Human Viruses
Structure:
- Lipid membrane envelope (from cell) enclosing nucleic acid
- Surface antigens - bind to cell receptors
- Nucleic Acid
  - DNA or RNA (not both)
  - Circular or linear
  - One or several molecules
  - Single or double-stranded
  - ~5,000 - ~200,000 bases

Antiviral therapy - General Principles
Virus is dependent on replication in host cells →
Antiviral must be selective for viral enzyme or protein, or inhibit virus-specific process
Usually antivirals inhibit replication, don’t kill virus → reliance on host immune response for ultimate virus elimination
High error rate of viral replication →
  - Rapid development of drug resistance →
  - Need to suppress virus replication rapidly and efficiently

Influenza (orthomyxovirus)
Segmented genome of 8 single-stranded viral RNAs (vRNA)
Hemagglutinin (HA) and Neuraminidase (NA) surface antigens
M1 - inner matrix protein
M2 - ion channel spans viral membrane
Transcriptase bound to each vRNA in the virion
Influenza - life cycle

Binds to sialic acid residues on cell surface
Enters cell by endocytosis, into endosome
Acidity of endosome activates M2 ion channel
H\(^+\) enters virion and destabilizes viral capsid
Viral and endosome membranes fuse
vRNA and transcriptase released into cytoplasm and transported to nucleus.

Influenza - life cycle

RNA replication -- No DNA stage
vRNA → mRNA → viral proteins (transcriptase)
vRNA → template RNA → vRNA (replicase)
Assembly at cell surface
Budding from cell membrane
Release requires sialic acid cleavage by NA

Amantadine {Symmetrel}

Structure - carbon-case amine
Discovery - large-scale screening in culture

Amantadine - mechanism

Accumulates in endosomes due to pH effects
Binds to M\(_2\) protein →
Blocks ion channel activation →
Blocks endosomal/viral membrane fusion →
Blocks viral uncoating
Amantadine - resistance
Genetic assignment of resistance to alteration in M2 protein
Virus shed from patients treated with amantadine will likely be amantadine-resistant
Amantadine-resistant virus are also rimantadine-resistant

Amantadine - Clinical Use
Dose 200 mg/day (Oral)
Only effective vs. Influenza A, not B
Prophylaxis - 50-90% decrease in infection if given prior to exposure
Alternative to vaccination
Duration of symptoms reduced by 1-2 days if given within 48 hr of onset
Effect on complications & mortality unclear

Amantadine: toxicity
CNS stimulation
Nervousness
Lack of concentration
Occasional seizures
Overdose - coma
Rimantadine - less CNS toxicity
-CHCH₃NH₂ instead of NH₂

Zanamivir (& Oseltamivir)
Neuraminidase inhibitors
Neuraminidase required for final release of virus
Effective vs. both Influenza A & B (very similar neuraminidase)
Administration
Zanamivir (Relenza) - 10 mg bid intranasal
Oseltamivir (Tamiflu) - 5 mg bid oral
Activated in liver
Reduction in duration of symptoms if given within 30 hr of infection
**Zanamivir (& Oseltamivir)**

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**Pharmacokinetics**

<table>
<thead>
<tr>
<th></th>
<th>Zanamivir</th>
<th>Oseltamivir</th>
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<tbody>
<tr>
<td>Absorption</td>
<td>4-17% of inhaled</td>
<td>75%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Minimal</td>
<td>90% activation Otherwise minimal</td>
</tr>
<tr>
<td>Half-life</td>
<td>2.5-5 hr</td>
<td>6-10 hr</td>
</tr>
<tr>
<td>Excretion</td>
<td>Renal</td>
<td>Renal</td>
</tr>
</tbody>
</table>

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**Some Miscellaneous Antivirals**

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<thead>
<tr>
<th>Virus</th>
<th>Interferon</th>
<th>Ribavirin</th>
<th>Palivizumab</th>
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<tr>
<td>Hepatitis C Virus</td>
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<tr>
<td>Respiratory Syncytial Virus</td>
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<td>Ribavirin</td>
<td>Palivizumab</td>
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**Hepatitis C Virus (flavivirus)**

**Structure:**
Envelope with inner capsid
One single-strand RNA of 9,400 bases
Dissimilar to Hepatitis A, B viruses (different families)

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**Interferon {Roferon, others}**

The body’s natural defense vs. viral infection

**Structure** - 166 amino acid protein

**Recombinant** protein made cheaply in bacteria

A **Cytokine** - signaling between cells
Induces **Antiviral State** in the cell
Inhibition of viral protein synthesis
Multiple mechanisms
Three types: alfa, beta, gamma
Interferon: 
Mechanisms of the Antiviral State

1. Protein kinase R phosphorylates eIF\(\alpha\) → Inhibition of protein chain initiation
2. dsRNA (from virus replication) → 2′-5′ oligoadenylate synthesis → Activation of ribonuclease L → mRNA degradation
3. Phosphodiesterase → tRNA degradation

Interferon - Clinical Use
Surprisingly limited, given its broad antiviral activity in cell culture
Treatment of chronic **Hepatitis C Virus**
Injection subQ or IM, 3 million units, 3× week

Interferon - Toxicities
Hematological - anemia, neutropenia
Systemic - flu-like symptoms, headache, fatigue
CNS - depression

Respiratory Syncytial Virus (RSV; paramyxovirus)
Structure:
One single-strand vRNA, 15.2 kb
**Life cycle** similar to Influenza
No DNA stage
Main cause of lower respiratory infection in infants and children - can be life-threatening

Ribavirin {Virazole}
**Structure** - a nucleoside, analogue of guanosine
Interferes with viral RNA replication
Ribavirin - Mechanism
Pairs with both C and U during replication
G:C  Rv:C  Rv:U  A:U
Partial block to replication
Ribavirin and many replication errors in new vRNA

Ribavirin - Clinical Use
For **Respiratory Syncytial Virus**
Esp. in infants & children
Aerosol 20 mg/ml, 12-18 hr/day, 3-7 days
For **Hepatitis c Virus**
1000-1200 mg/day oral  {Rebetol}
In combination with interferon ONLY
Decreased mortality for some viral hemorrhagic fevers

Ribavirin - Toxicity
Aerosol:  Conjunctival or Bronchial Irritation
(Protect health care staff)
Oral:  Hemolytic anemia

Palivizumab {Synagis}
Structure - a humanized mouse monoclonal Ab
Targets RSV for normal Ab-mediated immunity
Previous use of  RSVIG from human donors
1. Immunize mice with L glycoprotein from RSV
2. Isolate B-cell clone, clone IgG sequence
3. Use gene-splicing to replace mouse constant Ig segments with human constant segments
4. Reintroduce into mouse B cells for production
Avoid antigenicity of mouse mAb

Palivizumab - Structure
Humanized Monoclonal Antibody

Palivizumab - Clinical use
Prophylaxis against RSV for at-risk children
0-2 yrs; e.g., bronchopulmonary dysplasia
Treatment of severe RSV pneumonia in infants, premature, immunocompromised
Usually with Ribavirin
Administration - IM or IV
Toxicity - increased serum aminotransferase
**Summary**

**Amantadine**, Rimantadine  
Influenza A only,  \( R_X \) & \( P_X \)  
Inhibits uncoating, blocks M2 ion channel  
Tox: CNS stimulation, rare seizures

**Zanamavir**, Oseltamivir  
Influenza A & B  
Blocks budding, inhibits neuraminidase

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**Summary**

**Interferon alfa**  
Chronic hepatitis C  
Establishes antiviral state, inhibits translation of viral mRNA into proteins  
Tox: CNS, systemic, anemia, neutropenia

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**Summary**

**Ribavirin**  
Blocks viral RNA replication - nucleoside  
Respiratory Syncytial virus (infants)  
Hepatitis C (oral, with Interferon)  
Tox: Conjunctival or bronchial irritation

**Palivizumab**  
Ab against viral L glycoprotein (surface antigen)  
RSV  \( R_X \) & \( P_X \)  
Tox: elevated serum aminotransferase