Antiviral Agents
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Challenges to the Development of Effective Antiviral Agents

- Myriad number of agents
- Need knowledge of replication at molecular level to define targets
  - Viruses as intracellular parasites make targeting more difficult to avoid host toxicity
- Lack of culture systems for some agents hinders development
- High through-put screening plus ‘rational’ drug design are both labor intensive and expensive

Diagnosis of Viral Infections

- Clinical suspicion
  - Is syndrome diagnostic of a specific entity?
  - Is viral disease in the differential diagnosis of a presenting syndrome?
- Knowledge of appropriate specimen(s) to send
  - Blood
  - Body fluids
  - Lesion scraping
  - Tissue
  - Proper transport is essential

Herpes Zoster

Progress in Antiviral Therapy

<table>
<thead>
<tr>
<th>virus</th>
<th>Acyclovir, famciclovir, valacyclovir, ganciclovir, cidofovir, formivirsen, valganciclovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>HN-1</td>
<td>21 approved agents</td>
</tr>
<tr>
<td>Influenza</td>
<td>Amantadine, rimantadine, ribavirin, oseltamivir</td>
</tr>
<tr>
<td>Resp. syncytial virus</td>
<td>Ribavirin, RSV immune globulin, palivizumab</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>3TC, FTC, adebovir, tenofovir</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>pegIFN-ribavir</td>
</tr>
<tr>
<td>Papillomaviruses</td>
<td>IFN, tacediflur</td>
</tr>
<tr>
<td>JC virus</td>
<td>TCelebovir</td>
</tr>
<tr>
<td>Rhinoviruses</td>
<td>Tremacam (rsICAM-1)</td>
</tr>
</tbody>
</table>
Non-HIV Antiviral Therapy: Targets

- Herpesviruses
- Respiratory viruses
- Hepatitis viruses
- Others

Anti-Herpesvirus Agents

- Acyclovir
- Valacyclovir
- Famiclovir
- Ganciclovir
- Valganciclovir
- Foscarnet
- Cidofovir
- Formivirsen
- Trifluridine
- Idoxuridine

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
<th>Active Moiety</th>
<th>Target Agents</th>
<th>Route of Admin</th>
<th>Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>Acyclic nucleoside</td>
<td>Tri-phosphate</td>
<td>HSV, VZV</td>
<td>Oral, intravenous, topical</td>
<td>Renal, Neuro</td>
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<tr>
<td>Val-ACV</td>
<td>Ester prodrug of acyclovir</td>
<td>Tri-phosphate</td>
<td>HSV, VZV</td>
<td>Oral</td>
<td>Renal, Neuro</td>
</tr>
<tr>
<td>Penciclovir</td>
<td>Acyclic nucleoside</td>
<td>Tri-phosphate</td>
<td>HSV</td>
<td>Topical</td>
<td>Local irritation</td>
</tr>
<tr>
<td>Famciclovir</td>
<td>Ester prodrug of penciclovir</td>
<td>Tri-phosphate</td>
<td>HSV, VZV</td>
<td>Oral</td>
<td>Headache, nausea</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>Acyclic nucleoside</td>
<td>Tri-phosphate</td>
<td>CMV, HSV, VZV</td>
<td>Intravenous, oral, intraocular</td>
<td>Hematologic</td>
</tr>
<tr>
<td>Val-GCV</td>
<td>Ester prodrug of ganciclovir</td>
<td>Tri-phosphate</td>
<td>CMV</td>
<td>Oral</td>
<td>Hematologic</td>
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<tr>
<td>Foscarnet</td>
<td>Pyrophosphate analog</td>
<td>Parent drug active</td>
<td>CMV, HSV</td>
<td>Intravenous, Renal, metabolic</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>Nucleotide analog</td>
<td>Di-phosphate</td>
<td>CMV, HSV, HPV, pos</td>
<td>Intravenous, Renal, ocular</td>
</tr>
<tr>
<td>Formivirsen</td>
<td>Antisense oligo-RNA binds to CMV mRNA</td>
<td>Parent drug active</td>
<td>CMV</td>
<td>Intraocular, Ocular</td>
</tr>
<tr>
<td>Trifluridine</td>
<td>Nucleoside analog</td>
<td>Tri-phosphate</td>
<td>HSV keratitis</td>
<td>Topical, Ocular</td>
</tr>
<tr>
<td>Idoxuridine</td>
<td>Nucleoside analog</td>
<td>Tri-phosphate</td>
<td>HSV keratitis</td>
<td>Topical, Ocular</td>
</tr>
</tbody>
</table>

**FIGURE 53-6:** Chemical structures of antiviral agents.
Acyclovir I
- Development represents a watershed in the field of antiviral chemotherapy
- Acyclic guanosine analog
- Active vs. HSV, VZV and modestly CMV
- Mechanism of action
  - Preferentially taken up by virally infected cells
  - Monophosphorylated by virally encoded thymidine kinases
  - Di- and triphosphorylation completed by cellular kinases
  - ACV-TP is the active moiety
    - Competitive inhibitor of viral DNA polymerase
    - Cellular DNA polymerases much less susceptible to inhibition
    - Leads to viral DNA chain termination

Acyclovir: Mechanism of Action

Anti-Respiratory Virus Agents
- Amantadine
- Rimantadine
- Zanamivir
- Oseltamivir
- Ribavirin

Amantadine and Rimantadine
- Tricyclic amines
- Active vs. influenza A only at clinically achievable concentrations
- Mechanism of action
  - Interference with function of viral M2 protein
    - M2 protein acts as an ion channel facilitating the hydrogen ion mediated dissociation of the matrix protein from the nucleocapsid
- Pharmacology:
  - Orally bioavailable
  - Amantadine: renal excretion
  - Rimantadine: hepatic metabolism and renal excretion
- Major toxicity
  - Neurotoxicity: amantadine > rimantadine
- Useful for treatment and prophylaxis of influenza A infections
- Resistance mediated by mutations in M2 coding region

Acyclovir II
- Pharmacology
  - Administered by oral, intravenous and topical routes
  - Oral bioavailability 15-30%
  - T1/2 3 hrs
  - Primarily renally excreted
- Toxicities
  - Headache, nausea
  - Renal
  - Neurologic
- Resistance
  - Mediated by mutations in viral thymidine kinase and/or viral DNA polymerase genes
  - TK-deficient and TK altered virus can be produced
  - Clinically significant infections can be caused by drug resistant HSV and VZV

FIGURE 11-7. Chemical structures of amantadine and rimantadine.
Influenza Virus Replication Cycle

Uncoating of Influenza Virus

Zanamivir and Oseltamivir I

Zanamivir and Oseltamivir II

Zanamivir and Oseltamivir III
### Zanamivir and Oseltamivir IV

**Indications**
- Treatment of influenza A and B within 24-48 hrs of symptom onset
- Prophylaxis
- N.B.: Neither drug interferes with antibody response to influenza vaccination

**Resistance**
- Reports beginning to appear in literature

### Ribavirin I

**Synthetic nucleoside analog**
- Active vs. broad range of RNA and DNA viruses
  - Flavi-, paramyxo-, bunya-, arena-, retro-, herpes-, adeno-, and posviruses
- Mechanism of action complex
  - Triphosphorylated by host cell enzymes
    - For influenza
      - Ribavirin-TP interferes with capping and elongation of mRNA and may inhibit viral RNA polymerase
    - For other agents
      - Ribavirin-MP inhibits inosine-5'-monophosphate dehydrogenase depleting intracellular nucleotide pools, particularly GTP

### Anti-Hepatitis Agents

**Hepatitis B**
- Lamivudine
  - Nucleoside analog first developed for HIV
  - Lower dose used for HBV (100 mg/day)
- Adefovir dipivoxil
  - Nucleoside analog first developed for HIV but nephrotoxic at higher doses
  - Approved for HBV at lower dose (10 mg/day)
- Entecavir
  - Most recently approved anti-HBV agent

**Hepatitis C**
- Interferon-alpha (pegylated)
- Ribavirin

### Ribavirin II

**Pharmacology**
- Aerosol and oral administration
- Hepatically metabolized and renally excreted

**Major toxicity**
- Anemia

**Indications**
- Aerosol treatment of RSV in children
- Oral treatment of HCV (in combination with pegylated IFN-alpha)

### Interferons I

**Part of cytokine repertoire**
- Possess antiviral, immunomodulatory and antiproliferative effects

**Types**
- Alpha/Beta (leukocyte/fibroblast)
  - Coding genes located on chromosome 9
  - At least 24 subtypes of alpha, 1 of beta
- Gamma
  - Coding gene located on chromosome 12
  - 1 subtype

### Interferons II: Mechanism of Action

**Act by inducing an antiviral state within cells**
- Bind to specific receptors on cell surface
- Receptor associated tyrosine kinases activated
  - Tyk2 and JAK1 for alpha and beta
  - JAK1 and JAK2 for gamma
- Cytoplasmic proteins (STAT) phosphorylated
  - Move to nucleus and bind to cis-acting elements in promoter regions of IFN inducible genes
Interferons III: Mechanisms of Action

- **Synthesis of 2'-5' oligoadenylate synthetase**
  - Activated by dsRNA
  - Convert ATP into a series of 2'-5' oligo(A)s
  - These activate RNase L which cleaves single stranded mRNAs

- **Synthesis of dsRNA-dependent protein kinase (PKR, eIF-2 kinase)**
  - PKR activated by dsRNA and autophosphorylated
  - In turn, phosphorylates alpha subunit of eukaryotic initiation factor 2
  - Protein synthesis is inhibited

- **Induction of a phosphodiesterase with inhibition of peptide chain elongation**
- **Synthesis of MxA protein which can bind to cytoskeletal proteins and inhibit viral transcriptases**
- **Induction of nitric oxide by gamma IFN in macrophages**

Interferons IV

- **Pharmacology**
  - Injected IM or SC
  - Renal excretion and inactivation in body fluids/tissues

- **Toxicities**
  - Flu-like symptoms
  - Hematologic effects
    - Leukopenia and thrombocytopenia
    - Neuropsychiatric effects
- **Antiviral indications**
  - IFN-alpha (pegylated) SC for HCV (in combination with ribavirin)
  - Intralvesional for condyloma acuminata
- Resistance can develop
  - Mutations in NS5A gene of HCV described

Passive Immunization for Viral Infections I

- **Human immune globulin**
  - Prevention of hepatitis A
  - Prophylaxis and treatment of enterovirus infections in neonates and in children with antibody deficiency
  - Treatment of B19 parvovirus infection in immunodeficient individuals

- **CMV immune globulin**
  - Prophylaxis of CMV in solid organ transplant recipients
  - Treatment of CMV pneumonia in combination with ganciclovir

- **Hepatitis B immune globulin**
  - Prophylaxis of hepatitis B infection

- **Rabies immune globulin**
  - Post-exposure prophylaxis for rabies (in combination with rabies vaccine)

Passive Immunization for Viral Infections II

- **Respiratory syncytial virus immune globulin**
  - Prevention of complications of RSV infection in young children

- **Palivizumab**
  - Humanized RSV monoclonal antibody
  - Prevention of complications of RSV infection in young children

- **Varicella-zoster immune globulin**
  - Prevention of varicella infection in immunocompromised children and adults within 96 hours of exposure

- **Vaccinia immune globulin**
  - Available from CDC for complications of smallpox (vaccinia) vaccination

Conclusions

- **Field of antiviral therapy has matured dramatically in past 30 years**
- **Greatest progress made for**
  - Herpesviruses
  - HIV
  - Respiratory viruses
  - Hepatitis viruses
- **Preventive vaccination remains the key to global control of viral infections**