/r + DSV	GZR/ EBR	SOF/ VEL/ VOX	GLE/ PIB
NRTIs	Abacavir	◆	◆	◆	◆	◆	◆	◆
	Emtricitabine	◆	◆	◆	◆	◆	◆	◆
	Lamivudine	◆	◆	◆	◆	◆	◆	◆
	Tenofovir disoproxil fumarate	◆	■	■	◆	◆	■	◆
	Tenofovir alafenamide	◆	◆	◆	■	◆	■	◆
NNRTIs	Efavirenz	◆	■*	●	●	●	●	●
	Etravirine	◆	◆	●	●	●	●	●
	Nevirapine	◆	◆	●	●	●	●	●
	Rilpivirine	◆	◆	◆	■	◆	◆	◆
Protease inhibitors	Atazanavir/ritonavir	◆	◆*	◆*	■	●	●	●
	Atazanavir/cobicistat	◆	◆*	◆*	●	●	●	●
	Darunavir/ritonavir	◆	◆*	◆*	■	●	■*	●
	Darunavir/cobicistat	◆	◆*	◆*	●	●	◆*	●
	Lopinavir/ritonavir	◆	◆*	◆*	●	●	●	●
Entry/Integrase inhibitors	Dolutegravir	◆	◆	◆	◆	◆	◆	◆
	Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate	◆	■*	■*	●	●	■*	◆
	Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide	◆	◆	◆	●	●	◆	◆
	Maraviroc	◆	◆	◆	■	◆	◆	◆
	Raltegravir	◆	◆	◆	◆	◆	◆	◆

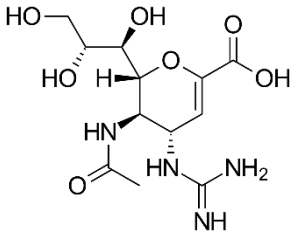
doi: 10.1016/j.jhep.**2018**.03.026.

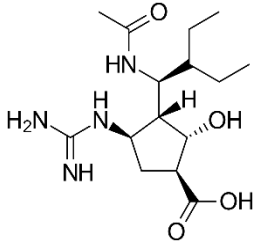
Agents for influensa



- Adamantins – Amantadin, Rimantadin
  - block uncoating by inhibiting M2 proton pumps
  - prevention, early treatment
  - only against influenza A – resistance possible.
  - side effects: nightmare, seizure, palpitation, dizziness
  - kidney, liver function checks, not with CNS treatments

- Neuraminidase inhibitors – Oseltamivir, Zanamivir, Peramivir, Lanimamivir
  - neuraminidase: release of virion from the cell
  - mainly effective in first days of the infection
  - Influensa A and B

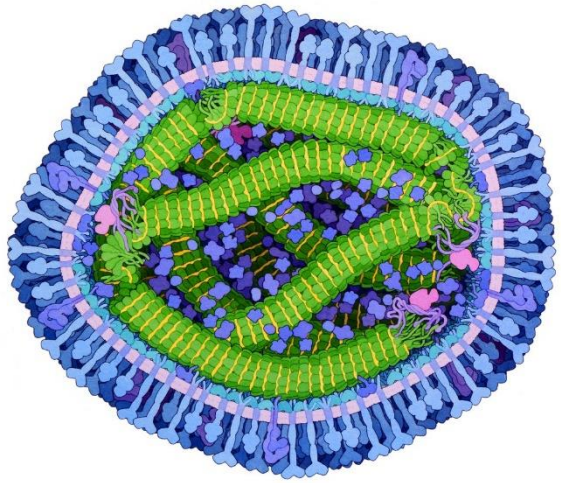




Antiviral agents with miscellaneous mode of action

- Imiquimod
  - Possibly induces INFα, TNFα production
  - local injection
  - for condyloma accuminatum (HPV) and for basal cell cc. Sometimes for acyclovir-resistant genital HSV.
- Palivizumab
  - Monoclonal antibody against RSV
  - im. monthly
  - for immuncompromised children in the RSV season, prevention.

Measles



https://en.wikipedia.org/wiki/Measles_morbillivirus#/media/File:231-Measles-virus-proteins.tif

- Morbilli virus
  - Paramyxoviridae
  - single stranded -RNA virus
- Vaccination
  - anti-vaxxers: endanger herd immunity
    - morbidity increases
- No antiviral therapy available
- Symptomatic treatment: hydration, pain management, vitamin A

Registration procedures for antiviral agents, how to get valid info

- EMA: centralized procedure
  - valid for all EU countries, same evaluation accepted by all parties
  - centralized post-marketing regualtions
  - marketing authorization holder: vendor decides on launch in given countries

- Sources of valid information on products
  - EMA: https://www.ema.europa.eu/en/medicines/field_ema_web_categories%253Aname_field/Human
  - National authorities: https://www.ema.europa.eu/en/medicines/national-registers-authorised-medicines
    - https://ogyei.gov.hu/gyogyszeradatbazis/
    - http://www.mhra.gov.uk/spc-pil/
    - https://www.pharmnet-bund.de/dynamic/de/arzneimittel-informationssystem/index.html
    - https://laegemiddelstyrelsen.dk/en/sideeffects/find-medicines/summaries-of-product-characteristics/#
  - NGO, independent sources, e.g.,
    - https://www.medicines.org.uk/emc
    - https://www.pharmindex-online.hu/
  - Recommendations
    - EMA: Guideline on the clinical evaluation of medicinal products indicated for the prophylaxis or treatment of respiratory syncytial virus (RSV) disease: from 2019
    - Medical associations, etc: European Association for the Study of the Liver: Recommendations on Treatment of Hepatitis C 2018

Novel antiviral agents approved between Dec 2017 and Dec 2019

Name	Components, mechanism of action	indication
EMA (and FDA)		
Maviret	glecaprevir (NS3/4A protease inhibitor) and pibrentasvir (NS5A inhibitor)	Treatment of chronic hepatitis C virus (HCV) infection in adults
letermovir (orphan drug)	CMV DNA terminase complex inhibitor	CMV prophylaxis in adult CMV-seropositive recipients
peramivir	neuraminidase inhibitor	Treatment of acute uncomplicated influenza in people 2 years of age
Vosevi	sofosbuvir (NS5B inhibitor), velpatasvir (NS5A inhibitor), voxilaprevir (NS3/4A protease inhibitor)	Treatment of chronic HCV infection in adults
doravirine	NNRTI	Treatment of adults infected with HIV-1
Delstrigo	doravirine (NNRTI), lamivudine (nucleoside analogue), tenofovir disoproxil (adenosine analogue)	Treatment of adults infected with HIV-1
Biktarvy	bictegravir (integrase strand transfer inhibitor), emtricitabine (NRTI), tenofovir alafenamide (NtRTI)	Treatment of adults infected with HIV-1
only FDA		
tecovirimat	orthopoxvirus-specific p37 envelope protein inhibitor	Treatment of smallpox
ibalizumab-uiyk	inhibitor of CD4-directed post-attachment of HIV-1	Treatment of multidrug resistant HIV-1 infection
baloxavir marboxil	polymerase acidic endonuclease inhibitor	Treatment of influenza in people over 12 years of age