Therapeutic Interventions Against HIV

- Restoration of the immune system
  - Immunomodulators ie. interleukin-2

- Vaccination to stimulate immune response

- **Inhibition of viral replication**
  - *Most* clinically successful strategy to date

Therapeutic Interventions

- Antiretroviral (ARV) agents = drugs used to inhibit HIV replication

- 2 primary groups of FDA approved drugs:
  - Reverse transcriptase inhibitors (RTIs)
    - Nucleoside/nucleotides (NRTIs)
    - Non-nucleoside (NNRTIs)
  - Protease inhibitors (PIs)
What to Know…

- Available antiretroviral agents
  - Mechanism of action
  - Current dosing strategies
  - Side effects
  - Common drug-drug interactions
- Department of Health & Human Services (DHHS) Treatment Guidelines 2002
  - Initiating & changing treatment
  - Medication adherence
  - Overall goals of therapy

Nucleoside Reverse Transcriptase Inhibitors

- Chemical derivatives of purine - & pyrimidine based nucleosides & nucleotides (n=7)
  - Thymidine analogs: zidovudine, stavudine
  - Cytosine analogs: lamivudine, zalcitabine
  - Inosine derivative: didanosine
  - Guanosine analog: abacavir
  - Adenosine derived nucleotide: tenofovir
Nucleoside Reverse Transcriptase Inhibitors

- **Prodrugs**
  - Require intracellular phosphorylation to a 5’ triphosphate moiety to be active
    - Cytoplasmic & mitochondrial kinases & phosphotransferases

- **Mechanism of action**
  - 5’ triphosphate competes with endogenous deoxynucleotides for reverse transcriptase
  - Prematurely terminates viral DNA elongation

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### Adult Antiretroviral Arsenal - 2003

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Dose</th>
<th>Schedule</th>
<th>Pills/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>abacavir</td>
<td>Ziagen®</td>
<td>300 mg</td>
<td>bid</td>
<td>2</td>
</tr>
<tr>
<td>didanosine</td>
<td>Videx®</td>
<td>200 mg</td>
<td>bid</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Videx EC®</td>
<td>400 mg</td>
<td>qd</td>
<td>1</td>
</tr>
<tr>
<td>lamivudine</td>
<td>Epivir®</td>
<td>150 mg</td>
<td>bid</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>300 mg</td>
<td>qd</td>
<td>1</td>
</tr>
<tr>
<td>stavudine</td>
<td>Zerit®</td>
<td>30 or 40 mg</td>
<td>bid</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Zerit XR®</td>
<td>75 or 100 mg</td>
<td>qd</td>
<td>1</td>
</tr>
<tr>
<td>zalcitabine</td>
<td>Hiva®</td>
<td>0.75 mg</td>
<td>tid</td>
<td>3</td>
</tr>
<tr>
<td>zidovudine</td>
<td>Retrovir®</td>
<td>300 mg</td>
<td>bid</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 mg</td>
<td>tid</td>
<td>6</td>
</tr>
</tbody>
</table>

### Adult Antiretroviral Arsenal - 2003

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Dose</th>
<th>Schedule</th>
<th>Pills/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>zidovudine + lamivudine</td>
<td>Combivir®</td>
<td>300/150 mg</td>
<td>bid</td>
<td>2</td>
</tr>
<tr>
<td>Combivir® + abacavir</td>
<td>Trizivir®</td>
<td>300/150/300 mg</td>
<td>bid</td>
<td>2</td>
</tr>
</tbody>
</table>

### Nucleoside reverse transcriptase inhibitors (combination)
NRTIs: Clinical Caveats

- Most can be taken with or without food
  - Didanosine EC - empty stomach
  - Tenofovir - with food

- Combinations to avoid:
  - Zidovudine and stavudine
  - Zalcitabine and didanosine or lamivudine or stavudine

- Dose reduce didanosine to 250 mg when co-administering with a tenofovir containing regimen

Nucleoside Reverse Transcriptase Inhibitors

- Examples of adverse events:
  - Zidovudine – GI intolerance, headache, anemia
  - Didanosine (buffered) – diarrhea
  - Abacavir – rash, hypersensitivity reaction (3-5%)

- Adverse events 2º to mitochondrial dysfunction (?)
  - Zidovudine – myopathy
  - Didanosine, zalcitabine, stavudine – peripheral neuropathy
  - Didanosine, stavudine – pancreatitis
  - Class - hyperlactatemia; lactic acidosis with hepatomegaly and steatosis (rare), fat maldistribution (lipoatrophy)
Non-nucleoside Reverse Transcriptase Inhibitors

- Chemically heterogeneous compounds (n=3)
  - Nevirapine
  - Delavirdine
  - Efavirenz
- Do not require intracellular activation
- Bind noncompetitively to reverse transcriptase to inhibit its activity

Adult Antiretroviral Arsenal - 2003

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Dose</th>
<th>Schedule</th>
<th>Pills/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine</td>
<td>Viramune®</td>
<td>200 mg</td>
<td>qd x 14d then bid</td>
<td>1 x 14 days then 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>400 mg</td>
<td>qd x 14d then 2 caps qd</td>
<td>1 x 14 days then 2</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>Rescriptor®</td>
<td>400 mg</td>
<td>tid</td>
<td>6</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Sustiva®</td>
<td>600 mg</td>
<td>qd</td>
<td>1</td>
</tr>
</tbody>
</table>
**NNRTIs: Clinical Caveats**

- Most can be taken with or without food
  - Efavirenz - empty stomach
- Antacids reduce delavirdine absorption - separate administration
- Lead-in dosing for nevirapine
  - May reduce incidence of AEs
  - Compensates for metabolic autoinduction processes

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**NNRTIs: Clinical Caveats**

*Source of many drug-drug interactions!!!*

<table>
<thead>
<tr>
<th>Drug</th>
<th>CYP Substrate</th>
<th>Inhibition</th>
<th>Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-nucleoside reverse transcriptase inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>delavirdine</td>
<td>3A4</td>
<td>3A4, 2C9, 2C19</td>
<td>-</td>
</tr>
<tr>
<td>efavirenz</td>
<td>2B6, 3A4</td>
<td>2B6, 3A4, 2C9/19</td>
<td>3A4</td>
</tr>
<tr>
<td>nevirapine</td>
<td>3A4, 3A5</td>
<td>-</td>
<td>3A4</td>
</tr>
</tbody>
</table>

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**Non-nucleoside Reverse Transcriptase Inhibitors**

- Examples of adverse effects
  - Efavirenz – abnormal dreams, insomnia, hallucinations, depression
  - Nevirapine – clinical (symptomatic) hepatitis (rare)
  - Delavirdine – headaches
- Class associated with 3-5 fold increases in liver transaminases (transient) & rash (NVP>>DLV>EFV)
  - NVP lead-in dosing strategy may reduce incidence of rash and hepatotoxicity
Protease Inhibitors

- Chemically unique compounds (n=6)
  - Amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir (soft & hard gel formulations)

- Mechanism of action
  - Inhibit HIV protease
  - Block the maturation process of HIV
  - Resulting virions are immature & noninfectious

Adult Antiretroviral Arsenal - 2003

<table>
<thead>
<tr>
<th>Generic</th>
<th>Brand</th>
<th>Std Dose</th>
<th>Schedule</th>
<th>Pills/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amprenavir</td>
<td>Agenerase®</td>
<td>1200 mg</td>
<td>bid</td>
<td>16</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Crizalva®</td>
<td>800 mg</td>
<td>tid</td>
<td>6</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Viracept®</td>
<td>750 mg</td>
<td>tid</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1250 mg</td>
<td>bid</td>
<td>10</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Norvir®</td>
<td>600 mg</td>
<td>bid</td>
<td>12</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Fortovase®</td>
<td>1200 mg</td>
<td>tid</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Invirase®</td>
<td>600 mg</td>
<td>tid</td>
<td>9</td>
</tr>
<tr>
<td>Lopinavir/ Ritonavir</td>
<td>Kaletra®</td>
<td>400/100 mg</td>
<td>bid</td>
<td>6</td>
</tr>
</tbody>
</table>

Pharmacokinetic Enhancement

- PIs inhibit gut & hepatic CYP3A metabolism
- Metabolic 3A4 inhibition:
  \[ RTV >> IDV = NFV = APV > SQV = LPV \]
- Low-dose ritonavir (100 or 200 mg bid) + 2nd PI
Pharmacokinetic Enhancement

- **PK advantages**
  - Improves drug exposure (Cmax, AUC, Cmin)
  - Reduces interpatient PK variability
  - Increases half-life which allows bid or qd dosing
  - Improves potency & activity against resistant virus

- **Adherence advantages**
  - Diminished food restrictions
  - Reduced dosing frequency & daily pill burden

- **Offsets negative drug-drug interactions**

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**Single Dose: Ritonavir + Lopinavir**

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**IDV/RTV Twice-Daily Pharmacokinetics**

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Steady-State Plasma Amprenavir Concentrations

Antiretroviral Arsenal - 2003

<table>
<thead>
<tr>
<th>Generic</th>
<th>PI Dose (mg)</th>
<th>RTV Dose (mg)</th>
<th>Schedule</th>
<th>Pills/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>amprenavir</strong></td>
<td>600 or 750</td>
<td>100 or 200</td>
<td>bid</td>
<td>10 to 14</td>
</tr>
<tr>
<td></td>
<td>1200</td>
<td>200</td>
<td>qd</td>
<td>10</td>
</tr>
<tr>
<td><strong>indinavir</strong></td>
<td>800</td>
<td>100 or 200</td>
<td>bid</td>
<td>6 or 8</td>
</tr>
<tr>
<td><strong>saquinavir-sgc</strong></td>
<td>400</td>
<td>400</td>
<td>bid</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>1600</td>
<td>100</td>
<td>qd</td>
<td>9</td>
</tr>
<tr>
<td><strong>saquinavir-hgc</strong></td>
<td>1000</td>
<td>100</td>
<td>bid</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>1600</td>
<td>100</td>
<td>qd</td>
<td>9</td>
</tr>
</tbody>
</table>

Note: Nelfinavir is poorly “boosted” by RTV

PIs: Clinical Caveats

- Food and fluid recommendations for STD dose:
  - Amprenavir - with or without food
  - Indinavir - empty stomach; fluids!!!
  - Ritonavir - with food
  - Lopinavir, saquinavir (sgc) - with food (>30% fat)
  - Saquinavir (hgc), nelfinavir - high fat (>50%) meal

- RTV Boosted dosing - with or without food (may reduce GI intolerances)
  - Lopinavir/ritonavir - with food (30% fat)
PIs: Clinical Caveats

Source of many drug-drug interactions!!!

<table>
<thead>
<tr>
<th>Drug</th>
<th>CYP substrate</th>
<th>Inhibition</th>
<th>Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>ampranavir</td>
<td>3A4, 2C19</td>
<td>3A4</td>
<td>3A4?</td>
</tr>
<tr>
<td>indinavir</td>
<td>3A4</td>
<td>3A4</td>
<td>-</td>
</tr>
<tr>
<td>lopinavir</td>
<td>3A4</td>
<td>3A4</td>
<td>-</td>
</tr>
<tr>
<td>nelfinavir</td>
<td>3A4, 2C19, 2D6</td>
<td>3A4, 2B6</td>
<td>glucuronyl transferase, 3A4?</td>
</tr>
<tr>
<td>ritonavir</td>
<td>3A4&gt;2D6&gt;2C1&gt;2A6&gt;1A2&gt;2E1</td>
<td>3A4</td>
<td>3A4, 1A2, 2C9, glucuronyl transferase</td>
</tr>
<tr>
<td>saquinavir</td>
<td>3A4</td>
<td>3A4</td>
<td>-</td>
</tr>
</tbody>
</table>

Protease Inhibitors

• Examples of adverse effects
  – Amprenavir – GI intolerance (N/V/D), rash
  – Indinavir – GI intolerance, nephrolithiasis
  – Nelfinavir – diarrhea
  – Saquinavir – GI intolerance
  – Ritonavir – GI intolerance, circumoral paresthesias
  – Class - increases in liver transaminases (often transient)

• Class may be associated with metabolic disturbances over time – dyslipidemias (↑ TG, ↑ LDL & ↓ HDL), hyperglycemia (worsening/new onset DM - insulin resistance), fat maldistribution (hyperadiposity)
Use of Antiretroviral Therapy
Multicenter AIDS Cohort Study (MACS)

Mortality of HIV Disease

Department of Health & Human Services (CDC) Treatment Guidelines for HIV Infected Adults & Adolescents
*Annals of Internal Medicine 2002;137:381-433*
Goals of Therapy

• **Virologic endpoints:**
  – Suppress HIV replication as much as possible (<50 copies/mL) for as long as possible
  – Prevent development of resistance

• **Immunologic endpoints:**
  – Boost/maintain CD4 lymphocyte count to level that will prolong time to disease progression

• **Clinical endpoints:**
  – Reduce morbidity/mortality, improve QOL

When to Initiate Treatment…

• Treatment decisions should be **guided** by viral load & CD4 lymphocyte count

• **Acute HIV infection** - studies ongoing

• **Chronic HIV infection:**
  – Asymptomatic
  – Symptomatic (advanced disease) – muscle wasting, oral candidiasis, unexplained fever x 2 weeks, AIDS defining illnesses

<table>
<thead>
<tr>
<th>Clinical Category</th>
<th>CD4+ T Cell Count</th>
<th>Plasma HIV RNA</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>symptomatic (AIDS, severe sx)</td>
<td>any</td>
<td>any</td>
<td>treat</td>
</tr>
<tr>
<td>asymptomatic, AIDS</td>
<td>&lt;200 cells/mm³</td>
<td>any</td>
<td>treat</td>
</tr>
<tr>
<td>asymptomatic</td>
<td>&gt;200 but &lt;350 cells/mm³</td>
<td>any</td>
<td>offer treatment; controversy exists</td>
</tr>
<tr>
<td>asymptomatic</td>
<td>&gt;350 cells/mm³</td>
<td>&gt;55,000*</td>
<td>controversy exists; treat vs. defer</td>
</tr>
<tr>
<td>asymptomatic</td>
<td>&gt;350 cells/mm³</td>
<td>&lt;55,000*</td>
<td>controversy exists; many would defer</td>
</tr>
</tbody>
</table>

*by bDNA or RT-PCR
†Adapted from: DHHS Guidelines for the use of Antiretroviral Agents in HIV-infected Adults & Adolescents
When to Initiate Treatment…

- In asymptomatic persons with CD4 count >200 cells/mm³ there must be a balance:
  - Patient readiness
    - 90-95% adherence may be needed to maintain suppression of viral replication
  - Risks & benefits of antiretroviral therapy
  - Prognosis for disease-free survival as determined by baseline CD4 count & viral load levels

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Early Therapy

- **Risks**
  - Drug-related reduction in quality of life
  - Greater cumulative drug-related AEs
  - Earlier development of drug resistance with suboptimal suppression
  - Limiting future treatment options

- **Benefits**
  - Easier to control viral replication
  - Delay/prevent immune system deterioration
  - Lower risk of viral resistance with complete suppression
  - Possible decreased risk of HIV transmission

(Adapted from: DHHS Guidelines for the use of Antiretroviral Agents in HIV-infected Adults & Adolescents)
Delayed Therapy

**Risks**
- Irreversible immune system depletion
- Harder to suppress viral replication
- Increased risk of HIV transmission

**Benefits**
- Avoid negative effects on quality of life
- Avoid drug-related adverse effects
- Delay development of drug resistance
- Preserve future treatment options

Adapted from: DHHS Guidelines for the use of Antiretroviral Agents in HIV-infected Adults & Adolescents

When to Initiate Treatment…

- The **first** ARV treatment regimen has the **best** chance of long term success!

Tools to Achieve Therapy Goals

1) Maximize medication adherence
2) Use of resistance testing to select active drugs
3) Rational selection & sequencing of drug therapy
   - Preservation of future treatment options
   - Class-sparing treatment regimens
1) Strategies to Improve Adherence

- Discuss, anticipate, treat side effects
- Simplify regimen
- Avoid adverse drug interactions
- Negotiate treatment plan
- Use multiple education encounters
- Involve family and friends
- Individualize regimens
- Written schedule
- Reminder tools
- Support groups
- Use health care teams
- Consider co-diagnoses (e.g., depression)
- More provider access
- Regular monitoring
- Adherence training

2) Viral Resistance

- Primary
  - Initial infection with drug-resistant HIV
  - Antiretroviral naïve persons
  - 5-10% incidence depending upon population

- Secondary
  - Emergence of HIV variants with reduced susceptibility to antiretroviral agents
  - Antiretroviral experienced persons

2) Viral Resistance Testing

- Two methods that measure viral resistance:
  - Viral genotype
    - Tests the virus for genetic mutations associated with reduced susceptibility to ARV drugs
  - Viral phenotype
    - Measures viral growth in the presence of various concentrations of ARV drugs - reported as a fold change in IC_{50} (drug concentration needed to inhibit viral growth by 50%)
- Guide selection of active drugs
### NNRTI-Sparing Regimen

- **Example 1:**
  - lopinavir/ritonavir 400/100 mg po bid
  - zidovudine/lamivudine 300/150 po bid

- **Example 2:**
  - nelfinavir 1250 mg po bid
  - stavudine 40 mg po bid
  - lamivudine 150 mg po bid

### PIs + NRTIs

- **Advantages**
  - Well-documented efficacy
  - Continued benefits despite breakthrough
  - Resistance requires multiple mutations
  - Targets RT and PR
  - Preserves NNRTIs

- **Disadvantages**
  - May be difficult to adhere to
  - Long-term side effects: fat maldistribution, hyperlipidemia, insulin resistance
  - Development of cross-class resistance
  - Drug interactions with PIs
PI-Sparing Regimen

- **Example 1:**
  - efavirenz 600 mg po qhs
  - lamivudine 300 mg po qd
  - tenofovir 300 mg po qd

- **Example 2:**
  - nevirapine 200 mg po qd x 14d then 200 mg po bid
  - zidovudine/lamivudine 300/150 po bid

NNRTI + NRTIs

- **Advantages**
- Spares PI side effects
- Easier to use and adhere to
- Fewer drug interactions
- Preserves PIs

- **Disadvantages**
- Comparibility to PI-based regimens unknown
- Resistance conferred by a single or limited mutation(s)
- Development of cross-class resistance
- Targets RT only

PI- & NNRTI-Sparing Regimen

- **Example 1:**
  - abacavir/zidovudine/lamivudine 300/300/150 mg po bid

- **Example 2:**
  - tenofovir 300 mg po qd
  - lamivudine 300 mg po qd
  - didanosine EC 250 mg po qd
Triple NRTIs

- Advantages
  - Easy to use and adhere to
  - Preserves PIs & NNRTIs
  - Limited cross-class resistance
  - Limited drug interactions

- Disadvantages
  - Long-term efficacy vs. PI unknown
  - Less effective vs. NNRTI?
  - Efficacy vs. high viral loads (>100,000) may be suboptimal
  - Targets RT only

When to Change Therapy...

- Situations to consider:
  - Incompletely suppressive treatment regimen
    - Monotherapy, dual NRTI therapy
  - Viremia initially suppressed (<50 copies/mL) on a potent treatment regimen but repeatedly detectable
  - Viremia never suppressed despite a potent treatment regimen
  - CD4+ T cell counts persistently declining
  - Clinical deterioration

What to Change to...

- When basing a change in therapy on viral load, confirm with a second viral load test
- For true virologic failure
  - Use at least 2 & preferably 3 new drugs
  - Attempt to minimize cross-resistance
  - Resistance testing may guide selection
- For intolerance or toxicity
  - Substitute the offending agent