Antiviral Agents

CHAPTER 30

Drugs Used to Treat Viral Infections

Patrick M. Woster

Drugs covered in this chapter:

INHIBITORS OF VIRAL ATTACHMENT, PENETRATION OR EARLY REPLICATION
- Amantadine
- Amphotericin B methyl
- Ester
- Interferon/PEG-IFN
- Rimantadine
- Tecovirimat

NEURAMINIDASE INHIBITORS
- Oseltamivir
- Peramivir
- Zanamivir
- Baloxavir marboxil

FUSION INHIBITORS
- Enfuvirtide
- Maraviroc

ACYCLIC NUCLEOLSIDE ANALOGUES
- Acyclovir
- Adefovir dipivoxil
- Cidofovir
- Famciclovir
- Ganciclovir
- Penciclovir
- Valacyclovir

CONVENTIONAL NUCLEOSIDE ANALOGUES
- Ribavirin

NONNUCLEOSIDE ANALOGUES
- Foscarnet
- Letermovir

ANTIRETROVIRAL AGENTS—NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS
- Abacavir
- Didanosine
- Emtricitabine
- Lamivudine
- Stavudine
- Tenofovir disoproxil
- Zidovudine

ANTIRETROVIRAL AGENTS—NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS
- Delavirdine
- Doravirine
- Efavirenz
- Etravirine
- Nevirapine
- Rilpivirine

HIV PROTEASE INHIBITORS
- Atazanavir
- Darunavir
- Fosamprenavir
- Indinavir
- Lopinavir
- Nelfinavir
- Ritonavir
- Saquinavir
- Tipranavir

INHIBITORS OF HCV PROTEASE NS3/NS4A
- Glecaprevir
- Grazoprevir
- Paritaprevir
- Voxilaprevir

INHIBITORS OF HCV PROTEASE NS5A AND NS5B
- Daclatasvir
- Dasabuvir
- Elbasvir
- Ledipasvir
- Ombitasvir
- Pibrentasvir
- Sofosbuvir
- Velpatasvir

DRUG COMBINATIONS FOR HCV INFECTION
- Epclusa
- Harvoni
- Mavyret
- Technivie
- Viekira Pak/Viekira XR
- Zepatier

HIV INTEGRASE INHIBITORS
- Dolutegravir
- Elvitegravir
- Raltegravir
- Bictegravir

Steps in Viral Life Cycle: A DNA Virus

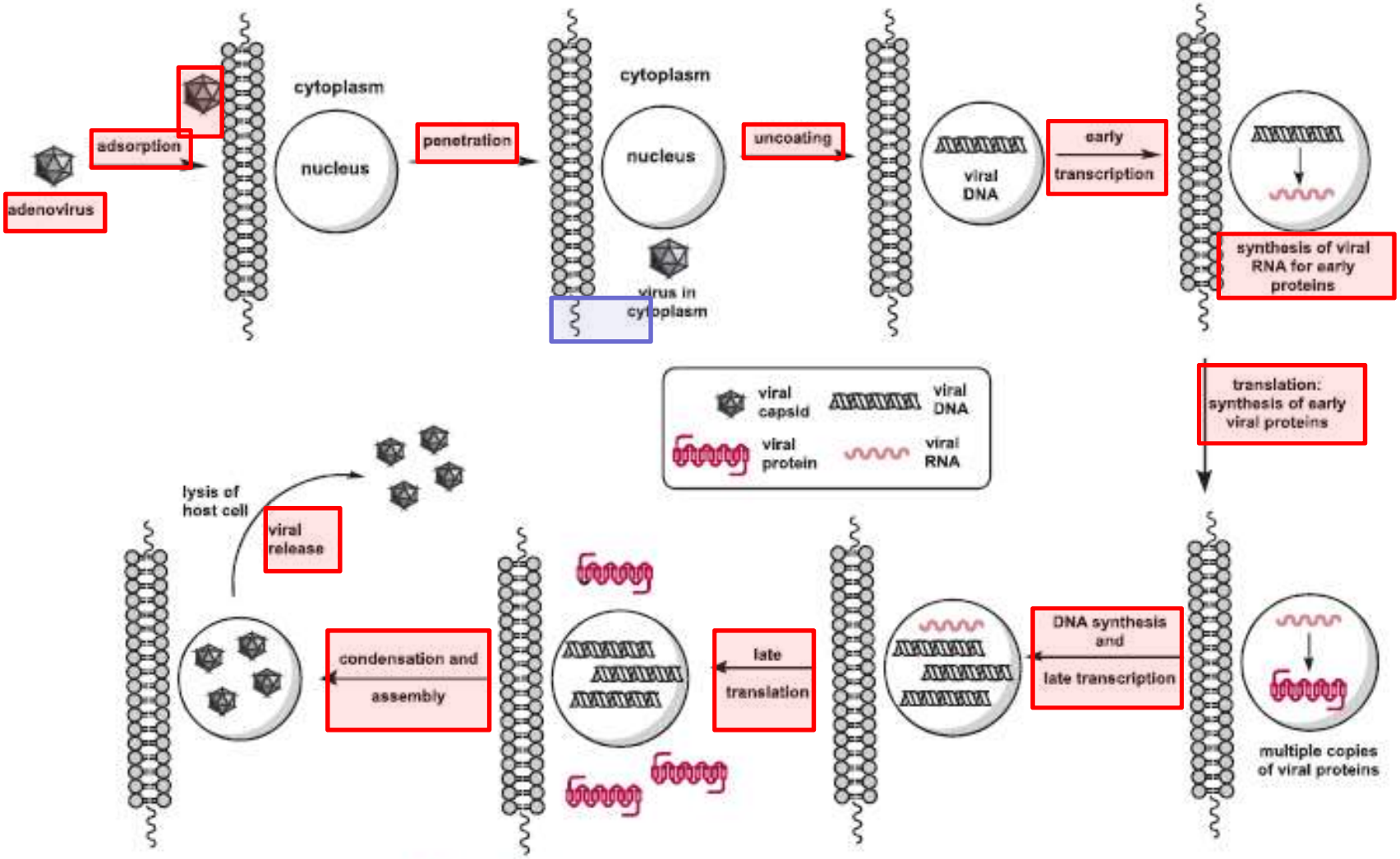

Figure 30.1 Steps involved in the viral life cycle.

Steps in Viral Life Cycle: A RNA Virus: HIV (RNA Virus) Replicative Cycle

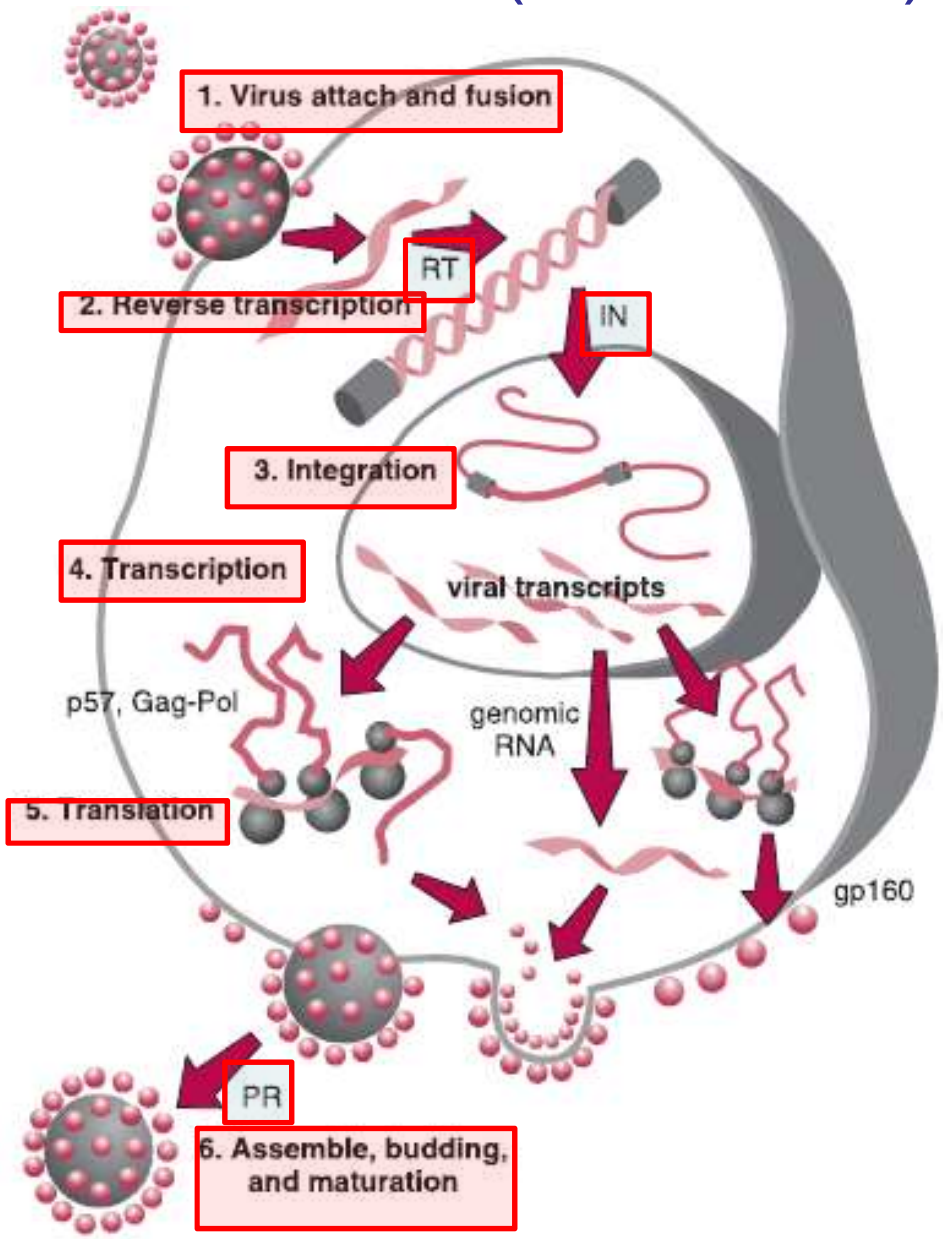

Figure 30.2 Replicative cycle of human immunodeficiency virus (HIV). (1) The virus gp120 protein binds to CD4 resulting in fusion of the viral envelope and the cellular membrane and the release of viral nucleocapsid into the cytoplasm. (2) The nucleocapsid is uncoated and viral RNA is reverse transcribed by reverse transcriptase (RT). (3) The resulting double-stranded proviral DNA migrates into the cell nucleus and is integrated into the cellular DNA by integrase (IN). (4) Proviral DNA is transcribed by the cellular RNA polymerase II. (5) The mRNAs are translated by the cellular polysomes. (6) Viral proteins and genomic RNA are transported to the cellular membrane and assemble. Immature virions are released. Polypeptide precursors are processed by the viral protease (PR) to produce mature viral particles. Used with permission from Tyler KL, Fields BN. *Fields Virology*. 2nd ed. New York: Raven Press; 1990:191-239.

Viral Life Cycle

a- Adsorption, fusion, attachment: recognition process: receptors & coreceptors

b- Entry & penetration: endocytosis

c- Uncoating & NA (DNA & RNA) transfer

d- Early transcription: production of viral mRNA & early proteins

e- Early translation of viral mRNA into enzyme for viral DNA synthesis

f- Synthesis of viral DNA & late transcription of viral mRNA

g- Late translation of mRNA into viral structure proteins

h- Assembly of virus: assemble into capsid

i- Release & budding to release new virus: exocytosis

Foye's 2019

Classes of Antiviral Agents

1- Penetration interfering agents; chemokine binders:

1a- Early step antiviral agents

1b- NeurAminidase Inhibitors (NAIs): anti Influenza virus

1c- HIV fusion inhibitors against gp41/ gp120 & CCR5 as antagonist: anti HIV

2- DNA interfering agents; DNA polymerase inhibitors:

2a- Acyclic nucleoside analogues (antimetabolite)

2b- Conventional nucleoside analogues (antimetabolite)

2c- Non-nucleoside analogues

2d- agents affecting translation by the ribosome

2e- Endonuclease inhibitor: anti Influenza virus

3- INtegrase (Strand Transfer) Inhibitors (IN(ST)Is): anti-retrovirus: anti HIV

4- Reverse Transcriptase Inhibitors (RTIs): anti HIV

4a- Nucleoside RTI (NRTI)

4b- Non- Nucleoside RTI (NNRTI): anti HIV

5- PRotease Inhibitors (PRIs): anti HIV & anti HCV

6- RNA dependent RNA polymerase (RdRp) Inhibitors

7- siRNA

8-Vaccines

1- Prevention of Virus Attachment
Prevention of Virus Penetration
Penetration Interfering Agents

1a- Early step antiviral agents

1b- NeurAminidase Inhibitors (NAIs): anti-influenza virus

1c- HIV Fusion Inhibitors: anti HIV

1- Prevention of Virus Attachment
Prevention of Virus Penetration
Penetration Interfering Agents

Prevent Virus Uncoating
&
Early Viral Replication

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- Baloxavir marboxil

FUSION INHIBITORS

- Enfuvirtide
- Maraviroc

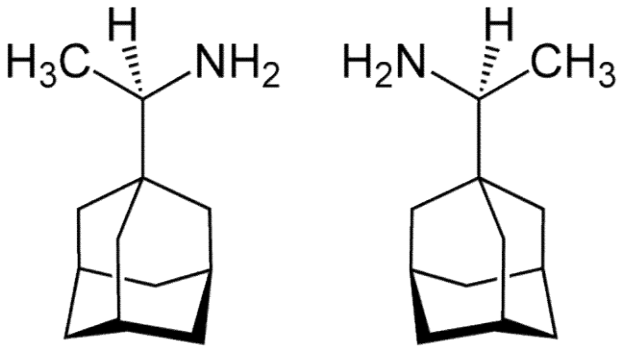
1a- Early Step Antiviral

- MOA: inhibit virus attachment
  inhibit virus penetration
  inhibit virus uncoating & early viral replication
  inhibit NA transfer into host cell
- Drugs:

✓ amantadine

✓ rimantadine

✓ amphotericin B Me ester



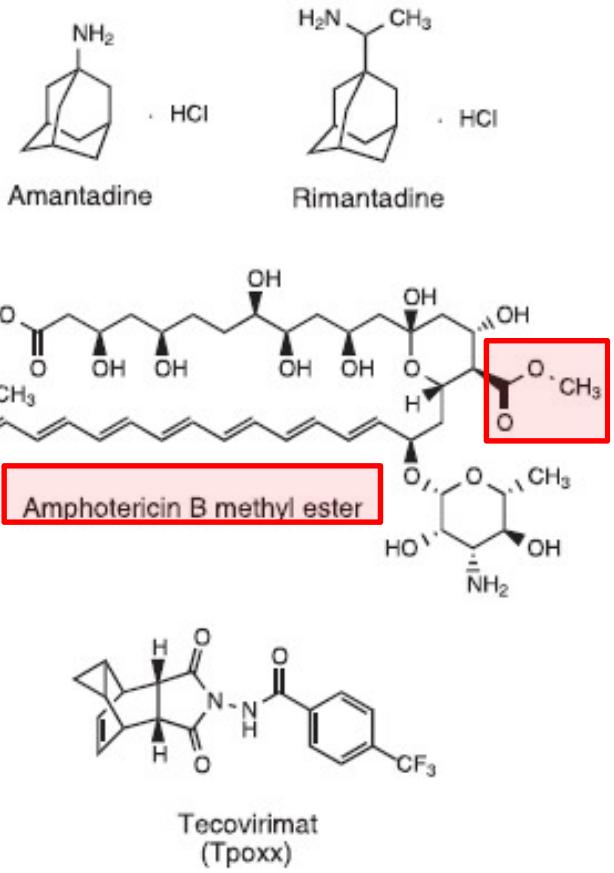
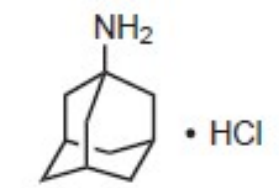


Figure 30.4 Agents that inhibit virus attachment, penetration, and early viral replication.

1a- Early Step Antiviral: Amantadine

- Amantadine . HCl: Symmetrel®



Amantadine

✓ adamantan-amine HCl

✓ Symmetrical primary tricyclic amine

- MOA:

✓ inhibit penetration of RNA virus to host cell

✓ inhibit early stages of viral replication by blocking the uncoating of the viral genome

✓ Inhibit viral replication by blocking the proton selective ion channel in influenza virus

- Clinical indication:

✓ influenza virus

✓ Respiratory Syncytial Virus (RSV)

✓ some RNA viruses

- Well absorbed; crosses BBB; saliva & nasal secretions & breast milk distribution
- SEs: CNS problems

1a- Early Step Antiviral: Rimantadine

- Rimantadine: Flumadine®:

✓ α-methyl-1-adamantane-methyl-amine HCl

✓ Comparing to amantadine: more effective & less CNS SEs.

- MOA:

✓ interfere with virus uncoating by inhibiting the release of specific proteins

✓ Inhibit RT

✓ Inhibit synthesis of virus-specific RNA

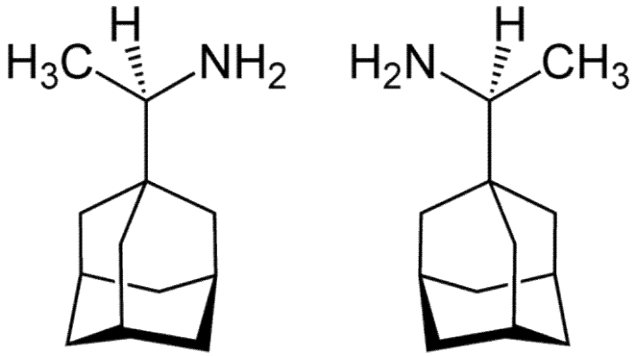
✓ Not inhibit virus adsorption or penetration

✓ Virus static effect early in the virus replication

- Clinical indication:

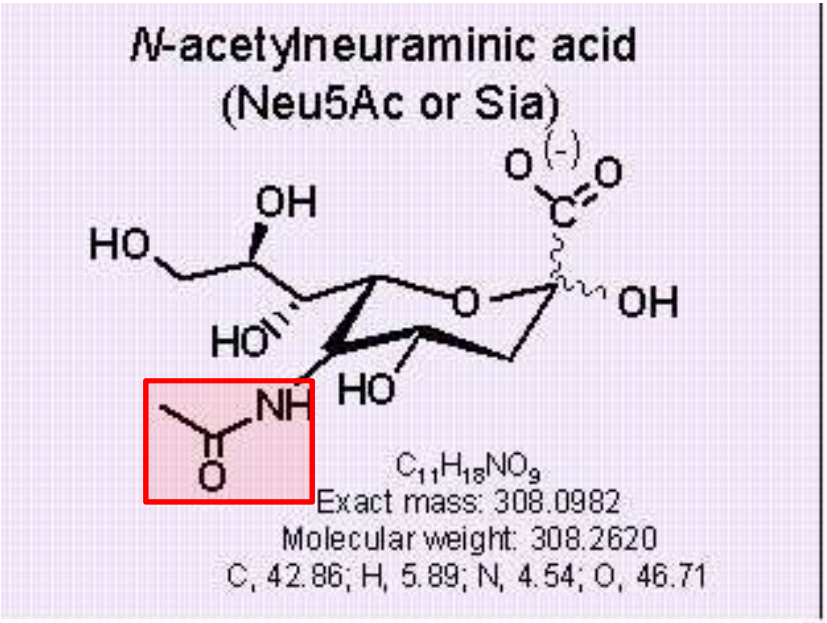
✓ influenza virus

- SEs: CNS problems

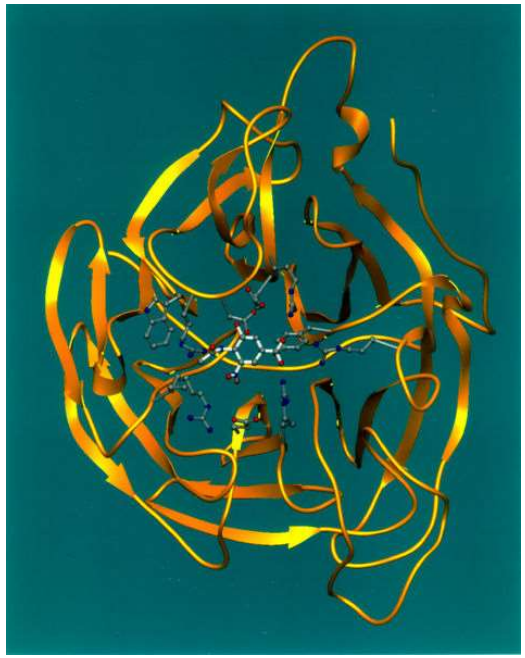


1b- NeurAminidase Inhibitors (NAIs)

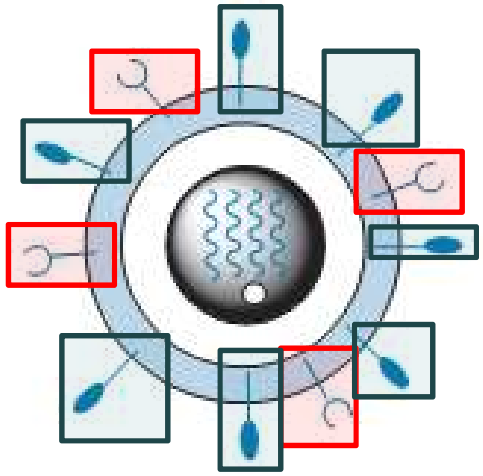
- Neuraminidase (NA): motivate host cell penetration for virus cell by cleaving **sialic acid = Sia = N-Acetyl-neuraminic acid = Neu-5-Ac = NA-5-Ac**
- Especial in influenza viruses types A & B
- How about budding?
- Hence NAIs: antiviral; block the spread of the influenza

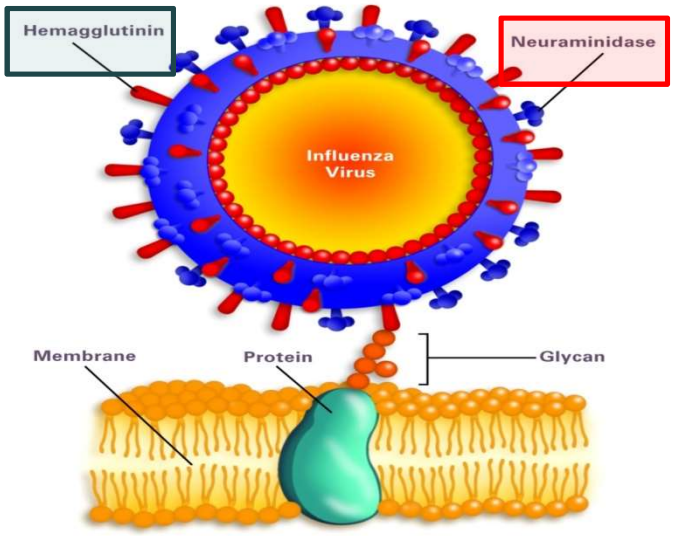


Ribbon diagram of NA



Functional Protein Structures in Membranous Layer of Influenza Virus: Hemagglutinin (G-Pr) & Neuraminidase (Pr)





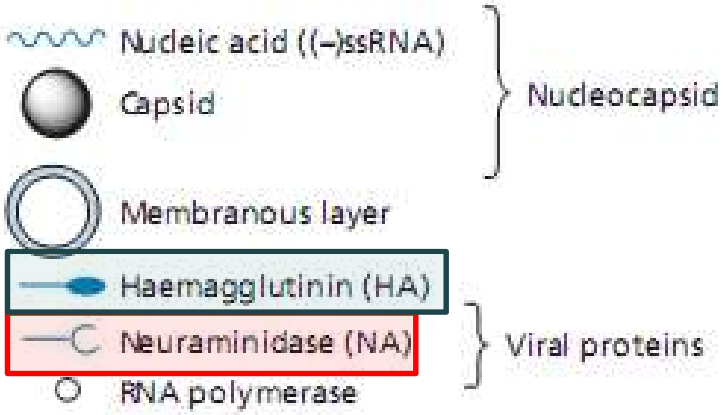
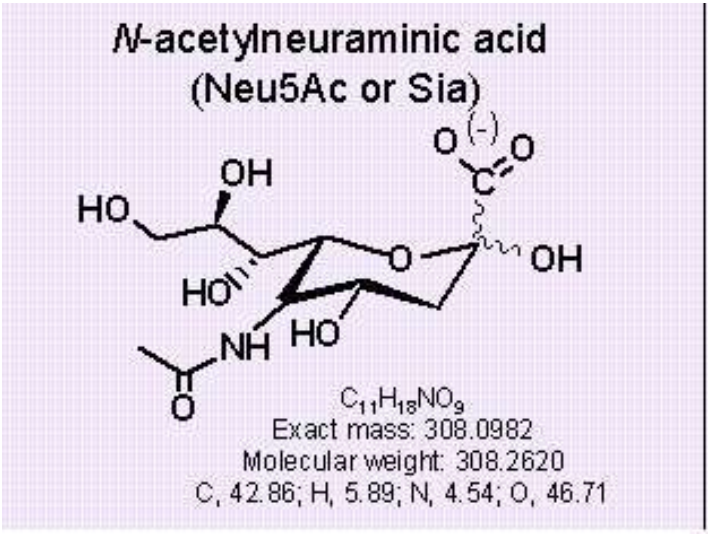


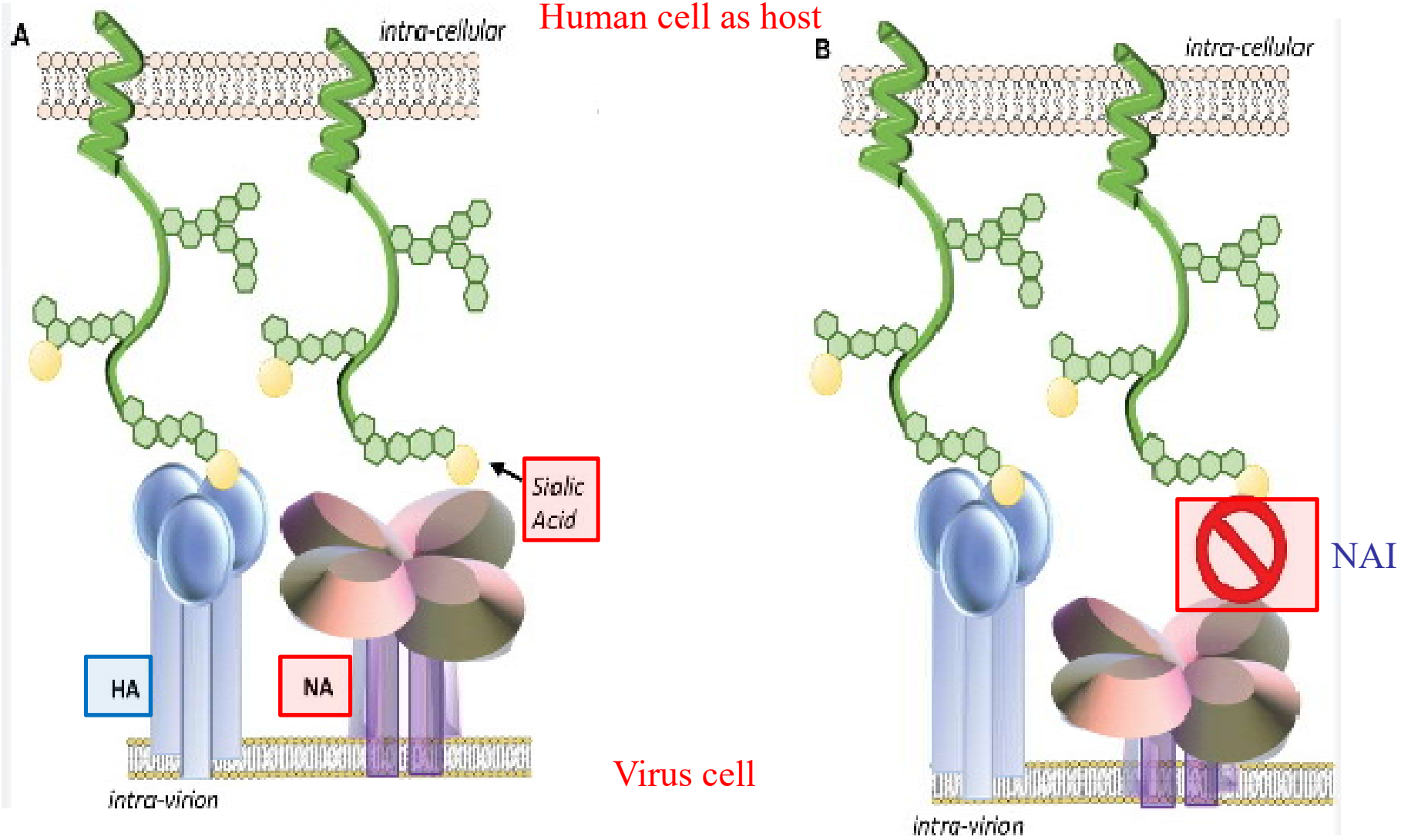
FIGURE 20.1 Diagrammatic representation of the flu virus.



SRAmini Oct2024

Consider Function of NA & Effect of NAI

Human cell as host



Virus cell

Normal Function of NeurAminidase (NA) in Cell Penetration of Influenza Virus

- Hydrolysis of:
- ✓ sialic acid-sugar-GP
- ✓ stabilized carbonium cation
- ✓ through oxonium cation
- ✓ called oxo-carbonium cation

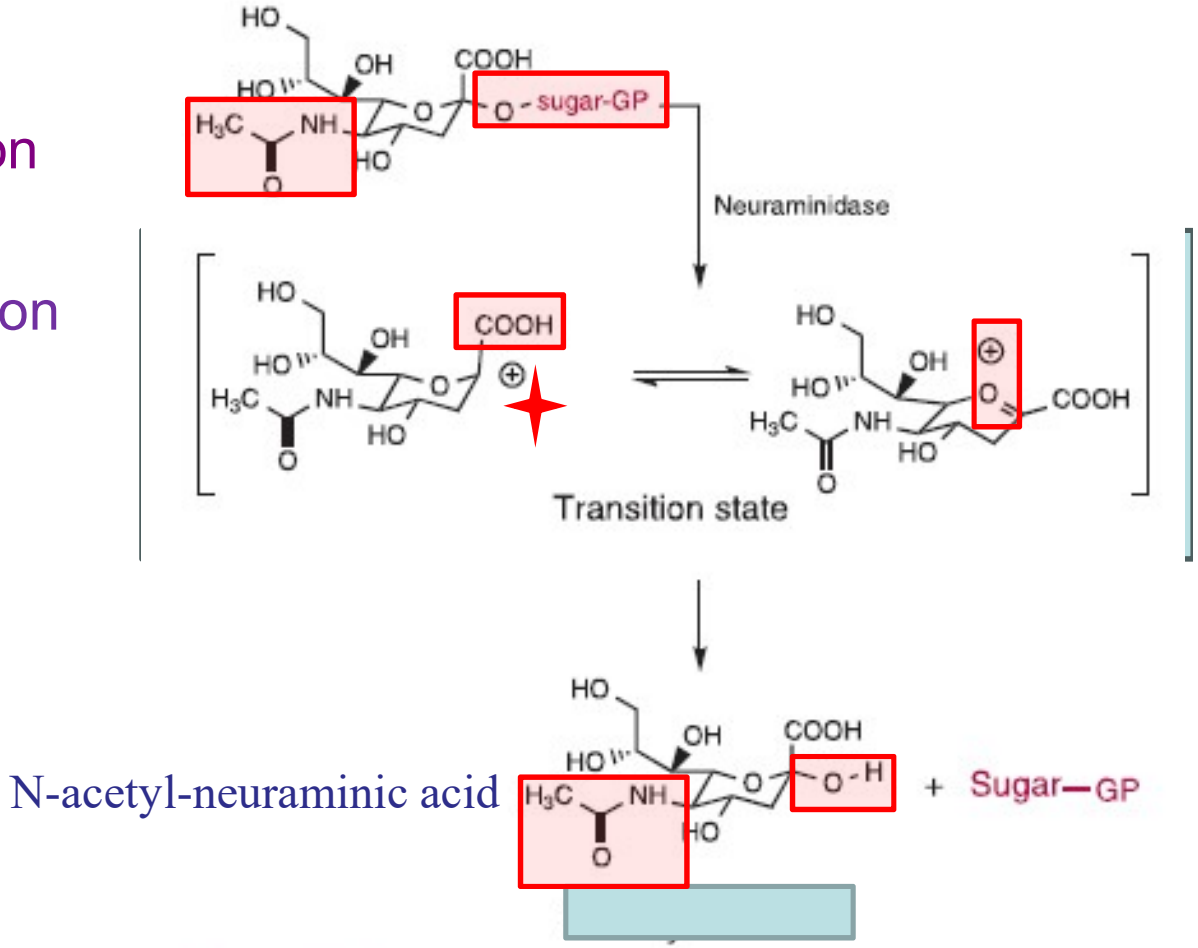
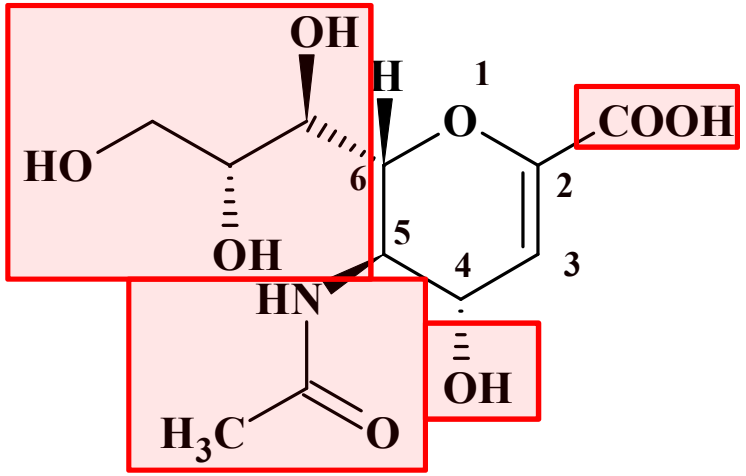


Figure 30.5 Neuraminidase-catalyzed removal of a sialic acid residue from a glycoprotein chain. *NA*, neuraminidase; *GP*, glycoprotein.

1b- NA Inhibitors:
First Designed NAI: DANA

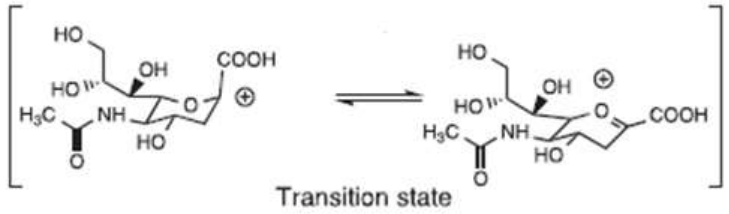
- NA Inhibitors were designed as transition state based inhibitors:
- DANA: 2-Deoxy-2,3-dehydro-N-Acetyl-Neuraminic Acid

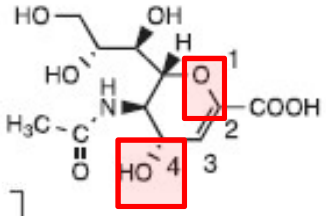


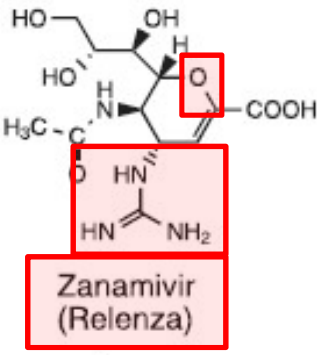
- ✓ O1: pyran ring
- ✓ C2- carbonyl of COOH (carboxylic acid): bind Arg
- ✓ C4-OH: salt bridge to Glu119
- ✓ C5- carbonyl of $COCH_3$ (acetyl): bind Arg
- ✓ C6: glycerol: hydrophobic interactions

1b- NA Inhibitors: Transition State Based Inhibitors

- Competitive inhibitor
- Chemistry:

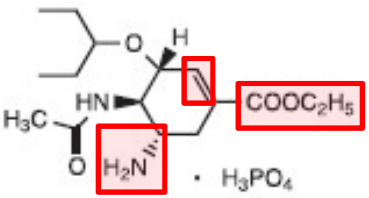


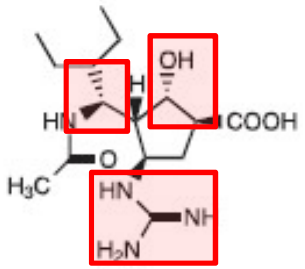




- SAR: …
- Introduced NAIs:

✓ DANA: no specific virus





✓ Zanamivir = 4-Guanidine-DANA

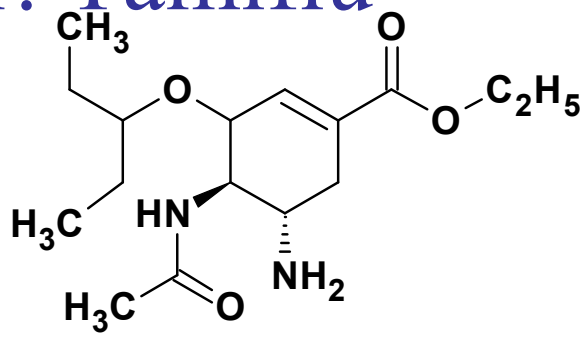
✓ Oseltamivir:

C4-amino DANA

Figure 30.6 Sialic acid derivatives DANA (2-deoxy-2,3-dehydro-N-acetylneuraminic acid), zanamivir, oseltamivir phosphate, peramivir, and baloxavir that act as inhibitors of neuraminidase.

✓ Peramivir

1b- NA Inhibitors: Oseltamivir: Tamiflu®



- Chemistry: …
- NA interaction points:

✓ C2 –CO-: binds to Arg118 & Arg292 & Arg371

✓ C4-amino: salt bridge to Glu119: provide phosphate salt

✓ C5-CO-: binds to Arg152

✓ C6-substitute: pentyl-oxy: maximum binding: hydrophobic interactions to: Glu, Ala, Arg, Ile

✓ maximum binding: C6-3-pentyloxy

- C2-ester: prodrug: orally effective: the first oral NA-inh.
- Ammonium phosphate
- MOA: NAI designed as transition state based inhibitors
- Competitive inhibitor of NA
- Against both influenza type A & type B
- Before virus exposure as prophylactic & after virus exposure as treatment

1b- Metabolic Activation of NAIs as Prodrugs

- Oseltamivir: C4-amino DANA mimic analogue

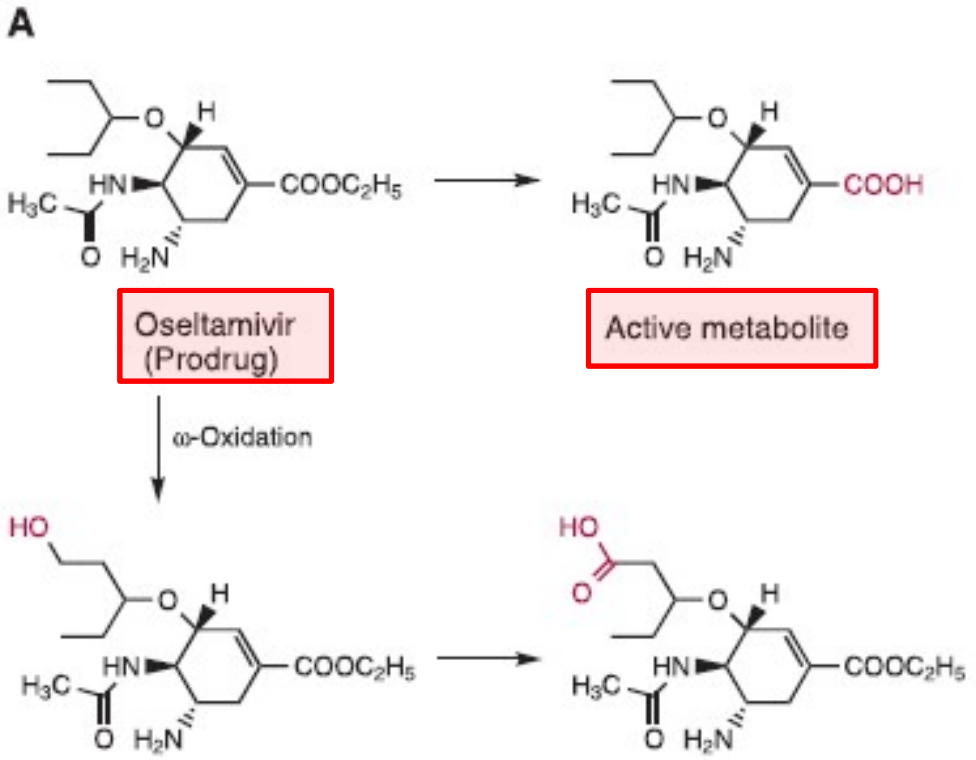
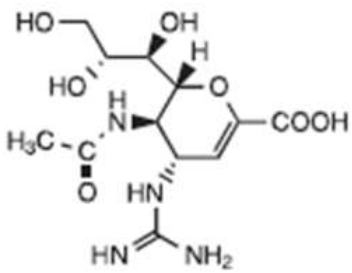


Figure 30.7 A, Metabolism of oseltamivir by deethylation and ω-oxidation.

1b- NA Inhibitors: Zanamivir



Zanamivir
(Relenza)

- Chemistry: 4-Guanine-DANA
- NA interaction sites:

✓ C2-CO-: binds Arg118 & Arg292 & Arg371

✓ C4-gaunidine: salt bridge to Glu119 & charge- charge interaction to Glu227 (R^4:C(=NH)NH_2)

✓ C5-CO-: binds Arg152

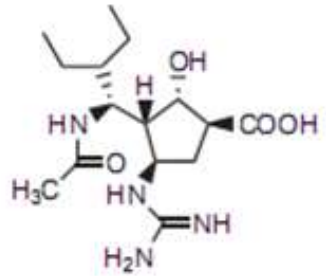
✓ C6: hydrophobic interactions

- MOA: NAI designed as transition state based inhibitors
- Competitive inhibitor of NA
- Against both influenza type A & type B
- Dosage forms: powder for oral inhalation (using disk-haler device); nasal; IP; IV
- Orally: inactive due to lack of systemic absorption
- Before virus exposure as prophylactic & after virus exposure as treatment

1b- NA Inhibitors: Peramivir

- Chemistry:

✓ cyclopentane ring



Peramivir

✓ C6 of NA: mimicked by a C5-methylene substitute

✓ no glycerol chain as C6-substitute

✓ iso-pentyl mimics glycerol

- Clinical phase III
- Against hospitalized & severe H1N1 influenza
- Applied in zanamivir & oseltamivir resistant cases

2- Viral DNA Interfering Agents:
Agents Interfering Viral Nucleic Acid Replication:

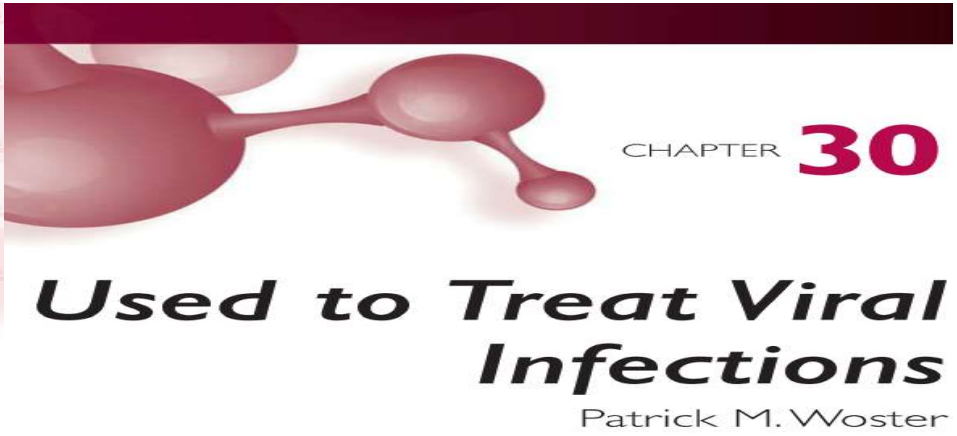
2a- Acyclic Nucleoside Analogues

2b- Conventional Nucleoside Analogues

2c- Non-Nucleoside Analogues

2d- Agents Affecting Translation by the Ribosome

2e- Endonuclease inhibitors



2a: Acyclic Nucleoside Analogues

ACYCLIC NUCLEOLSIDE ANALOGUES

- Acyclovir
- Adefovir dipivoxil
- Cidofovir
- Famciclovir
- Ganciclovir
- Penciclovir
- Valacyclovir

CONVENTIONAL NUCLEOSIDE ANALOGUES

- Ribavirin
- Trifluorothymidine
- Vidarabine

2d: Agents Affecting Translation by the Ribosome

2e: Endonuclease inhibitors: Baloxavir

2c: Non-Nucleoside Analogues

NON NUCLEOSIDE ANALOGUES

NONNUCLEOSIDE ANALOGUES

- Foscarnet
- Letermovir

MOA for Nucleosides as Anti-Metabolites

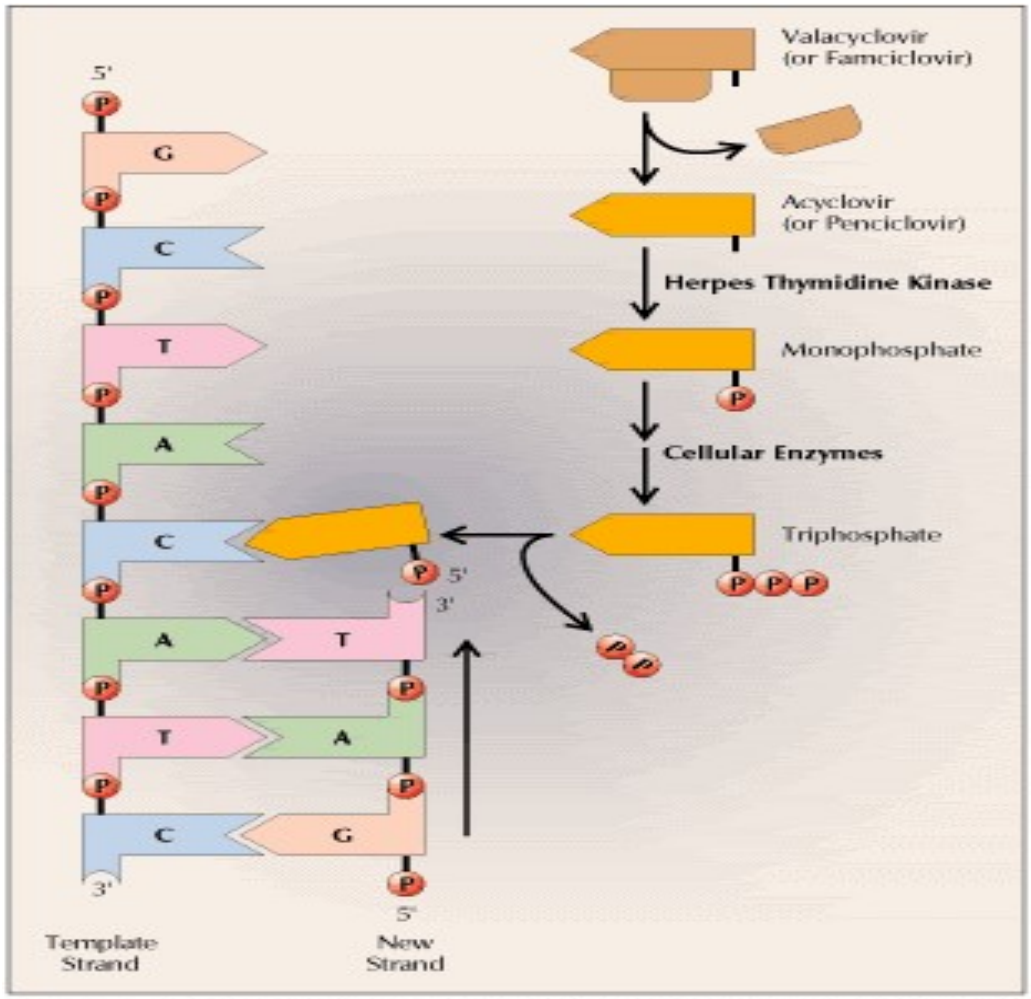
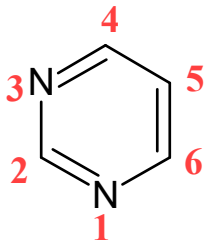
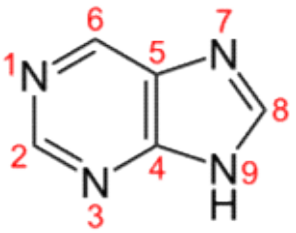


Figure 4. The three nucleoside ana-logs currently available to treat HSV infection are famciclovir, valacyclovir, and acyclovir. On absorption, famciclovir is converted to penciclovir and valacyclovir to acyclovir. Phosphorylation of penciclovir and acyclovir to nucleotides is initiated by HSV-produced thymidine kinase. Once in triphosphate form, the penciclovir and acyclovir molecules are incorporated into [illegible] normally occupied by deoxyguanosine (G), thereby terminating the DNA chain.

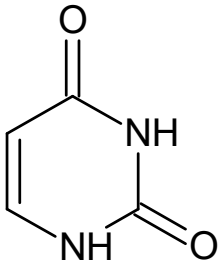
www.racoon.com/herpes/sacks/

Nucleic Acid Components

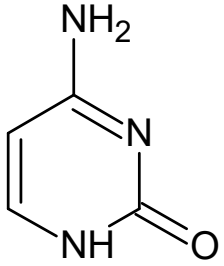




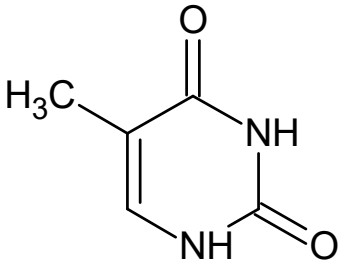
- Pyrimidine: U, C, T



Uracil

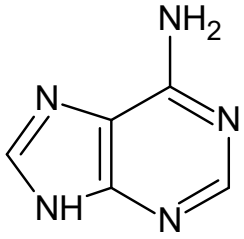


Cytosine

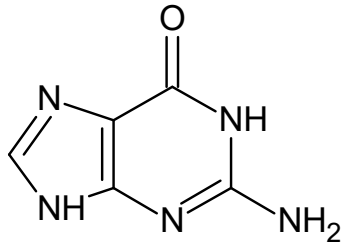


Thymine

- Purine: A, G

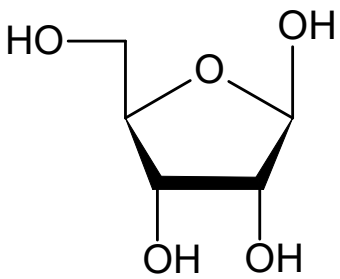


Adenine

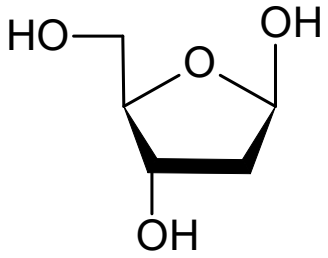


Guanine

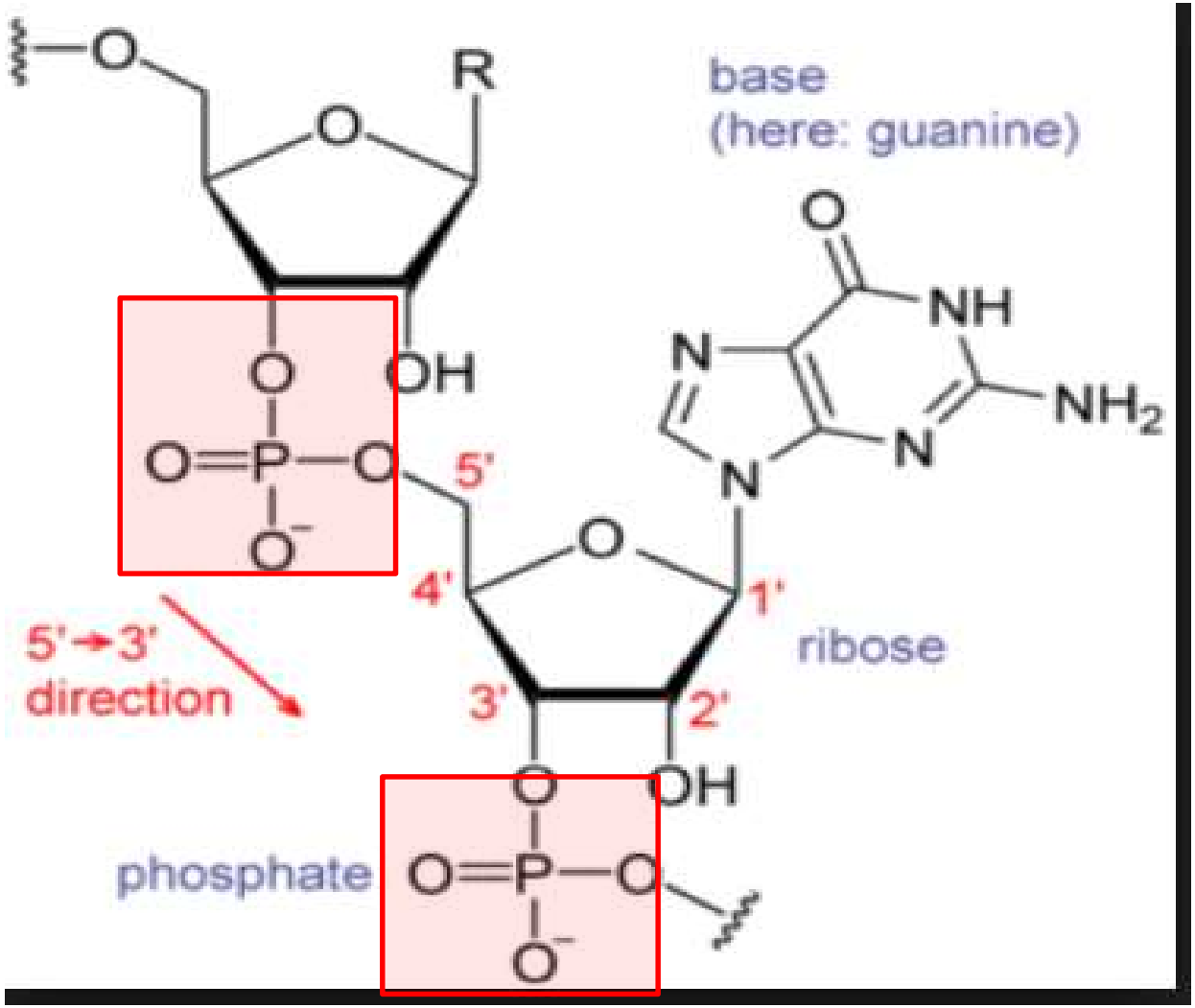
- Ribose



- 2-Deoxyribose



GMP in NA Backbone



2a- Acyclic Nucleoside Analogues

Chapter 38

Antiviral Agents and Protease Inhibitors

Patrick M. Woster

Drugs Covered in This Chapter*

CHAPTER 30

Drugs Used to Treat Viral Infections

Patrick M. Woster

2a

ACYCLIC NUCLEOLSIDE ANALOGUES

- Acyclovir
- Adefovir dipivoxil
- Cidofovir
- Famciclovir
- Ganciclovir
- Penciclovir
- Valacyclovir

2a- Acyclic Nucleoside Analogues

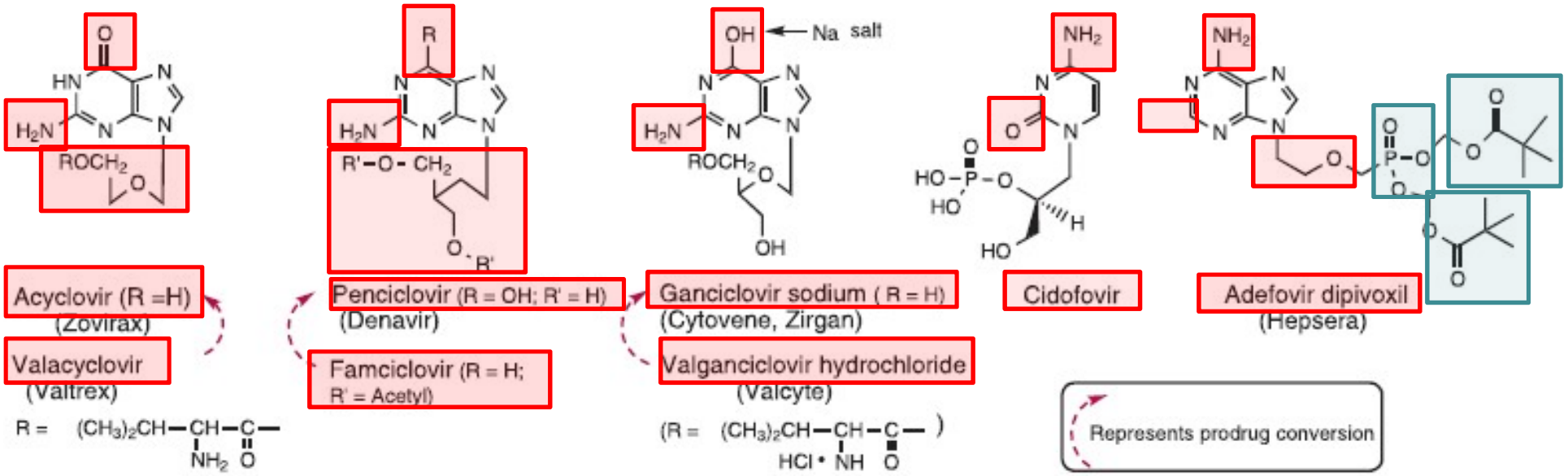


Figure 30.8 Agents that interfere with viral nucleic acid replication: acyclic nucleosides.

2- Viral DNA Interfering Agents:
2a- Acyclic Nucleoside Analogues

- Preferential uptake to infected cells

✓ Prodrug: so have active metabolite

- MOA: three mechanisms:

➢ Conversion to active mono-phosphate drug by viral thymidine kinase

✓ di & tri-phosphate by normal cellular guanosine monophosphate kinase

➢ Viral DNA polymerase inhibition with IC50 < cellular DNA polymerase

➢ Incorporated into viral DNA

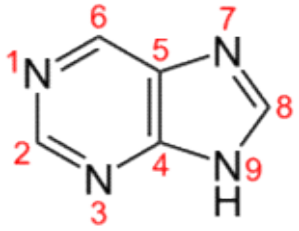
➢ terminates further elongation of DNA chain

✓ reduce DNA synthesis in infected cells without significantly disturbing uninfected cells

- Preferential by herpes infected cells

2a- Acyclic Nucleoside Analogues

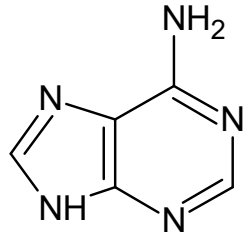
- Chemistry:



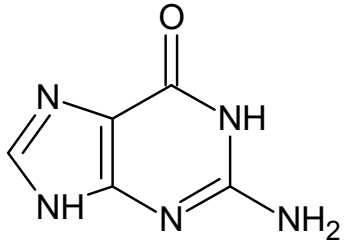
✓ purine analogue:

guanine & adenine analogues

6-deoxy Guanine analogues



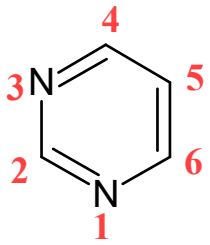
Adenine

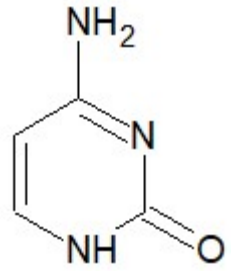


Guanine

✓ pyrimidine analogue:

cytosine analogue



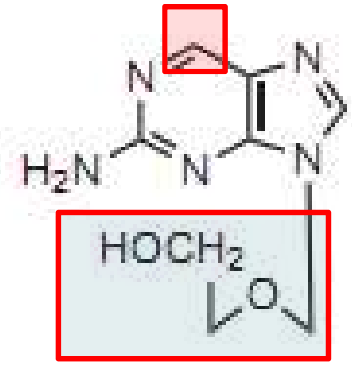


Cytosine

- SAR
- MOA: as a prodrug: …

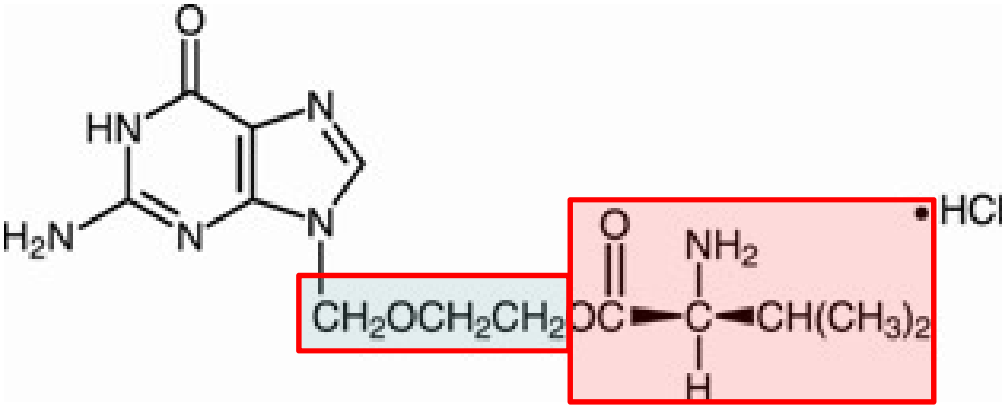
2a- Acyclic Nucleoside Analogues: Acyclovir Prodrugs

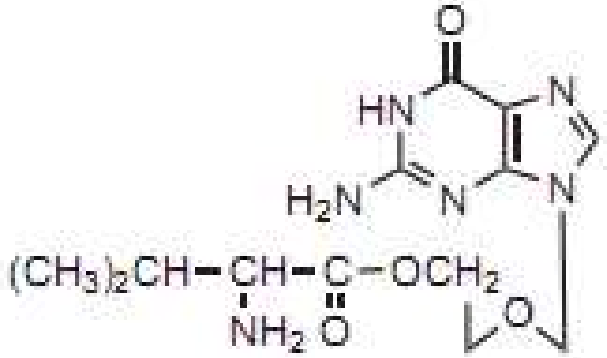
- 6-Deoxy- acyclovir



6-Deoxyacyclovir

- Valacyclovir (Valtrex®)





Valacyclovir

Metabolic Reactions / Activations

- for

✓ Acyclovir

&

✓ Valacyclovir

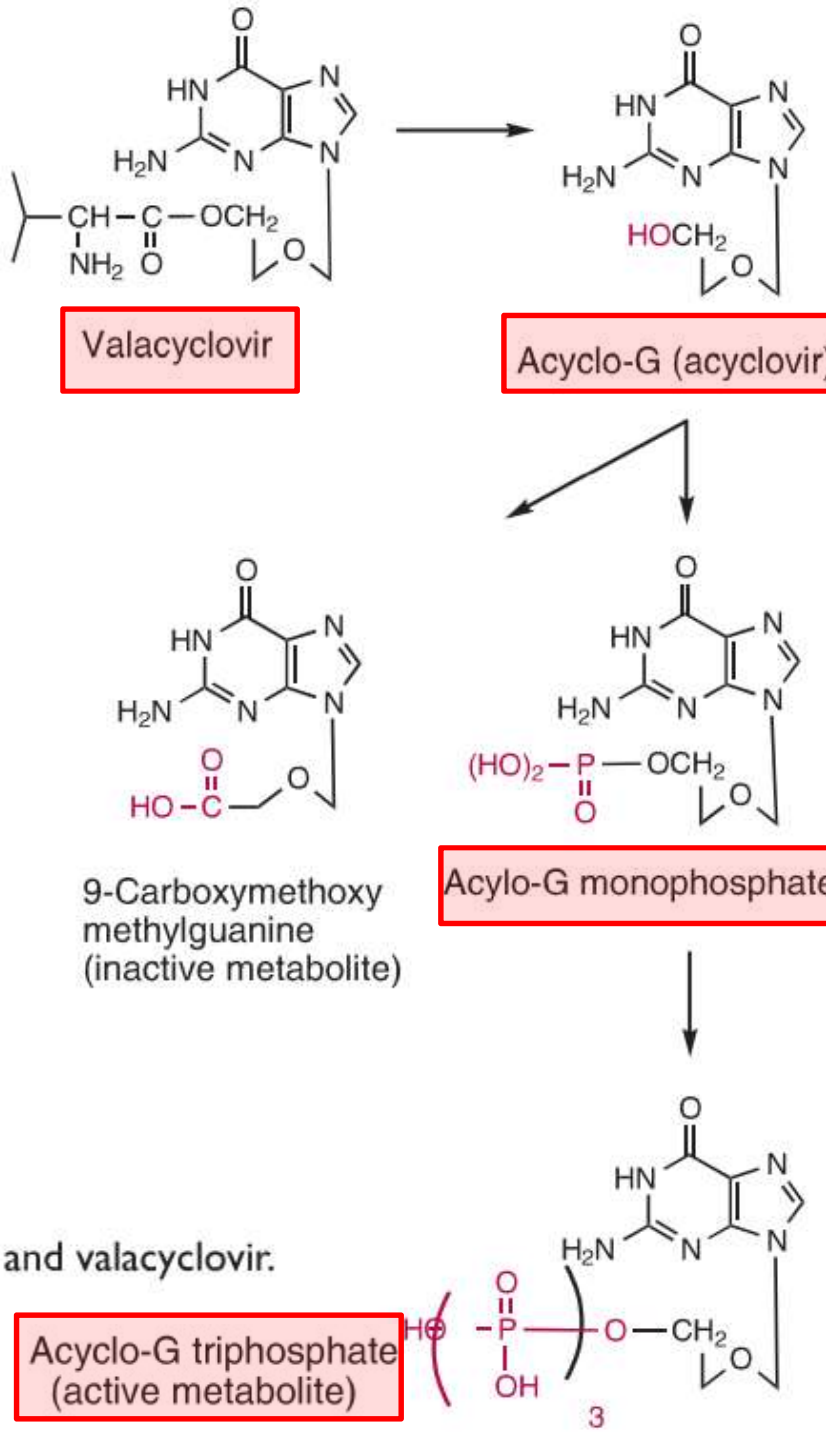
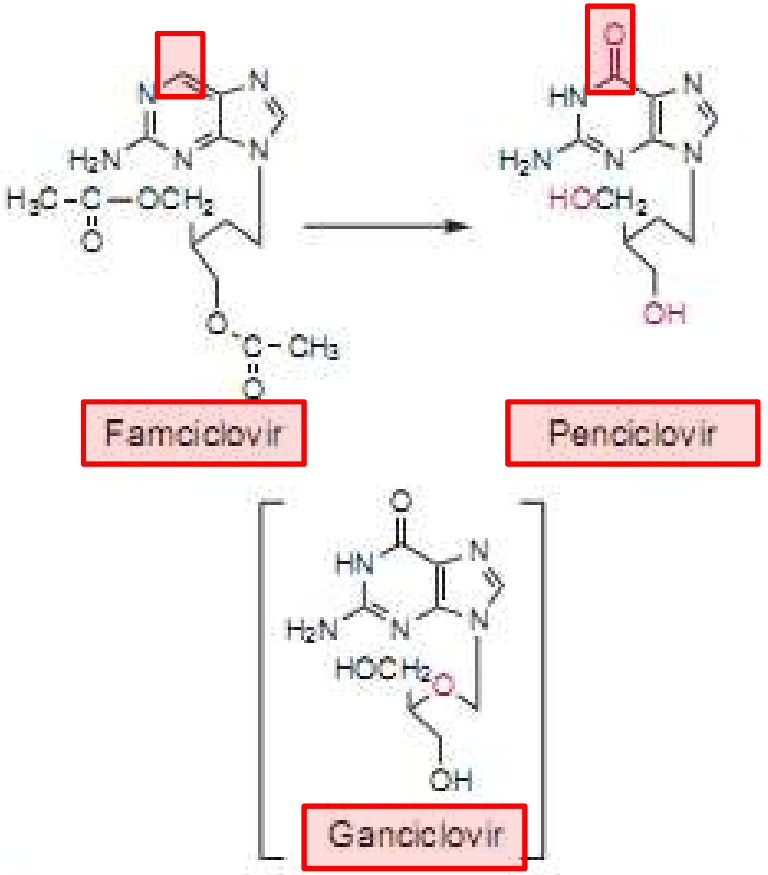


Figure 30.9 Metabolic reactions of acyclovir and valacyclovir.

2a- Acyclic Nucleoside Purine Analogues: Famciclovir

- Famciclovir: acetylated 6-deoxy-penciclovir
- ✓ 6-deoxy diacetyl ester of penciclovir
- Penciclovir: activated as triphosph(oryl)ates

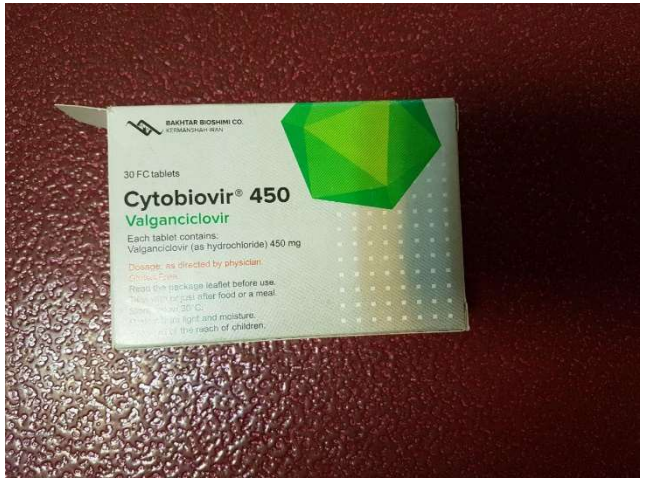


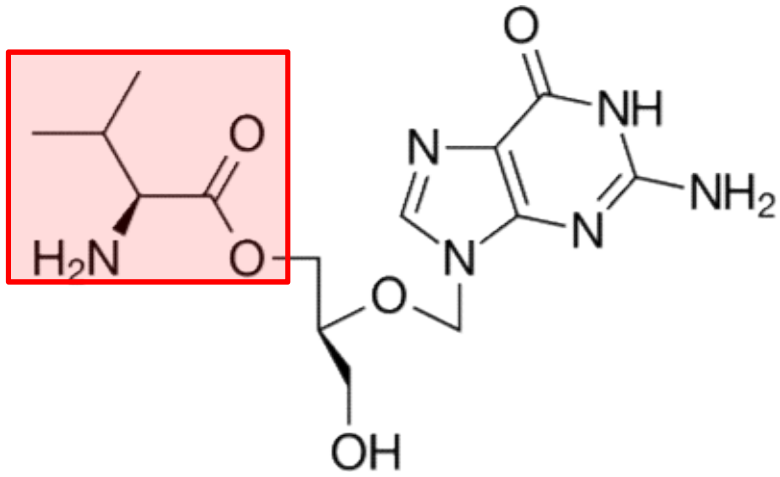
SRAm

IGURE 38.9 Metabolic activation of famciclovir.

2a- Acyclic Nucleoside Purine Analogues: Ganciclovir Analogue: Valganciclovir

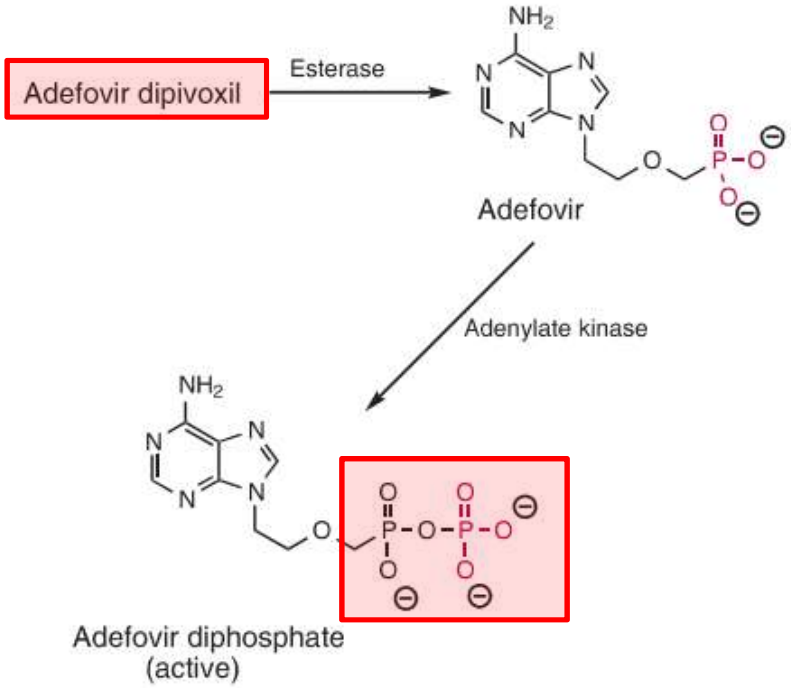
- Cytobiovir®
- What is the advantage?





2a- Acyclic Nucleoside Analogues: Adefovir

- Adenine analogue
- Prodrug: activation by adenylate kinase
- Adefovir dipivoxil: orally active



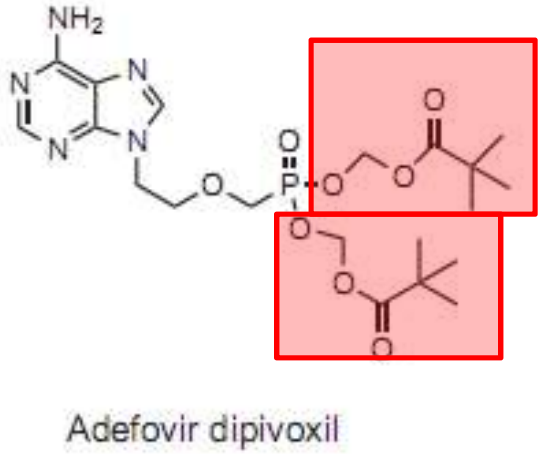


Figure 30.10 Activation of the prodrug adefovir dipivoxyl by esterase and adenylate kinase.

2b- Conventional Nucleoside Analogues

Chapter 38

Antiviral Agents and Protease Inhibitors

Patrick M. Woster

Drugs Covered in This Chapter*

CHAPTER 30

Drugs Used to Treat Viral Infections

Patrick M. Woster

2b

CONVENTIONAL NUCLEOSIDE ANALOGUES

CONVENTIONAL NUCLEOSIDE ANALOGUES

- Ribavirin
- Vidarabine

2b- Conventional Nucleoside Analogues

- SAR:
- ❖ Heterocycle ring: mimic purine/pyrimidir
- ✓ adenine; cytosine; uracil, thymine
- ✓bioisostere triazole analogues

- ❖ Sugar ring:
- ✓ ribose; deoxyribose; arabinose

- Discontinued mostly

except ribavirin

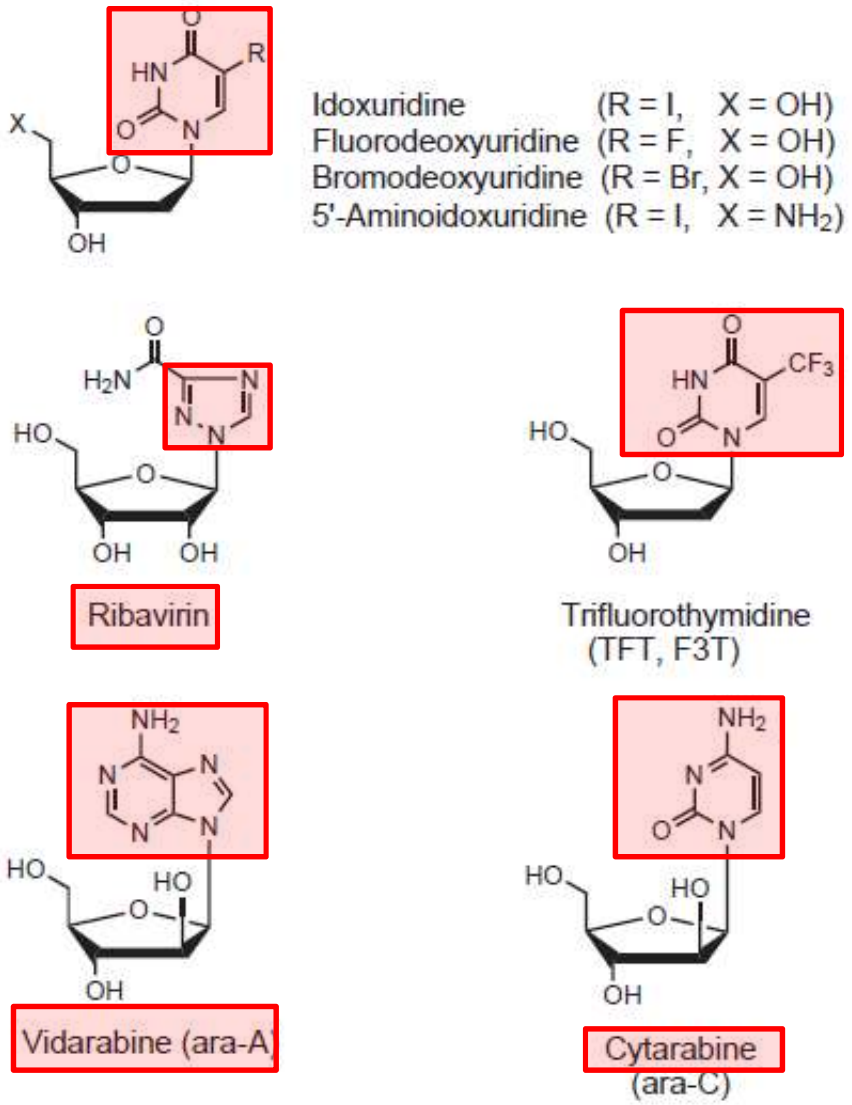


FIGURE 38.11 Agents that interfere with viral nucleic acid replication: conventional nucleosides.

2- Viral DNA Interfering Agents:
2b- Conventional Nucleoside Analogues

- Prodrug: active metabolite: triphosphate form
- MOA: three mechanisms:
- Interfering with viral DNA replication

✓ based through competitive inhibition

➢ First phosphorylated by the host cell virus encoded thymidine kinase to an active triphosphate

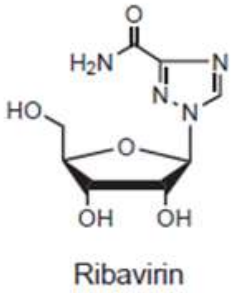
➢ Viral DNA polymerase inhibition with IC50 < cellular DNA polymerase

✓ Incorporated into viral DNA during NA synthesis: false pairing system: replaces thymidine

➢ Terminates further elongation of DNA chain

➢ When transcription occurs: faulty viral proteins: defective viral particles

2b- Conventional Nucleoside Analogues: Ribavirin



Ribavirin

- Chemistry: assumed as guanosine analogue
- ✓ ribofuranosyl-triazole-carboxamide
- Prodrug: active metabolite by adenosine kinase: tri-phosphate
- MOA: inhibit viral specific RNA polymerase
- ✓ disrupting messenger RNA & DNA synthesis

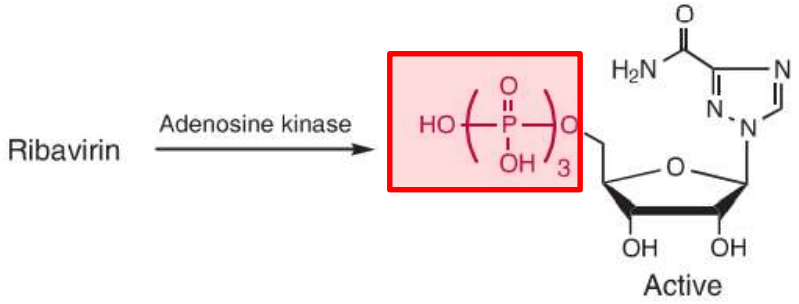


Figure 30.11 Agents that interfere with viral nucleic acid replication: conventional nucleosides.

- Dosage forms: oral ; IV; aerosol

2- Viral DNA Interfering Agents:

2c- Non-Nucleoside Analogues

Chapter 38

Antiviral Agents and Protease Inhibitors

PATRICK M. WOSTER

Drugs Covered in This Chapter*

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Drugs Used to Treat Viral Infections

Patrick M. Woster

2c

NONNUCLEOSIDE ANALOGUES

- Foscarnet
- Letermovir
- Telaprevir

2c- Non-Nucleoside Viral Replication Inhibitors

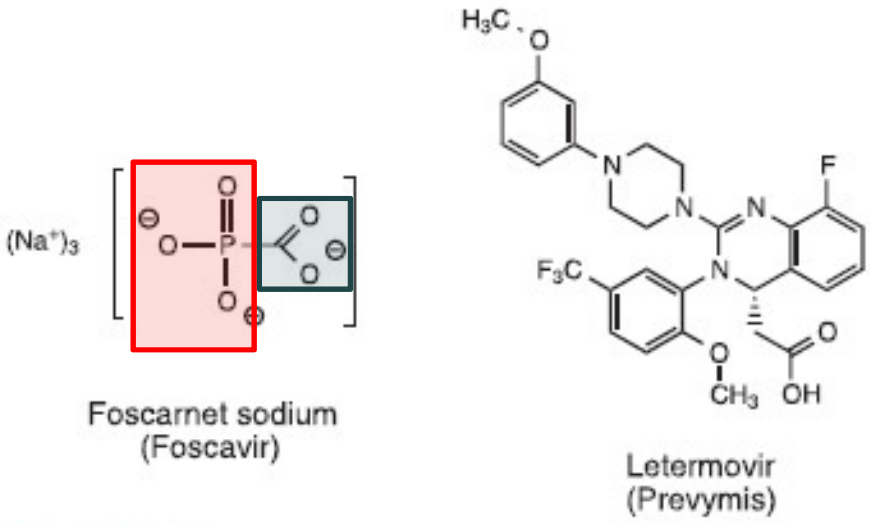
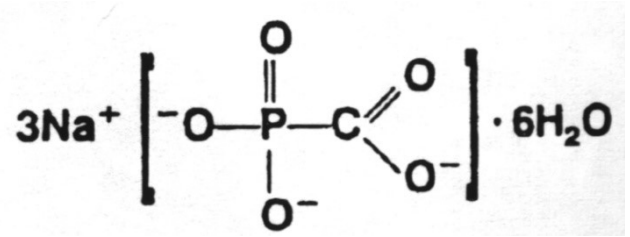


Figure 30.12 Nonnucleoside inhibitors of viral replication.

2c- Non-Nucleoside Analogues: Foscarnet

- Trisodium phospho-formate hexa-hydrate
- = Phosphono-formic acid
- Not requires phosphorylation step



- CSF & eye penetration

- Against CMV retinitis in AIDS patients
- In combination with Ganciclovir in ganciclovir resistant viruses
- In combination with zidovudine(ZDV): synergism against CMV

2- Viral DNA Interfering Agents:

2e- Endonuclease Inhibitors