HIV Management Strategies

Alan Taege, M.D.
Director HIV Care
Infectious Disease
Medicine

When to start

Start early
- Preserve immune function
- Prevention of non-AIDS illnesses
- Prevent AIDS defining illness
- Probably reduces transmission
- Safer medications available
- More choices for 2nd line

Start late
- Side effects of meds
- Expense
- Resistance over time and loss of choices
- Lack of motivation d/t non-serious nature
- There may be some non-progressors
### DHHS Treatment Guidelines

<table>
<thead>
<tr>
<th>CD4+ Counts, cells/mm³</th>
<th>1998</th>
<th>2001</th>
<th>2006</th>
<th>2008</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 350</td>
<td>Offer if HIV-1 RNA &gt; 20,000 copies/mL</td>
<td>Consider if HIV-1 RNA &gt; 55,000 copies/mL</td>
<td>Consider if HIV-1 RNA ≥ 100,000 copies/mL</td>
<td>Consider in certain groups*</td>
<td>Treat at 350-500; consider for &gt; 500†</td>
</tr>
<tr>
<td>200-350</td>
<td>Offer if HIV-1 RNA &gt; 20,000 copies/mL</td>
<td>Offer, but controversy exists</td>
<td>Offer after discussion with patient</td>
<td>Treat</td>
<td>Treat</td>
</tr>
<tr>
<td>&lt; 200 or symptomatic disease</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
<td>Treat</td>
</tr>
</tbody>
</table>

### WHO Should Start Antiretroviral Therapy? One View

<table>
<thead>
<tr>
<th>Clinical Category</th>
<th>CD4+</th>
<th>My View</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS-defining illness or severe symptoms</td>
<td>Any value</td>
<td>Treat</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>&lt;200/μL</td>
<td>Treat</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>200-500/μL</td>
<td>Treat</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>&gt;500/μL</td>
<td>Treat if patient is ready!</td>
</tr>
</tbody>
</table>

### Subgroups for Consideration of Early Initiation of Antiretroviral Therapy

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Antiretroviral Therapy Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breastfeeding</td>
<td>- Antiretroviral therapy has been shown to reduce transmission through breastfeeding</td>
</tr>
<tr>
<td></td>
<td>- Should be considered in areas where formula feeding is associated with increased mortality</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>- Antiretroviral therapy may reduce inflammation associated with HIV replication, but must be balanced against the adverse lipid effects of certain antiretroviral medications</td>
</tr>
<tr>
<td>HBV</td>
<td>- Effective treatment for HBV contains agents that are at least partially suppressive of HIV replication, so fully suppressive antiretroviral therapy is recommended when treating HBV in HIV/HBV-coinfected patients</td>
</tr>
</tbody>
</table>

---

### Subgroups for Consideration of Early Initiation of Antiretroviral Therapy

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Antiretroviral Therapy Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV</td>
<td>- Antiretroviral therapy is associated with slower fibrosis and reduced HCV-related mortality in HIV/HCV-coinfected patients</td>
</tr>
<tr>
<td>HIVAN</td>
<td>- Antiretroviral therapy slows progression of HIVAN but does not reverse existing damage. Consider in patients with suspected HIVAN because biopsy confirmation is rare</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>- Antiretroviral therapy dramatically reduces mother-to-child transmission</td>
</tr>
<tr>
<td>Sexual transmission</td>
<td>- Antiretroviral therapy reduces the infectiousness of HIV-infected persons; test and treat is a new prevention strategy</td>
</tr>
</tbody>
</table>
Other tests used in HIV

- Resistance testing
  - Genotype
  - Phenotype
  - Virtual phenotype
- HLA B57*01
- Tropism assay (Enhanced trophile assay)

CDC Survey Update: Patterns of Transmitted Drug Resistance

![Bar graph showing patterns of transmitted drug resistance over time](image)

- Any resistance
- NNRTI
- NRTI
- PI
- MDR

<table>
<thead>
<tr>
<th>Year</th>
<th>Any resistance</th>
<th>NNRTI</th>
<th>NRTI</th>
<th>PI</th>
<th>MDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>8.8</td>
<td>2.1</td>
<td>0.8</td>
<td></td>
<td>1.3</td>
</tr>
<tr>
<td>2000</td>
<td>7.1</td>
<td>1.0</td>
<td></td>
<td></td>
<td>0.9</td>
</tr>
<tr>
<td>2003-2006</td>
<td>10.4</td>
<td>6.9</td>
<td></td>
<td></td>
<td>3.6</td>
</tr>
<tr>
<td>2007</td>
<td>15.6</td>
<td>8.8</td>
<td>7.1</td>
<td>2.2</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Decreasing Prevalence of Resistance Mutations at Failure, by ARV Class over a 7-Year Period (CNICS)

In those with resistance
- 2-class resistance declined from 58% to 32%
- 3-class resistance declined from 18% to 7%

HIV medications

- Older classes
  - Nucleoside reverse transcriptase inhibitors (NRTIs)
  - Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
  - Protease inhibitors (PIs)

- New classes
  - Fusion inhibitors
  - Entry Inhibitors
  - Integrase inhibitors
**Principles of therapy**

- Monotherapy and dual therapy do not work (called anti-retroviral therapy ART)

- Addition of a protease inhibitor to a NRTI *backbone* – Highly active ART (HAART)

- Later NNRTI as good as PI
Some terms

• **Boosting**
  – Adding low dose ritonavir to another PI so as to increase its levels, half life
• Treatment *naïve*
• Treatment *experienced*
• Salvage therapy
• Intensification

Principles of therapy – a scheme

2 NRTI’s

- Tenofovir or Abacavir
- Lamivudine or Emtricitabine

+ NNRTI or PI (boosted) or Integrase
More terms

- Potency of a drug
- Genetic barrier to resistance
- Viral fitness
- Signature mutations
- Immune reconstitution syndrome
- Long term non-progressors
- Long term survivors

Beware of Drug Interactions

- PIs especially ritonavir are potent inhibitors of the CYP P450 system and P-glycoprotein
  - Statins

- Other drug interactions
  - OTC drugs: St. John’s wort
  - Famotidine/Antacids
Effect of HAART on T cells

• Effective viral suppression leads to:
  – expansion/improvement in memory T cells initially (correlated with degree of suppression)
  – loss of T cell activation markers leading to decreased inflammatory cytokines like TNFα, decreased apoptosis
  – later expansion of naïve T cell compartment
  – T cells directed against environmental antigens
Immune Restoration Disease

- Paradoxical response to HAART and recovery of CD4 counts
  - diagnosis of previously unrecognized opportunistic infections in the months following initiation of HAART
  - worsening of symptoms of a treated opportunistic infection after initiation of HAART (TB as a model)
- Presentations are often atypical and accompanied by fever

Immune Restoration Disease

- MAC
- TB
- CMV
- Hep B and C
- Cryptococcus
- Histoplasmosis
- Herpes Zoster
- Progressive Multifocal Leukoencephalopathy
- Graves/SLE/ sarcoidosis/ autoimmune thyroiditis
- Lymphoma, KS
Prophylaxis

<table>
<thead>
<tr>
<th>CD4 criteria</th>
<th>Medication</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 200</td>
<td>TMP-SMX</td>
<td>Inhaled Pentam or Dapsone</td>
</tr>
<tr>
<td>&lt;100</td>
<td>TMP-SMX</td>
<td>Dapsone + Pyrimethamine</td>
</tr>
<tr>
<td>&lt;50</td>
<td>Azithromycin</td>
<td>Clarithromycin or Rifabutin</td>
</tr>
<tr>
<td>&lt;150</td>
<td>Itraconazole</td>
<td></td>
</tr>
<tr>
<td>&lt;250</td>
<td>Fluconazole</td>
<td>Itraconazole</td>
</tr>
</tbody>
</table>

*Note: Tuberculosis – should check for this at least once and treat if PPD > 5mm*

DHHS. Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents – 2008. Adapted from Table 1

Per-Person Survival Gains (months)

Walensky et al, CROI 2005, Abs 143
Cleveland Clinic

Every life deserves world class care.