Antivirals

PHRM 203
Allison Beale
Overview

• Agents to treat
  – Respiratory viruses
  – Herpes and cytomegalovirus
  – Locally active antivirals (*Herpes & Papilloma viruses*)
  – HIV and AIDS
  – Hepatitis viruses
# Types of Influenza Viruses

**Orthomyxoviruses**

<table>
<thead>
<tr>
<th>Virus</th>
<th>Subtype</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td>Hemagglutinin (H) - 16 subtypes plus various strains</td>
<td>Natural host = birds. May infect humans, pigs, other mammals. Rapidly mutate. <strong>H1N1</strong> = recent “swine” flu. <strong>H5N1</strong> = potential pandemic “avian” flu</td>
</tr>
<tr>
<td></td>
<td>Neuraminidase (N) - 9 subtypes plus various strains</td>
<td></td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>No subtypes, various strains</td>
<td>Moderate mutation rate – humans only</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td>No subtypes or strains</td>
<td>Minor cause of disease – humans, swine</td>
</tr>
</tbody>
</table>
Structure of Influenza A viron

8 RNA strands code for

- **HA** - surface fusion glycoprotein allows entrance, antigenic
- **NA** - allows exit
- **NP** - nucleoprotein
- **M1** - matrix protein
- **M2** - matrix protein
- **NS1, NEP** - Non-structural proteins
- **PA, PB1, PB1-F2PB2** - RNA polymerases

www.influenzareport.com/ir/images/virus.jpg
# Influenza Antivirals

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amantidine (Symmetrel)</td>
<td>Parkinson’s, Influenza A, drug-induced extrapyramidal symptoms. Used off label to treat fatigue associated with MS and sex dysfunction associated with SSRIs</td>
</tr>
<tr>
<td>Oseltamivir (Tamiflu)</td>
<td>Influenza including Avian flu</td>
</tr>
<tr>
<td><strong>Ribavirin</strong></td>
<td>Chronic hepatitis C (only in combo therapy), Respiratory syncytial virus (RSV- kids only). Off label: influenza A and herpes</td>
</tr>
<tr>
<td>Rimantadine (Flumadine)</td>
<td>Influenza A</td>
</tr>
<tr>
<td>Zanamivir (Relenza)</td>
<td>Influenza</td>
</tr>
</tbody>
</table>
## Influenza Antiviral Mechanisms

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
</tr>
</thead>
</table>
| Amantidine (Symmetrel) | Antiviral: $\otimes$M2, an ion channel  
Anti parkinsonism: NMDA antagonist, anti-ACh, stimulates release of DA & NE from neurons |
| Oseltamivir (Tamiflu)  | Neuraminidase inhibitor                                                   |
| Rimantadine (Flumadine)| Antiviral: $\otimes$M2, an ion channel                                   |
| Zanamivir (Relenza)    | Neuraminidase inhibitor                                                   |
Amantadine

• **Warnings**
  – Suicide and overdose (lethal as low as 1gm)
  – May trigger epileptic attack
  – Congestive heart disease or peripheral edema may worsen
  – May cause
    • Mydriasis, don’t give to closed angle glaucoma patients
    • Parkinsonian crisis (rebound)
    • *Neuroleptic Malignant Syndrome*
    • Orthostatic hypotension

*Flu dosage in kids <10 yrs max. 150mg/day; in kids >10yrs = 200mg/day; in adults >65 yrs = 100mg/day*
Neuroleptic Malignant Syndrome

- Rebound effect of Amantidine use, characterized by:
  - Inability to regulate BT: fever or hyperthermia
  - Neurologic findings including muscle rigidity, involuntary movements, altered consciousness; mental status changes
  - Autonomic dysfunction, tachycardia, tachypnea, hyper- or hypotension
  - Laboratory findings such as creatine phosphokinase elevation, leukocytosis, myoglobinuria, and increased serum myoglobin

- Usually caused by DA receptor blockade in striatum
  - A potential problem with neuroleptic use
Oseltamivir

• Prodrug, co-administration with probenecid (reduces renal excretion)
  – Probenecid (Benuryl) 🍒
    • ↑Uric acid excretion in urine
    • Used to treat gout
    • Can double circulating levels of oseltamivir

• (O) May cause hallucinations and psychological problems
Herpes viruses

Herpes simplex virus 1

Varicella zoster virus, VZV
Shingles in a 7 yr old

www.microbiologybytes.com/blog/2008/07/14/cold-sore-secrets-revealed/

www.lib.uiowa.edu/hardin/md/dermatlas/shingles.html
Herpes

• Large family of DNA viruses
  – Life long infection
    • Mimic human interleukin 10
      – Anti-inflammatory cytokine
    • Down regulate major histocompatibility complex
  – Virus infects by binding to glycoprotein receptors on cell surface
  – Reactivation of latent virus
    • E.g., Shingles years after chicken pox (VZV)
# Herpes

<table>
<thead>
<tr>
<th>Name</th>
<th>Target</th>
<th>Latent site</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSV1, Herpes simplex</td>
<td>Mucoepithelial, 1(^o) oral</td>
<td>Neurons</td>
</tr>
<tr>
<td>HSV2</td>
<td>Mucoepithelial, 1(^o) genital</td>
<td>Neurons</td>
</tr>
<tr>
<td>VZV, Varicella zoster</td>
<td>Mucoepithelial</td>
<td>Neurons</td>
</tr>
<tr>
<td>EBV, Epstein-Barr</td>
<td>B &amp; epithelial cells</td>
<td>B cells</td>
</tr>
<tr>
<td>CMV, Cytomegalovirus (<em>Note: present in everyone</em>)</td>
<td>Monocyte, lymphocyte, epithelial cells</td>
<td>Monocyte, lymphocyte, epithelial cells</td>
</tr>
<tr>
<td>Roseoloviruses</td>
<td>T cells and ?</td>
<td>T cells</td>
</tr>
<tr>
<td>KSHV, Kaposi’s sarcoma</td>
<td>Lymphocytes and other cells</td>
<td>B cells</td>
</tr>
</tbody>
</table>
Herpes & associated diseases

- Alzheimer’s
  - HSV DNA in plaques
- Atherosclerosis
  - HSV initiate endothelium damage?
- Cholangiocarcinoma
  - EBV DNA present
- Crohn’s
  - HSV DNA associated
- Chronic fatigue syndrome
  - Roseolovirus associated
- Dysautonomia
  - Several HHV
- Fibromyalgia
  - Roseolovirus
- Multiple sclerosis
  - Roseolovirus
- Pancreatic cancer and pancreatitis
  - Oncolytic activity shown for Herpes saimiri (a primate virus)
## Herpes and Cytomegalovirus

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir (Zovirax)</td>
<td>Herpes simplex virus (HSV), Varicella Zoster virus (VZV)</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>IV only for CMV retinitis in AIDS patients</td>
</tr>
<tr>
<td>Famiclovir (Famvir)</td>
<td>HSV (penciclovir prodrug, (\Theta)’s viral DNA polymerase. Penciclovir is a guanine analog)</td>
</tr>
<tr>
<td>Foscarnet (Foscavir)</td>
<td>CMV retinitis &amp; acyclovir-resistant HSV in immunocompromised patients</td>
</tr>
<tr>
<td>Ganciclovir (Vitrasert)</td>
<td>Chronic CMV, implant for CMV retinitis</td>
</tr>
<tr>
<td>Valacyclovir (Valtrex)</td>
<td>HSV &amp; VZV (prodrug of acyclovir)</td>
</tr>
<tr>
<td>Valganciclovir</td>
<td>CMV retinitis in AIDS (prodrug of ganciclovir)</td>
</tr>
</tbody>
</table>
# Herpes and Cytomegalovirus

<table>
<thead>
<tr>
<th>Drug</th>
<th>Activation and action</th>
</tr>
</thead>
</table>
| Acyclovir (Zovirax), Famciclovir (Famvir), Ganciclovir (Vitraset), Valacyclovir (Valtrex), Valganciclovir | 1. Viral TK to mono, by cell TK to \( \mathbb{P}_3 \)  
2. Compete for RT binding site  
3. Incorporated into viral DNA  
4. Ends DNA elongation (not famciclovir) |
| Cidofovir (Vistide)                       | Enters cell as mono, then cell TK to \( \mathbb{P}_3 \)                                                                                                                                                                   |
| Foscarnet (Foscavir)                      | No viral activation needed, directly \( \Theta \)’s DNA polymerase by \( \otimes \) ing the pyrophosphate binding site. This \( \otimes \)’s the addition of deoxynucleotides because the pyrophosphate can not be cleaved from the deoxynucleotide-\( \mathbb{P}_3 \) Therefore, no elongation. |
Acyclovir

- Synthetic guanosine nucleoside analogue
- Indicated and used to treat
  - Herpes Simplex Virus, HSV-1
    - Cold sores
  - HSV-2
    - Genital herpes
  - Varicella-Zoster Virus (VZV)
    - Herpes virus that causes chicken pox
    - Used to treat Shingles as well as chicken pox
Acyclovir

- HSV Δ’s acyclovir to active form that also acts on HIV
  - Mechanism of action
    - HSV thymidine kinase phosphorylates acyclovir to acyclo-GMP
    - Cellular TK then phosphorylates it to acyclo-GTP
    - Incorporated as a substrate into viral DNA, acyclo-GTP terminates the DNA chain. Viral enzymes can’t fix chain.
    - Thus, acyclo-GTP Ω’s viral reverse transcriptase (a DNA polymerase)
  - Resistance
    - Δ’s in Thymidine Kinase and/or DNA polymerase (both coded by the virus)
      - TK phosphorylates the acyclovir
      - DNA polymerase synthesizes new DNA from viral RNA strand
  - Pharmacokinetics
    - Probenicid co-administered to slow renal excretion
    - Has caused fatal renal failure
A Beale  PHRM 203 Antivirals  18

Acyclovir mechanism

1. Viral Reverse Transcriptase (RT) - competes with native substrate, dGTP

2. DNA chain elongation - it's not the native substrate, so it terminates DNA chain & Viral enzymes can't fix the error

http://depts.washington.edu/hivaids/derm/case2/fig1d.html
Ganciclovir

• **Indications**
  – CMV retinitis in AIDS
  – CMV in organ transplant patients
  – Off label other CMV infections

• **Mechanism**
  – θ’s viral DNA polymerase
  – Insertion into viral DNA
Ganciclovir

• Boxed warnings
  1. May be carcinogenic, teratogenic and cause aspermatogenesis
  2. Granulocytopenia, anemia and thrombocytopenia common
  3. Oral formulations associated with rapid progression of CMV retinitis and should only be used for maintenance in patients needing to avoid daily injections
Foscarnet Sodium

- Injection only

- Indications:
  1. CMV retinitis in AIDs patients
  2. Mucocutaneous acyclovir-resistant HSV infections

- Boxed warnings:
  1. Renal toxicity
  2. May cause seizures (due to changes in electrolytes)
  3. Only for use in Immunocompromised CMV and acyclovir-resistant HSV patients
Locally active antiviral agents: 
**Herpes**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docosanol (Abreva)</td>
<td>Oral and facial herpes simplex</td>
</tr>
<tr>
<td></td>
<td>Topical</td>
</tr>
<tr>
<td>Fomivirsen (Vitravene)</td>
<td>Ophthalmic injection for <strong>CMV retinitis</strong> in HIV</td>
</tr>
<tr>
<td>Idoxuridine (Dendrid)</td>
<td>Ophthalmic solution for herpes simplex keratitis</td>
</tr>
</tbody>
</table>
Docosanolol (Abreva)

• Saturated fatty acid
  – May work by Θ’ ing viral fusion
  – Isolated from various plants including canola and peanuts

• 1st OTC antiviral (2000)
**Locally active antiviral agents:**

*Herpes & Papilloma viruses*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Imiquimod</strong> <em>(Aldara)</em></td>
<td>Genital and perianal warts, as well as various skin cancers, etc.</td>
</tr>
<tr>
<td><strong>Penciclovir</strong> <em>(Denavir)</em></td>
<td>Herpes labialis on face and lips</td>
</tr>
<tr>
<td><strong>Trifluridine</strong></td>
<td>Ophthalmic ointment for herpes simplex eye infections</td>
</tr>
<tr>
<td><strong>Vidarabine</strong> <em>(Vera-A)</em></td>
<td>Ophthalmic for herpes simplex infections unresponsive to idoxuridine</td>
</tr>
</tbody>
</table>
Imiquimod (Aldara)

• Mechanism for viral antiproliferative effects unknown
  – It does ↑ opioid growth factor receptor levels
    • This effect is required for antiviral activity
    • OGF is a negative regulator of cell proliferation
      – Embryonic development
      – Wound repair
      – Certain cancers
HIV AIDS

Normal retina

Retinas affected by CMV in HIV patient

www.stlukeseye.com/conditions/CMV.asp
HIV AIDs

- No vaccine or cure
- 2007 - 33.2 M people living with HIV
- Initial symptoms flu-like, then long latency
- Lots of opportunistic infections
- $\text{CD}_4^+$ T cells, dendritic cells and macrophages affected
- Genetic susceptibility differences

Kaposi’s sarcoma - NIH Image
HIV AIDS
Six major classes of HIV antiretrovirals

1. Nucleoside reverse transcriptase inhibitors - NRTIs
2. Nonnucleoside RTIs - NNRTIs
3. Protease inhibitors - PIs
4. Fusion inhibitors - FI
5. Integrase inhibitors - II
6. Chemokine receptor (CCR5) antagonists

Oral candidiasis (thrush) in HIV patient

www.lib.uiowa.edu/hardin/Md/cdc/6067.html
# HIV Antiretroviral Mechanisms

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>Incorporated into DNA chain ( \Theta ) ing reverse transcription and further elongation</td>
</tr>
<tr>
<td>NNRTI</td>
<td>( \Theta ) Reverse transcriptase</td>
</tr>
<tr>
<td>PI</td>
<td>( \Theta ) Protease ( \otimes ) ing viral particle assembly</td>
</tr>
<tr>
<td>II</td>
<td>( \Theta ) Integrase ( \otimes ) ing viral DNA incorporation into cell DNA</td>
</tr>
<tr>
<td>FI</td>
<td>( \otimes ) Entry, binding or fusion of virus to cell via several targets</td>
</tr>
<tr>
<td>CCR5</td>
<td>( \otimes ) Entry by ( \Theta ) ing a receptor used by the virus to bind cell</td>
</tr>
<tr>
<td>Step</td>
<td>Inhibitors</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Virus attachment</td>
<td>Anionic polymers</td>
</tr>
<tr>
<td>Virus entry</td>
<td>CD4 inhibitors, chemokine receptor inhibitors (CCR5), FI</td>
</tr>
<tr>
<td>Reverse transcription</td>
<td>NRTIs, NNRTIs</td>
</tr>
<tr>
<td>Integration of viral DNA into host genome</td>
<td>Integrase inhibitors</td>
</tr>
<tr>
<td>Transcription and translation</td>
<td></td>
</tr>
<tr>
<td>Proteolytic processing of viral proteins</td>
<td>PIs</td>
</tr>
<tr>
<td>Budding of new virus particles</td>
<td></td>
</tr>
<tr>
<td>Step 1: Virus attachment ( \Downarrow )</td>
<td>Anionic polymers</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Step 2: Virus entry ( \Downarrow )</td>
<td>Maraviroc (CCR5), Enfuvirtide (FI)</td>
</tr>
<tr>
<td>Step 3: Reverse transcription ( \Downarrow )</td>
<td>Efavirenz, Nevirapine, or tenofovir + emtricitabine</td>
</tr>
<tr>
<td>Step 4: Integration of viral DNA into host genome ( \Downarrow )</td>
<td>None available</td>
</tr>
<tr>
<td>Step 5: Transcription and translation ( \Downarrow )</td>
<td></td>
</tr>
<tr>
<td>Step 6: Proteolytic processing of viral proteins ( \Downarrow )</td>
<td>Atazanavir, Darunavir, Fosamprenavir, Lopinavir</td>
</tr>
<tr>
<td>Step 7: Budding of new virus particles</td>
<td></td>
</tr>
</tbody>
</table>
### Reverse Transcriptase Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>All are PO</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz (Sustiva)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ee FAV e renz</td>
<td></td>
<td>HAART in adults and kids</td>
</tr>
<tr>
<td>Emtricitabine (Emtriva)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Em trye SYE ta been</td>
<td></td>
<td>HAART &gt;8 yrs old</td>
</tr>
<tr>
<td>Nevirapine (Viramune)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ne VYE ra peen</td>
<td></td>
<td>HAART in adults and kids</td>
</tr>
<tr>
<td>Tenofovir (Viread)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ten OH foh veer</td>
<td></td>
<td>HAART in adults &amp; Hepatitis B</td>
</tr>
<tr>
<td>Zidovudine (INN) or azidothymidine (AZT)</td>
<td></td>
<td>HAART in pregnant women and adult accidental exposures</td>
</tr>
</tbody>
</table>

**HAART - Highly Active Antiretroviral Therapy**

**INN = International Non-proprietary Name**
Types of RTIs

RTIs are basically fake nucleosides

<table>
<thead>
<tr>
<th>Drug</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz and Nevirapine</td>
<td>Non-nucleoside reverse transcriptase inhibitors (NNRTIs) - bind to a different location than NARTIs or NtARTIs</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Nucleoside analogue (NARTIs or NRTIs) - cytidine</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Nucleotide analogue (NtARTIs) - adenosine</td>
</tr>
</tbody>
</table>

A problem with RTIs is that they cause mitochondrial toxicity that can lead to lactic acidosis, symptoms of which include: tiredness, muscle pain, nausea, vomiting, GIT pain, anorexia and shortness of breath.

They also cause body fat alterations (lipodystrophy) & altered lipid metabolism.
Nucleosides

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir (Ziagen) - guanosine</td>
<td></td>
</tr>
<tr>
<td>Didanosine (Videx) - adenosine</td>
<td>Part of HAART for HIV</td>
</tr>
<tr>
<td>Lamivudine (Epivir) - cytidine</td>
<td></td>
</tr>
<tr>
<td>Stavudine (Zerit) - thymidine</td>
<td></td>
</tr>
<tr>
<td>Tenofovir (Viread) - adenosine</td>
<td></td>
</tr>
<tr>
<td>Zidovudine (Retrovir) - thymidine</td>
<td>Note: don’t combine Stavudine with Zidovudine, they compete for activation</td>
</tr>
</tbody>
</table>
# Protease Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir (Reyataz)</td>
<td>Part of HAART</td>
</tr>
<tr>
<td>Darunavir (Prezista)</td>
<td>All boosted with <em>Ritonavir</em></td>
</tr>
<tr>
<td>Fosamprenavir (Lexiva, Telzer) prodrug of amprenavir</td>
<td></td>
</tr>
<tr>
<td>Ritonavir (Norvir)</td>
<td>P450↓</td>
</tr>
</tbody>
</table>

*Boosting is a result of the inhibition of CYP3A4, resulting in higher circulating levels of other PIs.*

**PIs stimulate liver triglyceride synthesis, leading to dyslipidemia that is a hallmark metabolic dysfunction in AIDs patients taking PIs**
# Fusion Inhibitor

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enfuvirtide (Fuzeon)</td>
<td>Part of HAART in HIV patients with evidence of HIV replication despite antiretroviral therapy</td>
</tr>
</tbody>
</table>
Maraviroc acts to block a chemokine receptor on cells that HIV uses for entry. HIV can use another receptor, so a screening test must be run to see if Maraviroc will be effective in a given patient.
Combos

• Initial regimens
  – Efavirenz + zidovudine + lamivudine
  – Efavirenz + tenofovir + emtricitabine (= Atripla®)
  – Lopinavir boosted with ritonavir + zidovudine + lamivudine
  – Lopinavir boosted with ritonavir + tenofovir + emtricitabine

• Fixed dose combos
  – Tenofovir + emtricitabine = Truvada®
Viral Hepatitis

- Liver inflammation due to viral infection
  - A - E, unrelated viruses with liver tropism
    - 95% of acute hepatitis
  - Other viruses
    - Yellow fever
    - Herpes family
      - Herpes simplex
      - Cytomegalovirus
      - Epstein-Barr virus

Jaundice
## Hepatitis A-E viruses

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transmission</strong></td>
<td>Fecal oral</td>
<td>Blood-borne</td>
<td>Blood-borne</td>
<td>Only infects with B</td>
<td>Fecal oral</td>
</tr>
<tr>
<td><strong>Incubation (days)</strong></td>
<td>15-45 Acute only</td>
<td>45-160 Acute &amp; chronic → cancer</td>
<td>15-150 Mostly chronic → cancer</td>
<td>30-60 Like B</td>
<td>15-60 Acute only but dangerous to pregnant women</td>
</tr>
<tr>
<td><strong>Prevalence</strong></td>
<td>1.4M/yr</td>
<td>2B infected at some time</td>
<td>150M infected at some time</td>
<td>15M infected</td>
<td>20M/yr</td>
</tr>
<tr>
<td><strong>Vaccine?</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No — but curable with interferon + ribaviron</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

A Beale

PHRM 203 Antivirals
# Hepatitis B treatment with RTIs

*Hepatitis B = 10th leading cause of death worldwide. 10’s of Millions infected.*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>All are PO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adefovir (Hepsera)</td>
<td>Treatment of chronic HBV with active viral replication and persistent elevations in liver enzymes</td>
<td></td>
</tr>
<tr>
<td>Entecavir (Baraclude)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamivudine (Epivir)</td>
<td>BOXED WARNINGS</td>
<td></td>
</tr>
<tr>
<td>Telbivudine (Tyzeka)</td>
<td>1. Lactic acidosis with hepatomegaly and steatosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Severe rebound</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Nephrotoxicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Resistance to RTI in HIV</td>
<td></td>
</tr>
</tbody>
</table>

*la-MI-vue-deen & tel BIV yoo deen*
Hepatitis B treatment with Interferon

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>IM or SC (in the evening if possible)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon alfa 2b (Intron A)</td>
<td>Treatment of chronic HBV with active viral replication and persistent elevations in liver enzymes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BOXED WARNINGS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>May cause life threatening:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Neuropsychiatric (suicide) up to 30%!</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Autoimmune disorders</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Ischemic disorders</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Infectious disorders</td>
<td></td>
</tr>
</tbody>
</table>

Pegylated interferon alfa-2a (Pegasys)
## Hepatitis C treatment with Interferon and ribavirin

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon alfa 2b (Intron A)</td>
<td>Treatment &amp; potentially CURE of chronic Hepatitis C with active viral replication and persistent elevations in liver enzymes</td>
</tr>
<tr>
<td>Pegylated interferon alfa-2a (Pegasys)</td>
<td>Interferon BOXED WARNINGS, on previous slide</td>
</tr>
<tr>
<td>Ribavirin (Rebetol)</td>
<td>Nucleoside analog - unknown mech.</td>
</tr>
</tbody>
</table>

**Ribavirin BOXED WARNINGS**

1. CAN NOT USE ALONE
2. Hemolytic anemia possible
3. Teratogen and fetotoxic