Antiviral chemotherapy and prophylaxis

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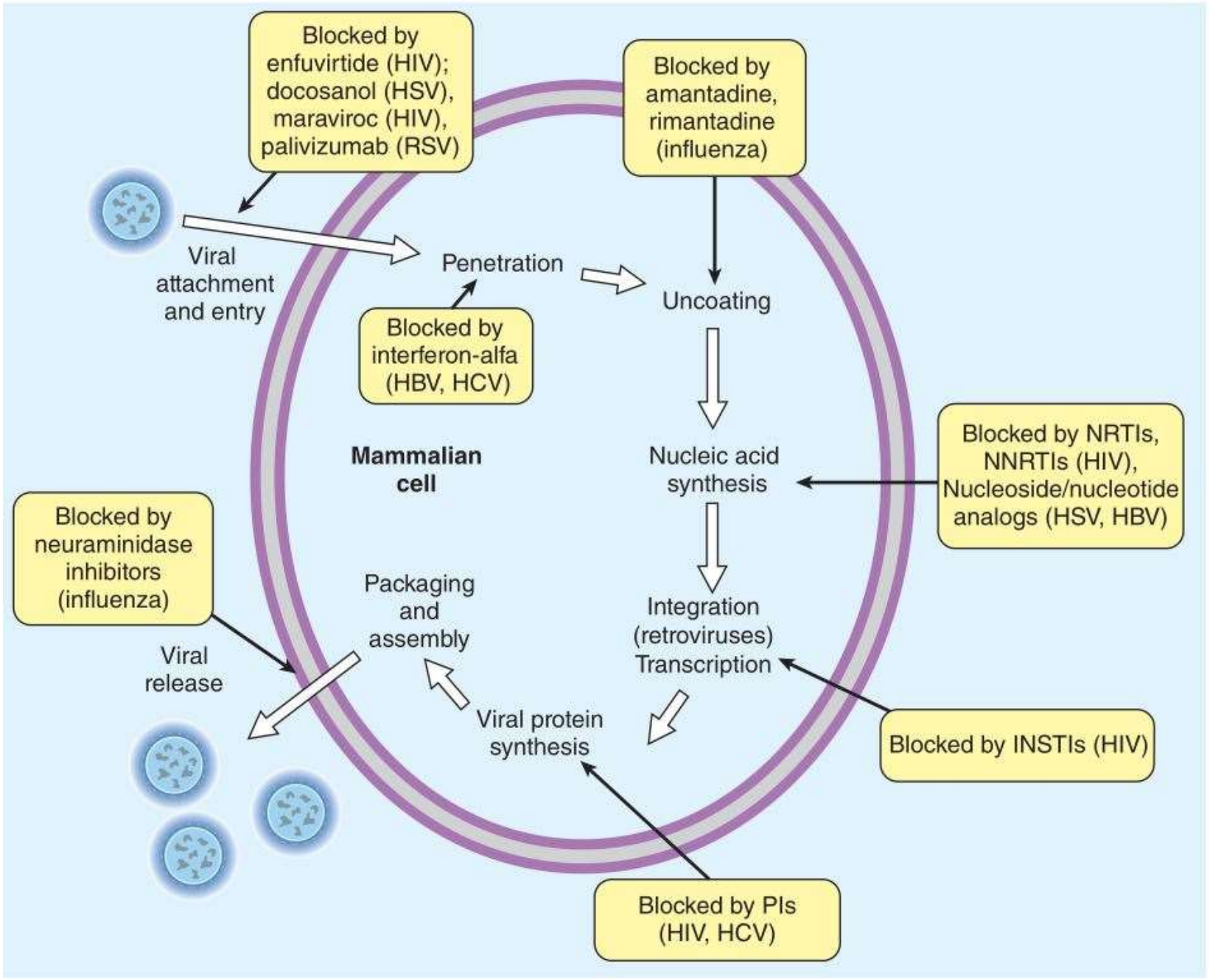
Antiviral chemotherapy: general characteristics

- obligate intracellular parasites
  - few selective targets → toxicity
- clinical symptoms appear late
- antimetabolites / more specific targets
  - virustatic
- one or more drugs
  - monotherapy – e.g. HSV (short term)
  - combination drug therapy – e.g. HIV (indefinite)
- drugs → against only a few virus groups
  - vaccines are important but not discussed

Antiviral agents are available against

- Influenza
- Hepatitis B & C
- HSV and VZV
- CMV
- ***Antiretroviral (HIV)***
- Other (e.g. RSV, Lassa)


Blocked by enfuvirtide (HIV); docosanol (HSV), maraviroc (HIV), palivizumab (RSV)
Blocked by amantadine, rimantadine (influenza)
Viral attachment and entry
Penetration
Uncoating
Blocked by interferon-alfa (HBV, HCV)
Mammalian cell
Nucleic acid synthesis
Blocked by NRTIs, NNRTIs (HIV), Nucleoside/nucleotide analogs (HSV, HBV)
Blocked by neuraminidase inhibitors (influenza)
Packaging and assembly
Integration (retroviruses) Transcription
Viral release
Viral protein synthesis
Blocked by INSTIs (HIV)
Blocked by PIs (HIV, HCV)

Influenza

- **immunization is preferred** BUT not always possible
  - allergy / new variant / closed community outbreaks
- available drugs
  - neuraminidase inhibitors (A and B)
    - oseltamivir, zanamivir & peramivir
  - viral uncoating inhibitors (adamantanes)
    - amantadine & rimantadine (only A)

recommendation for: severe infection / complications

Mechanism of action of antiinfluenza agents

neuramindase inhibitors

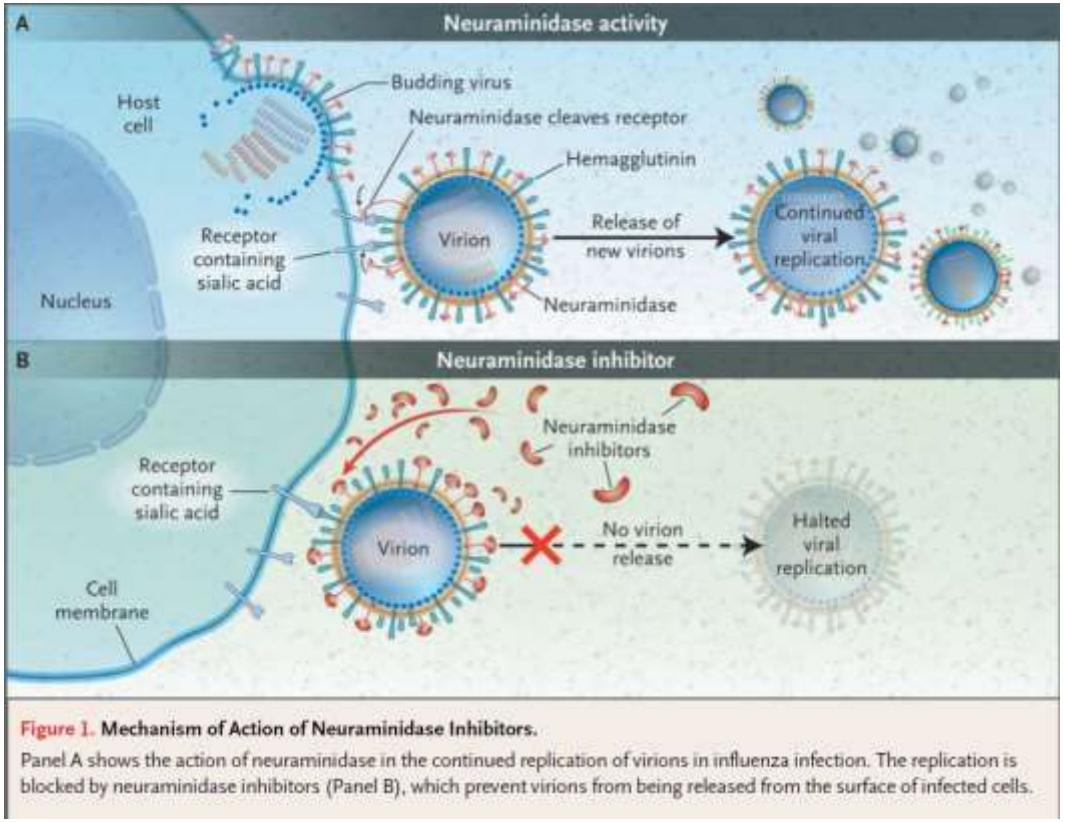


Figure 1. **Mechanism of Action of Neuraminidase Inhibitors.**

Panel A shows the action of neuraminidase in the continued replication of virions in influenza infection. The replication is blocked by neuraminidase inhibitors (Panel B), which prevent virions from being released from the surface of infected cells.

uncoating inhibitors

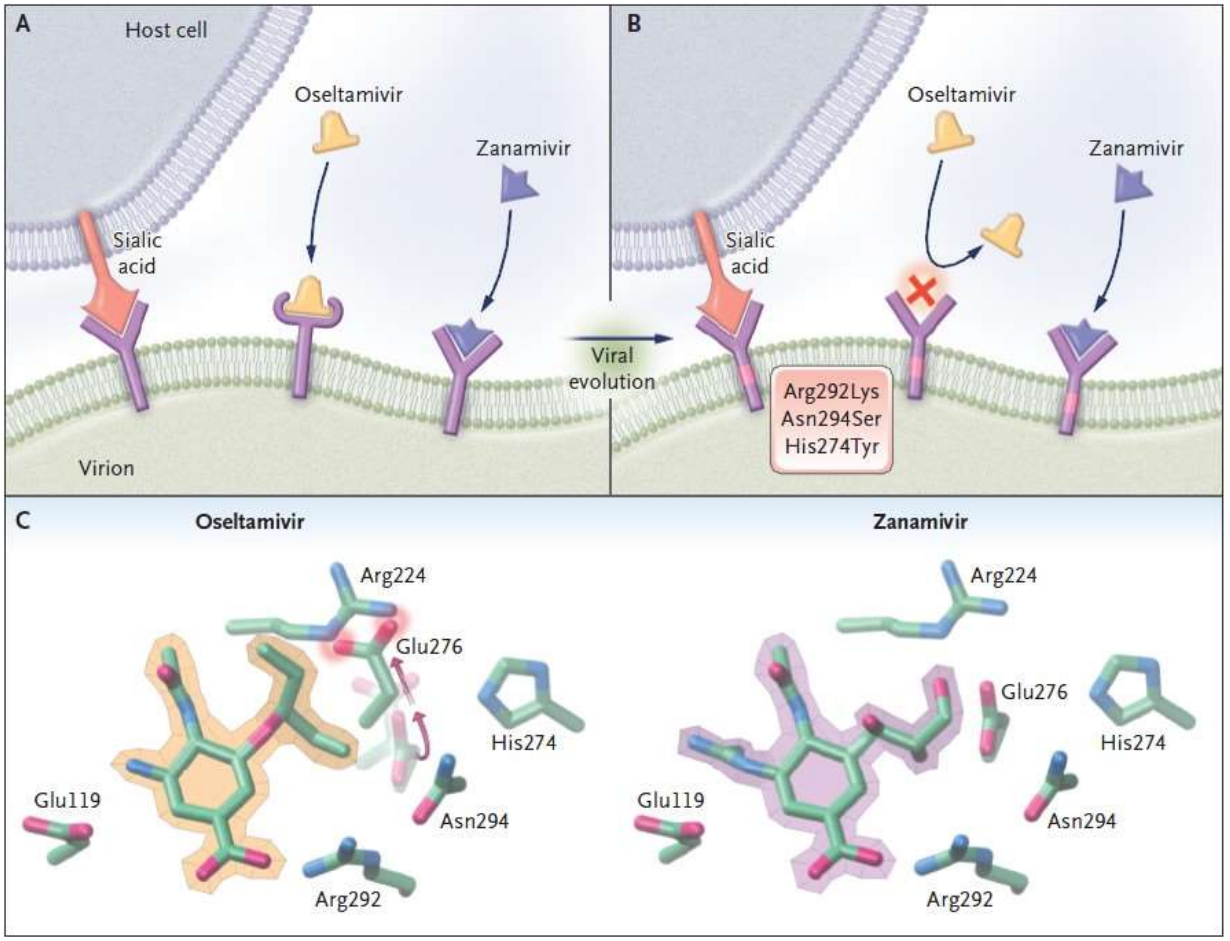
block M2 H^+ ion channel protein

Pharmacological characteristics of antiinfluenza agents

	amantadine	rimantadine	zanamivir	oseltamivir	peramivir
spectrum	A	A	A,B	A,B	A,B
route	oral	oral	inhaled	oral	intravenous
oral bioavail	>90%	>90%	<5%	80%	not applicab
metabolism	<10%	~75%	negligible	negligible	negligible
renal excreti	>90%	~25%	100%	95%	90%
t1/2	12-18	24-36	2.5-5	6-10	20

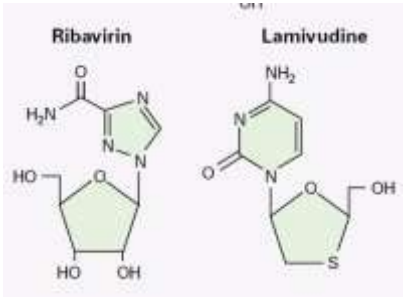
- for prophylaxis or treatment
- start within 48 hours after the onset of symptoms
- no interference with the immune response to influenza vaccine
- resistance
  - neuraminidase mutations → rare but existent / virulence ↓ (?)
  - M2 mutations – rapid / equally pathogenic (recently frequent)
- amantadine – Parkinson's disease – CNS adverse effects

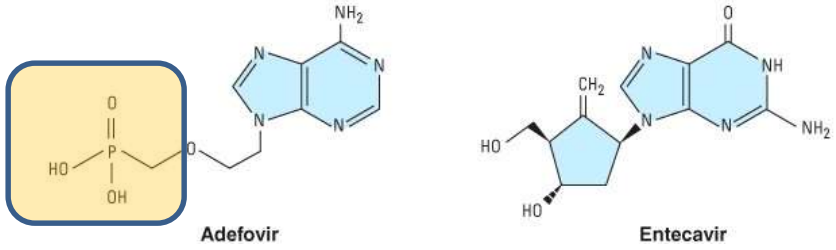
Mechanism of resistance to oseltamivir

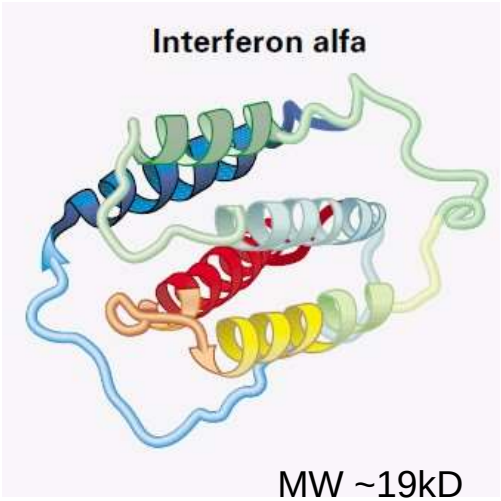


Hepatitis

- **Hepatitis B** – can be integrated into host genom
  - goals: supp. of HBV DNA / seroconversion of HBeAg (HBsAg) / ↓aminotransferases
  - lamivudine / adefovir / **entecavir** / **tenofovir** / telbivudine / (peg)IF-α-2b
- **Hepatitis C** – no integration – goal is eradication (SVR)
  - previous standard: peginterferon-α-2a or b + ribavirin
  - but see DAAs: e.g. 1st gen: boce**previr** / tela**previr** (2011)







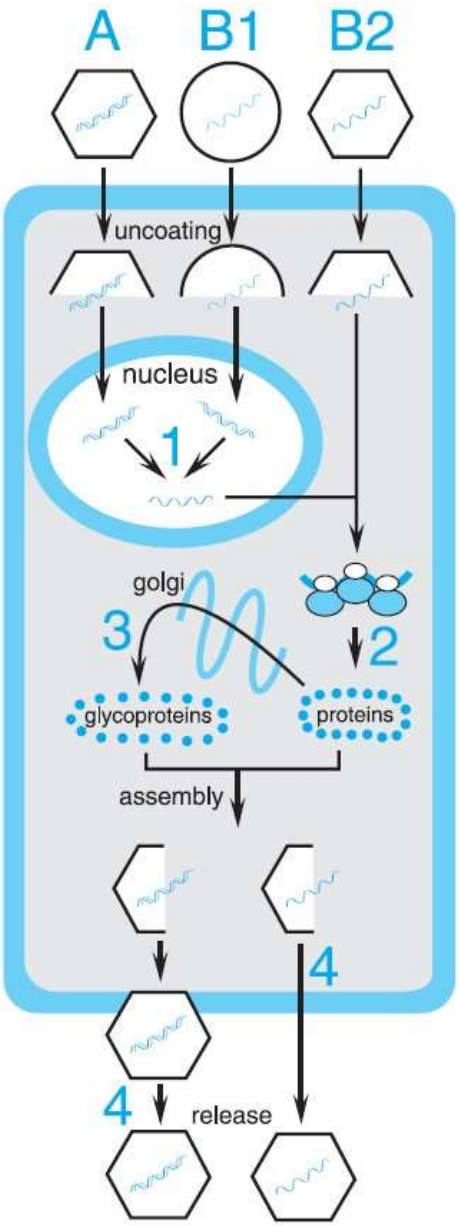
"-fovir"

- **nucleotide** analogs
- nephrotoxicity (least for tenofovir)
  - ade**fovir –** hepatitis B
  - cido**fovir –** CMV
  - teno**fovir –** hepatitis B / HIV

Mechanism of action of anti-hepatitis drugs

- IF-α – polypeptide (biological therapy)
  - **complex** antiviral, immunomodulatory and antiproliferative actions / binds to cell surface receptors → antiviral proteins ↑
- ribavirin – guanosine analog
  - GTP formation ↓ / prevents capping of viral mRNA / blocks RNA-dependent-RNA-polymerase
- lamivudine – cytosin analog
  - inhibits HBV **DNA-polymerase** (and HIV reverse transcriptase)
- adefovir → tenofovir – adenine *nucleotide* analogs
  - competitively inhibits HBV **DNA polymerase** → chain termination after incorporation into the viral DNA
- entecavir – guanosine analog
  - competitively inhibits HBV **DNA polymerase**
- telbivudine – thymidine analog
  - competitively inhibits HBV **DNA polymerase**

IFN → gene transcription → antiviral protein synthesis



Viruses

A. DNA

B. RNA

1. orthomyxoviruses and retroviruses
2. picornaviruses and most RNA viruses

IFN Effects

1. Transcription inhibition

activates Mx protein
blocks mRNA synthesis

2. Translation inhibition

activates methylase, thereby reducing mRNA cap methylation

activates 2'5' oligoadenylate synthetase —> 2'5'A —> inhibits mRNA splicing and activates RNaseL —> cleaves viral RNA

activates protein kinase P1 —> blocks eIF-2α function —> inhibits initiation of mRNA translation

activates phosphodiesterase —> blocks tRNA function

3. Protein processing inhibition

inhibits glycosyltransferase, thereby reducing protein glycosylation

4. Virus maturation inhibition

inhibits glycosyltransferase, thereby reducing glycoprotein maturation

causes membrane changes —> blocks budding

Interferon alpha

- Clinical characteristics
  - chronic HBV
    - INF-α-2b alone or in combination with lamivudine
  - HCV
    - in combination with ribavirin (pegylated form is better)
  - other uses
    - genital warts
    - Kaposi's sarcoma
    - leukemia (CML, hairy cell) / melanoma
- Pharmacokinetics
  - several forms (INF-α-2a, INF-α-2b)
  - pegylated – ↑ half-life and steadier concentrations → less frequent dosing
  - im., sc.

Interferon alpha

- Adverse effects
  - common
    - **flu-like syndrome**
    - gastrointestinal irritation: nausea, vomiting, and diarrhea
  - dose limiting (rare)
    - **bone marrow** suppression: granulocytopenia and thrombocytopenia
    - **neurotoxicity**: somnolence / behavioral disturbances / mental depression
    - profound fatigue / weight loss
    - autoimmune disorders: e.g. thyroiditis
  - very rare
    - cardiovascular problems: congestive heart failure
    - acute hypersensitivity reactions
    - hepatic failure
- Cautions
  - pregnancy ?
  - monitor thyroid / liver

Nucleoside / nucleotide analogs in hepatitis B

- **entecavir**
- adefovir / **tenofovir**
- lamivudine (emtricitabine)
- telbivudine

Entecavir

- Clinical characteristics
  - higher rates of HBV DNA viral suppression
  - plasma HBV DNA level and hepatic inflammation ↓
- Pharmacokinetics
  - oral bioavailability ~ 100% (on empty stomach)
  - renal excretion
- Adverse effects
  - well tolerated - headache, fatigue, dizziness, and nausea
- Resistance
  - no primary resitance
  - lamivudine resitance → decreased susceptibility to entecavir

Adefovir / Tenofovir

- Clinical characteristics
  - HBV replication ↓, improves liver histology and fibrosis but only while the drug is used
  - active against lamivudine resistant strains
  - **tenofovir** tends to provide **↑ rate of complete response**
  - **tenofovir ↓ resistance emergence**
- Pharmacokinetics
  - good oral availability
  - long intracellular half-life → once daily
  - **renal excretion** with glomerular filtration and tubular secretion (dose ↓ in renal insufficiency)
- Adverse effects
  - dose dependent **nephrotoxicity**
  - lactic acidosis and severe hepatomegaly with steatosis – also with other NRTIs

Lamivudine

- Clinical characteristics
  - safe to give to patients with decompensated liver disease
  - plasma HBV DNA level and hepatic inflammation ↓
  - used against HIV too
- Pharmacokinetics
  - good oral absorption
  - mostly renal excretion (70%, dose ↓ in renal insufficiency)
  - **prolonged intracellular half-life in HBV** → lower doses than in HIV
- Adverse effects
  - at the dose level used in HBV – **rare** headache, dizziness
- Resistance
  - quickly emerges after chronic therapy
    - 15–30% at 1 year / 70% at 5 years
  - mutations ⟶ increasing level of HBV DNA
  - cross resistance with emtricitabine and partially with entecavir but not with adefovir / tenofovir

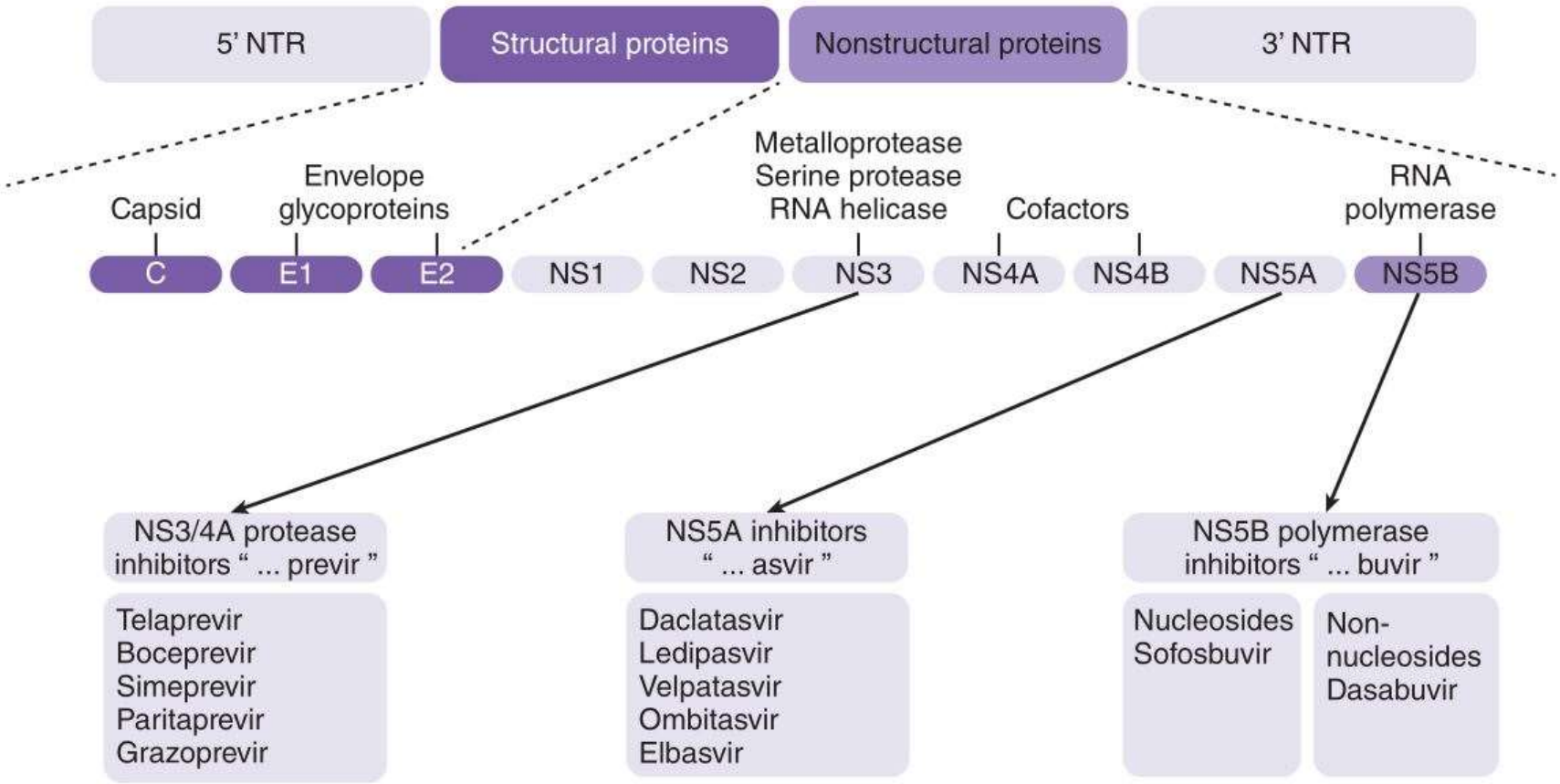
Telbivudine

- Clinical characteristics
  - ↑ efficacy vs. lamivudine
- Pharmacokinetics
  - good oral bioavailability – food independent
  - renal excretion – no CYP interactions
- Adverse effects
  - **mild non-specific**: headache, fatigue
  - **↑ creatine kinase** – myalgia / myopathy
  - lactic acidosis and severe hepatomegaly with steatosis
    - may occur
- Resistance
  - quick development
    - ≈ 20% at 1 year

Ribavirin
(nucleoside analog in hepatitis C)

- Clinical characteristics
  - **with INF-α in HCV**
  - viral hemorrhagic fevers (e.g. Lassa fever)
  - severe RSV infections in *infants and young children* (no benefit?)
- Pharmacokinetics
  - oral, iv., and aerosol
  - poor CNS penetration
  - excretion in the kidney (dose ↓ in renal insufficiency)
- Adverse effects
  - dose dependent hemolytic anemia
  - aerosol – bronchial irritation
  - absolutely **contraindicated in pregnancy**

Direct acting antivirals in hepatitis C



adverse effects, treatment duration, dosing frequency, interactions
combinations, IF free oral protocols

Characteristics of direct acting antivirals

- oral administration
- few side effects
- treatment duration: 8, 12, or 24 weeks
- SVR rates: >90%

NS3/4A protease and NS5B polymerase inhibitors in hepatitis C

- **boceprevir / telaprevir / simeprevir**
  - chronic **HCV genotype 1**
  - resistance → **in combination** only
  - CYP3A4 inhibition and metabolism
  - adverse effects
    - anemia (both)
    - dysgeusia (boceprevir)
    - skin rash (telaprevir)

- **sofosbuvir**
  - active against **genotype 1, 2, 3, or 4**
  - used alone or in combination – e.g. simeprevir, ribavirin
  - not a CYP substrate, inhibitor, or inducer – **low interactions**
  - common AEs: headache and fatigue

HSV & VZV

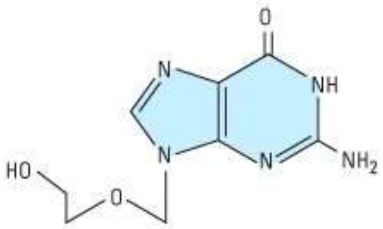
- **Acyclovir** ← Valacyclovir
- *Penciclovir* ← Famciclovir
- *Docosanol*
- *Trifluridine*

italic – topical only

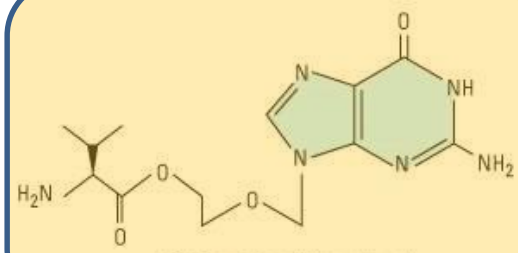
CMV

- **Ganciclovir** ← Valganciclovir
- Foscarnet
- Cidofovir
- Fomivirsen

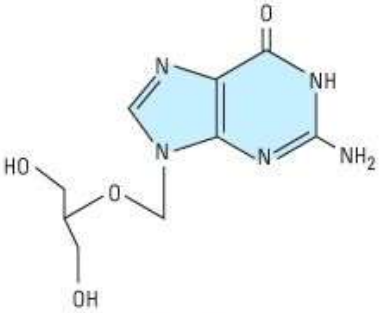
A. Antiherpes agents



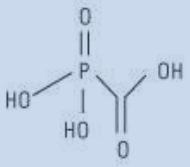
Acyclovir



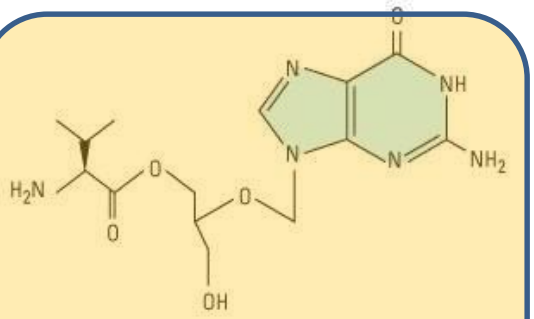
Valacyclovir (prodrug)



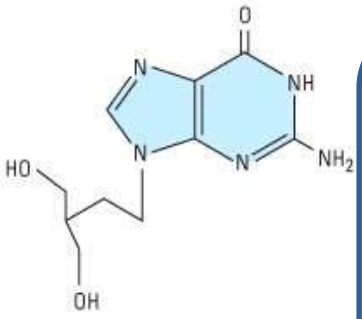
Ganciclovir



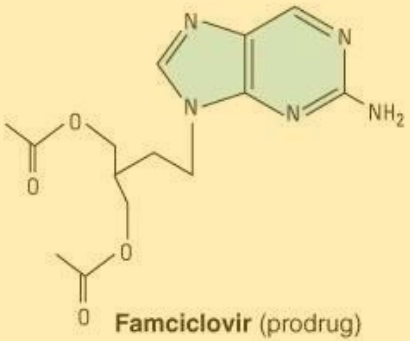
Foscarnet



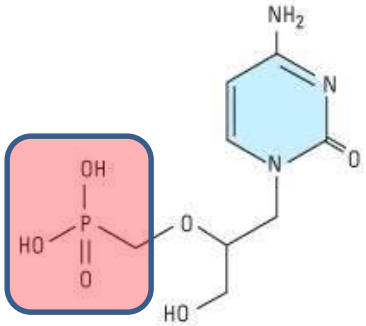
Valganciclovir (prodrug)



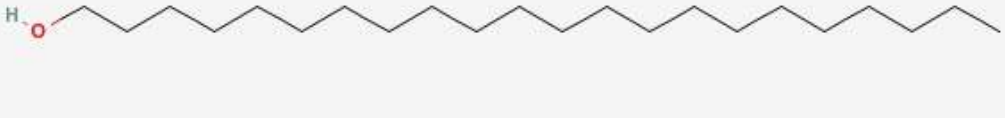
Penciclovir



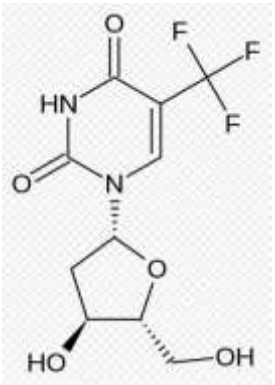
Famciclovir (prodrug)



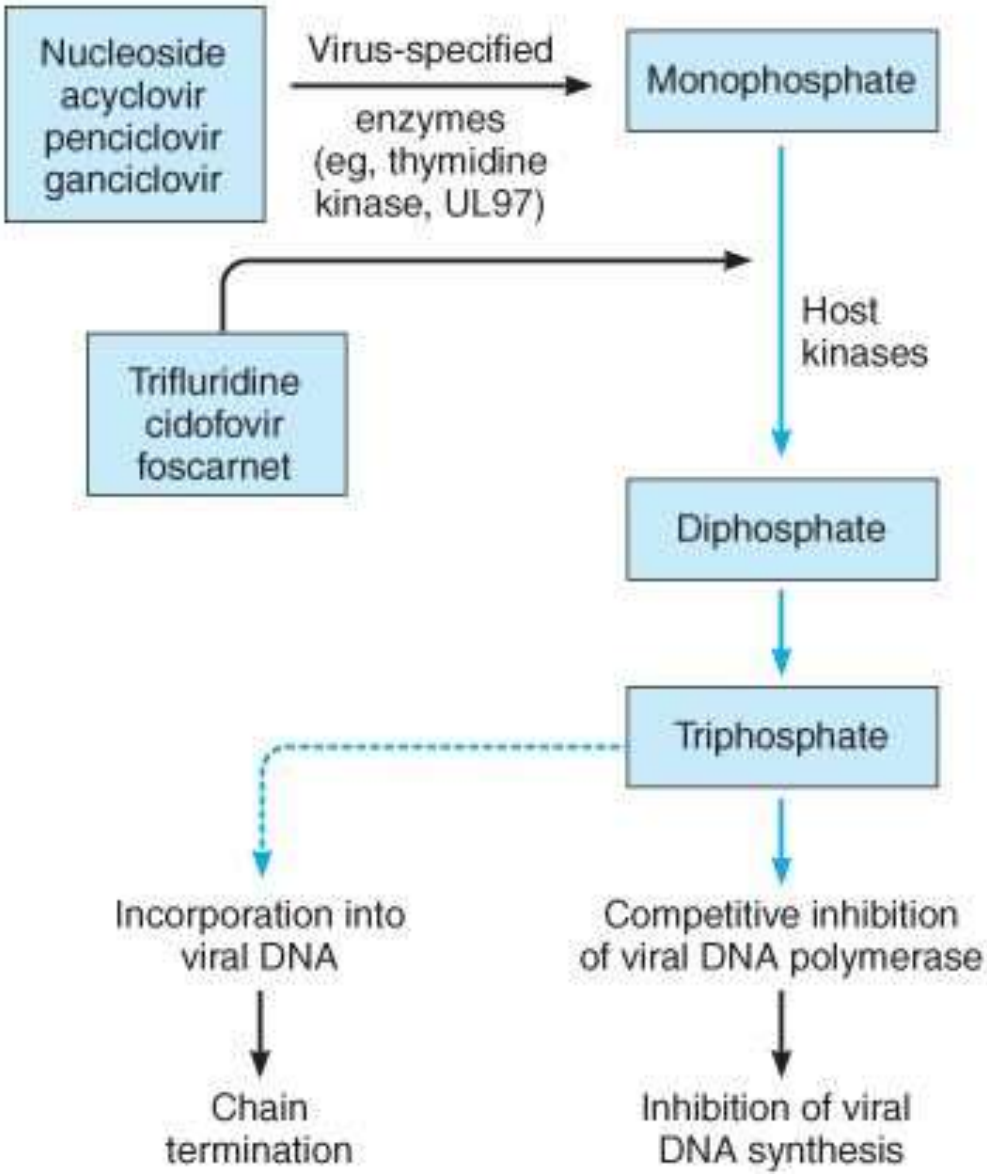
Cidofovir



docosanol



trifluridine


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

HSV, VZV and CMV infections

- effective during **acute phase**
- purine or pyrimidine analogs
  - acyclovir ← valacyclovir, penciclovir ← famciclovir
  - ganciclovir ← valganciclovir, cidofovir
  - **except** foscarnet, docosanol (and fomivirsen)
- inhibition of viral DNA synthesis
  - competition with deoxy-GTP for viral **DNA polymerase** → irreversible complex
  - incorporation into viral DNA → **chain termination**

Routes of administration

- HSV/VZV
  - acyclovir – iv., po., topical
  - valacyclovir, famciclovir – po.
  - penciclovir – topical
- CMV
  - ganciclovir – iv., po., intraocular implant
  - valganciclovir – po.
  - cidofovir, foscarnet – iv.
  - fomivirsen – intravitreal injection

Clinical applications

- genital herpes, zoster
  - po. acyclovir, valacyclovir or famciclovir
- severe HSV infection, herpes encephalitis, neonatal HSV, varicella or zoster in the immunocompromised host
  - iv. acyclovir
- recurrent herpes labialis
  - topical penciclovir
- CMV prophylaxis
  - po. ganciclovir or valganciclovir
- CMV retinitis
  - iv. ganciclovir, cidofovir, foscarnet, po. valganciclovir, intravitreal fomivirsen

Important pharmacokinetic properties

- acyclovir, ganciclovir
  - accumulates in renal failure
- cidofovir
  - prolonged dosage intervals (every 1-2 weeks)
- valacyclovir, valganciclovir, famciclovir
  - prodrugs
- fomivirsen
  - slowly cleared from vitreous body (2-4 weeks)

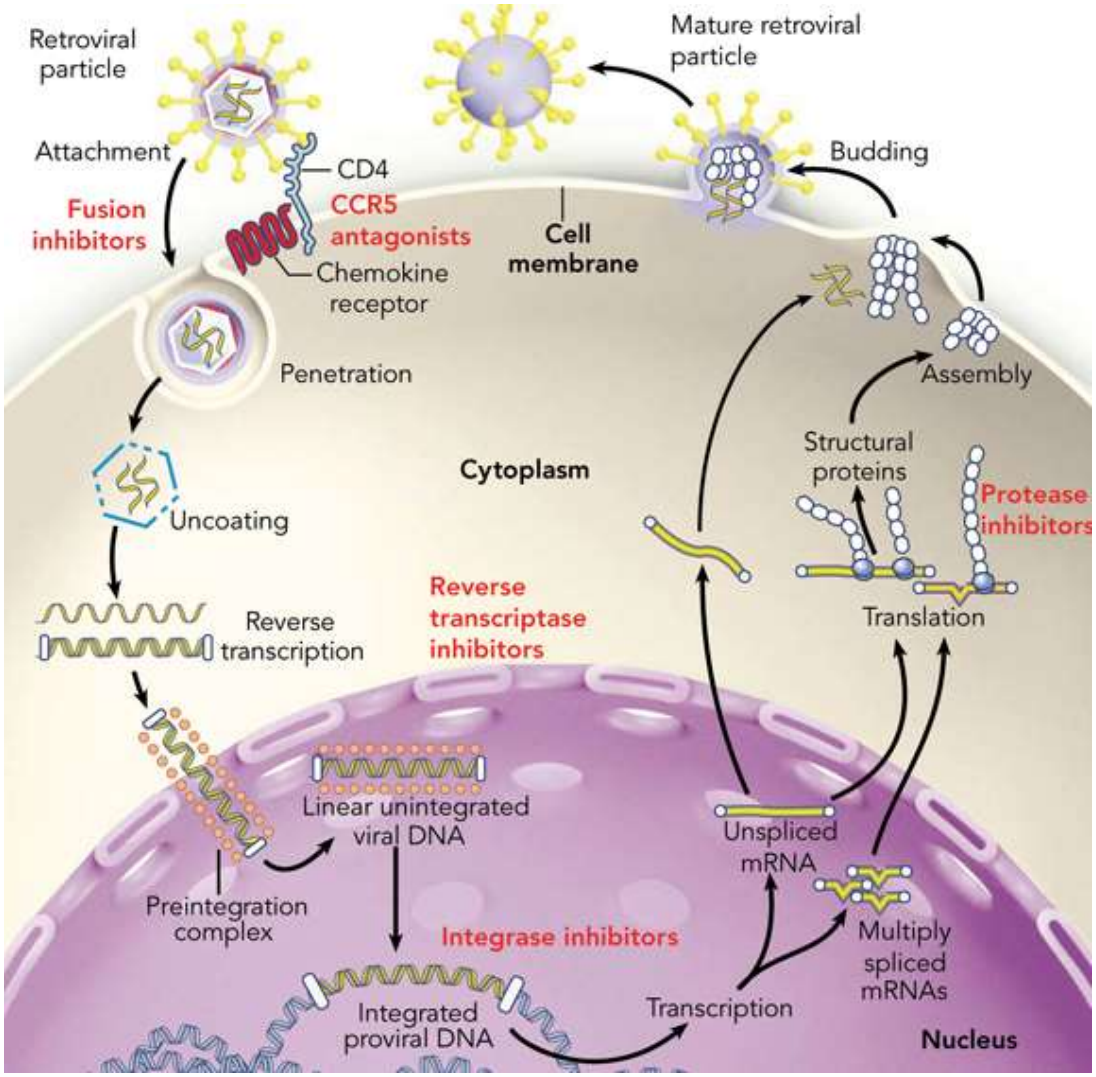
Important adverse effects

- nephrotoxicity
  - **cidofovir**, acyclovir, foscarnet
- testicular toxicity in animals
  - acyclovir, famciclovir
- myelosuppression
  - ganciclovir
- iritis, vitreitis
  - fomivirsen, 2-4 weeks interval after cidofovir

Resistance

- viral thymidine kinase
  - cross resistance; acyclovir / valacyclovir / famciclovir / ganciclovir / valganciclovir
- viral DNA polymerase
  - cross resistance to **cidofovir** / foscarnet
- no cross resistance with fomivirsen

Life cycle of HIV and site of action of antiretroviral therapy



Classification of anti-HIV drugs

- Entry inhibitors
  - Fusion inhibitors[1]
  - CCR5 antagonists[2]
- **Reverse transcriptase inhibitors (RTIs)**
  - **Nucleos(t)ide RTIs (NRTIs)**
  - **Non-nucleoside RTIs (NNRTIs)**
- Integrase strand transfer inhibitors[3]
- **Protease inhibitors**

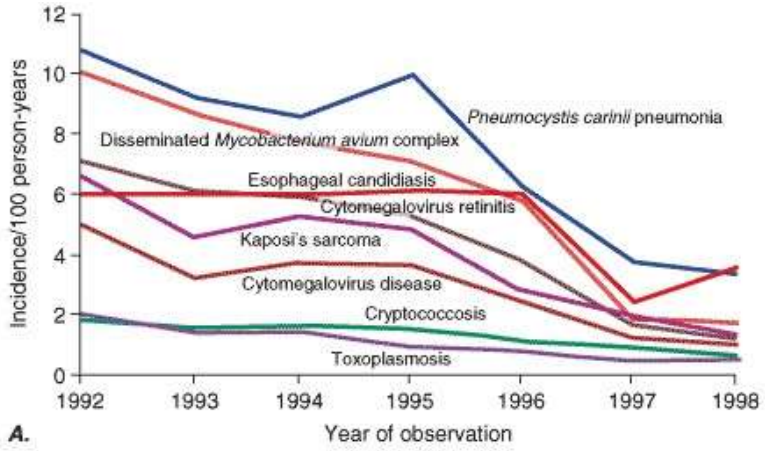
[1] Currently only one drug accepted for clinical use (enfuvirtide, 2003).
[2] Currently only one drug accepted for clinical use (maraviroc, 2007).
[3] Currently accepted for clinical use: raltegravir, dolutegravir, elvitegravir

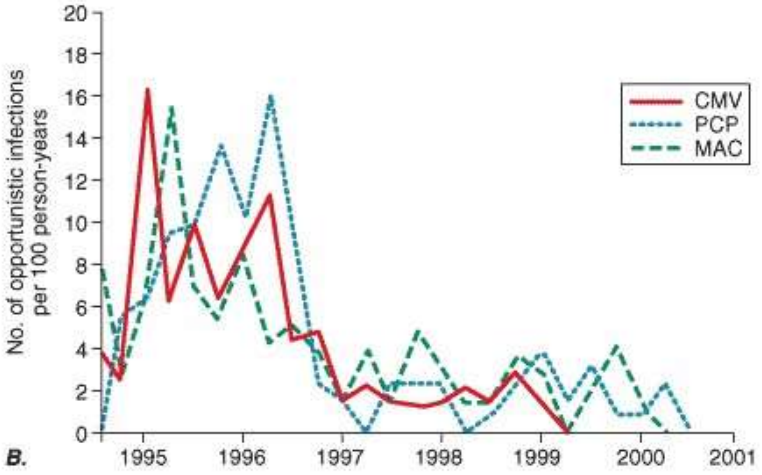
Antiretroviral drugs

- **N**ucleos(t)ide **R**everse **T**ranscriptase **I**nhibitors
  - **abacavir** / didanosine / **emtricitabine** / **lamivudine** / stavudine / **tenofovir** / zalcitabine / zidovudine
- **N**on**N**ucleoside **R**everse **T**ranscriptase **I**nhibitors
  - delavirdine / efavirenz / etravirine / nevirapine
- **P**rotease **I**nhibitors
  - **fosamprenavir** / **atazanavir** / darunavir / indinavir / **lopinavir+ritonavir** / nelfinavir / ritonavir / saquinavir / **tipranavir**
- Fusion inhibitor
  - enfuvirtide
- CCR5 inhibitor
  - maraviroc
- Integrase strand transfer inhibitors
  - raltegravir, dolutegravir, elvitegravir

Results of anti-HIV therapy

- effective control of HIV and significantly reduced morbidity and mortality (but no cure!)
- suppression of virological replication and an increase in CD4+ T cells with few adverse effects





Antiretroviral treatment goals

- eradication of HIV cannot be achieved with current regimens
- the primary goals for initiating antiretroviral therapy are to:
  - **reduce** HIV-associated **morbidity** and **prolong** the duration and quality of **survival**,
  - restore and preserve **immunologic function**,
  - maximally and durably **suppress plasma HIV viral load**
  - **prevent HIV transmission**

Current principles of HIV therapy

- ↓ virus replication
  - as much as possible for as long as possible
- at least 3 drugs simultaneously
  - for the entire duration of treatment
- earlier start of treatment seems to be better
  - independent of CD4 count
- treatment ↓ transmission
- drug resistance is a key problem
  - drug holidays are not recommended
- some drugs are well tolerated even long-term
  - lamivudine, emtricitabine, raltegravir, maybe dolutegravir
- common pharmacokinetic drug interactions – PIs / NNRTIs

Highly **A**ctive **A**nti**R**etroviral **T**herapy (**HAART**)

- combination of three antiretrovirals from at least two drug classes
  - 2 NRTI + INSTI / 2 NRTI + PI / 2 NRTI + NNRTI
- goals / results
  - suppress HIV viral load in plasma to below the limit of detection
  - restore immune function, as demonstrated by an increased number of CD4+ T cells
  - significant reductions in HIV-related morbidity and mortality
    - decreased incidence of opportunistic infections
    - decreased occurrence of drug resistant virus strains

Questions without definitive answers[1]

- When should therapy be started?
  - symptoms
  - CD4+ T-cell count
  - plasma viral load
- What is the best initial regimen?
  - HAART but the components should be individualized based on patient- and drug-specific factors
- When should a given regimen be changed?
- What should it be changed to when a change is made?

[1]Several international bodies publish guidelines for the use of antiretroviral therapy. e.g.: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research

What's New in the Guidelines? (Last updated July 14, 2016; last reviewed July 14, 2016)

Revisions to the January 28, 2016, version of the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* include key updates to several sections. Significant updates are highlighted throughout the document.

Current regimens recommended in treatment-naive patients

- "Recommended"
  - dolutegravir + **tenofovir/emtricitabine**
  - cobicistat-boosted elvitegravir + **tenofovir/emtricitabine**
  - raltegravir + **tenofovir/emtricitabine**
  - ritonavir-boosted darunavir + **tenofovir/emtricitabine**

Regimens are classified as "Recommended," "Alternative," "Acceptable," "Regimens that may be acceptable but more definitive data are needed," and "Regimens to be used with caution."

Nucleos(t)ide reverse transcriptase inhibitors (NRTIs)

drug name	analog of	FDA approval
zidovudine	**thymidine**	**1987**
stavudine	thymidine	1994
lamivudine	**cytosine**	**1995**
emtricitabine	**cytosine**	**2003**
zalcitabine	cytosine	1992
didanosine	adenosine	1991
tenofovir	**adenosine (nucleotide)**	**2001**
abacavir	guanosine	1998

General characteristics of NRTIs

- intracellular activation to triphosphate form
  - host cell kinases, phosphorylation
- mechanism of action
  - competitive inhibition of viral RNA-dependent DNA polymerase (= reverse transcriptase = RT)
  - incorporation into DNA → chain termination
- rapid emergence of resistance if used alone
- cross-resistance not complete – e.g. lamivudine vs. zidovudine
- potential for mitochondrial toxicity – DNA polymerase γ
  - lactic acidosis, severe hepatomegaly with steatosis (obesity, prolonged treatment, preexisting liver disease) – can be fatal
  - primarily for e.g. zidovudine, stavudine, didanosine

Zidovudine (AZT)

- first but still used
- combination formulation with lamivudine
- **bone marrow suppression**
- penetrates the central nervous system
- shown to be effective in
  - prevention of intrapartum mother-to-child transmission (vertical transmission)
  - post-exposure prophylaxis
- **decreased susceptibility to other drugs may enhance susceptibility in previously zidovudine resistant strains**

Lamivudine / emtricitabine

- **emtricitabine is a fluorinated analog of lamivudine**
- long intracellular half life
- lamivudine – HBV, too
- good oral biovailability
- in short term shown to be safe in mother and infant
- if HAART is not fully suppressive – quick resistance (M184V)
- **no severe adverse effects**

Abacavir

- the only guanosine analogue antiretroviral
- good oral bioavialability / hepatic glucuronidation
- combination formulation with lamivudine
- **severe hypersensitivity reactions (~4%)**
  - associated with HLA-B*5701, testing is recommended
  - can be fatal with re-challenge
- possible increase in risk of myocardial events
- resistance occurs slowly

Tenofovir

- nucleotide – only two phosphorylation
- oral bioavailability is low but increased with food
- long serum and ic. $t_{1/2}$ – 1x daily dosing
- **combination formulation with emtricitabine**
- most common are gastrointestinal adverse effects
- possibility of renal toxicity
- cross resistance with other NRTIs is not complete

Nonnucleoside reverse transcritpase inhibitors (NNRTI)

- delavirdine / efavirenz / etravirine / nevirapine

- **binding site is distinct** from NRTIs – allosteric inhibition
- non-competitive block / no phosphorylation
- no cross resistance with NRTIs / no activity against HIV-2
- very rapid emergence of resistance if used as monotherapy
- cross resistance among NNRTIs – etravirine is partly exception
- GI intolerance / skin rash
- metabolism by CYP3A4 system – drug interactions
  - nevirapine – inducer / delaviridine – inhibitor / efavirenz, etravirine – mixed
- efavirenz: CNS side effects / teratogenic
- nevirapine: hepatotoxicity / rash / role in vertical transmission
- etravirine: newest / may be effective in resistant

Protease inhibitors (PI)

- **fosamprenavir** / **atazanavir** / **darunavir** / indinavir / **lopinavir+ritonavir** / nelfinavir / ritonavir / saquinavir / tipranavir

- aspartate protease encoded by the gag/pol gene
- resistance – multiple point mutations in the pol gene
- extent of cross resistance is variable
- used in combinations with RTIs as components of HAART
- significant impact on the efficacy of antiretroviral therapy
- activity against HIV-1 and HIV-2 / no intracellular activation
- CYP metabolism – interactions (ritonavir inhibits most) – **boosted PI**
- carbohydrate and lipid metabolism disorders (atazanavir is exception)
  - lipid-regulating proteins - structural homology
  - hyperglycemia, insulin resistance, altered body fat distribution
  - 30-50% in HAART, onset after ~1 year

Other antiretrovirals

- enfuvirtide
  - synthetic 36 amino acid peptide – sc. inj.
  - binds to gp41 subunit on viral envelope – prevents fusion of viral and cellular membranes / no HIV-2 activity
  - previously treated patients who are unresponsive (persistent virus replication)
- maraviroc
  - CCR5 binding / used in case of failure with other agents / not CXCR4
  - oral administration / no severe adverse effects until now
- dolutegravir, elvitegravir, raltegravir
  - integrase strand transfer inhibitors
  - oral administration
  - elvitegravir requires boosting
  - raltegravir has no interaction with CYP450 system
  - dolutegravir may retain activity in case of raltegravir and elvitegravir resistance