Basic HAART and Drug Interactions

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Figure A: Prognosis According to CD4 Cell Count and Viral Load in the Pre-HAART and HAART Eras
23 YEARS OF HAART

We now have:

- 7 Nucleoside/tide analogs (4 combos)
- 4 Non-nucleoside analogs (1 combo)
- 9 Protease Inhibitors
- 1 Fusion Inhibitors
- 1 CCR5 antagonist
- 1 Integrase Strand Transfer Inhibitor
Goal of Therapy

- Maximally and durably suppress plasma HIV viral load (<48 copies/ml)
- Reduce HIV-associated morbidity and prolong survival
- Improve quality of life
- Restore and preserve immunologic function (raise CD4 count) and
- Prevent HIV transmission
Pharmaceutical Goals

- Minimize toxicity: short-term vs. long-term
- Minimize schedule demands: simplify dosing
- Minimize numbers of pills, medications
- Minimize food/fluid restrictions
Which Therapy is Best?

The regimen that the patient can take

*every dose every day*

*at the same time.*
What drug to use when?

- Guidelines
  - DHHS
  - IAS-USA
- Patient assessment and education
- Genotype/Phenotype
## Starting Therapy

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength</th>
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</thead>
<tbody>
<tr>
<td>AIDS-Defining Illness</td>
<td>AI</td>
</tr>
<tr>
<td>CD4 &lt; 350</td>
<td>AI</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>AI</td>
</tr>
<tr>
<td>HIV-Associated Nephropathy (HIVAN)</td>
<td>AII</td>
</tr>
<tr>
<td>Hepatitis B Virus (HBV) co-infection</td>
<td>AIII</td>
</tr>
<tr>
<td>[when HBV treatment is indicated]</td>
<td></td>
</tr>
<tr>
<td>CD4 350-500</td>
<td>A/BII†</td>
</tr>
<tr>
<td>CD4 &gt; 500</td>
<td>B/CIII‡</td>
</tr>
</tbody>
</table>

† Panel divided, 55% voted for strong recommendation (A) and 45% voted for moderate recommendation (B) (A/B-II).
‡ Panel divided, 50% favor starting antiretroviral therapy at this stage of HIV disease (B); 50% view initiating therapy at this stage as optional (C) (B/C-III).
Recommended HAART* in Treatment Naïve Patients

*highly active ant-retroviral therapy

- 1 NNRTI + 2 NRTI’s
  EFV + TDF + FTC (Atripla®)
- 1 PI (preferable PI/r) + 2 NRTI’s
  ATV/r + TVD
  DRV/r + TVD
- 1 INSTI + 2 NRTI’s
  RAL + TVD

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents Page 37
Panel also recommends that medication selection...

- Individualized based on viral efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, and co-morbid conditions.

- Based on individual patient characteristics and needs, in some instances, an alternative regimen may actually be a preferred regimen for a patient.
HIV Life Cycle

1. Binding
2. Fusion
3. Reverse Transcriptase
4. Integration
5. Protein Production
6. Viral Assembly
7. Budding
NRTI’s…

- Considered the backbone of HAART therapy
- All but Abacavir® need dosing adjustments for renal insufficiency
- All have black box warnings (hepatitic steatosis and lactic acidosis)
- Short term side effects mostly GI related
- Long term- PN, lipoatrophy
Nucleoside Reverse Transcriptase Inhibitors (NRTI)

- **Abacavir (ABC) Ziagen®**
  - HSR
- **Didanosine (ddI) Videx EC®**
  - PN, Pancreatitis
- **Emtricitabine (FTC) Emtriva®**
  - HA, N
- **Lamivudine (3TC) Epivir®**
  - HA, N
- **Stavudine (d4T) Zerit®**
  - PN, Pancreatitis
- **Tenofovir (TDF) Viread®**
  - N/V/gas
- **Zidovudine (AZT, ZDV) Retrovir®**
  - BMS
NRTI’s combo

- AZT + 3TC = Combivir®
- AZT + 3TC + ABC = Trizivir®
- 3TC + ABC = Epzicom®
- TDF + FTC = Truvada®
- TDF + FTC + EFV = Atripla®
NRTI Structures

Adenosine

Cytosine

Guanine

Thymine

Didanosine (ddI)

Zalcitabine (ddC)

Abacavir (ABV)

Zidovudine (ZDV)

Lamivudine (3TC)

Amdoxovir (DAPD)

Stavudine (d4T)

Emtricitabine (FTC)

Tenofovir (TDF)

NNRTI’s

• Class issues
  – Rash (Can treat through depending on severity)
  – ^LFT’s, Hepatotoxicity is concern
  – Cross resistance

  – Elimination
    – Both CYP3A4 substrate and inhibitor
    – Drug interactions
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

- **Delavirdine (DLV) Rescriptor®**  
  - 400mg po TID

- **Efavirenz (EFV) Sustiva® Atripla®**  
  - 600mg po qHS

- **Etravirine (ETR) Intelence®**  
  - 200mg po BID

- **Nevirapine (NVP) Viramune®**  
  - 200mg daily x 2 weeks then BID
Protease Inhibitors

- Class toxicities
  - Short term - N/V/D
  - Long term - insulin resistance, lipodystrophy, metabolic
  - lipid abnormalities
  - LFT elevations
  - ^risk of bleeding with hemophilia

- Most have drug interactions due to CYP metabolism in the liver requiring dosage adjustments of PI’s or other agent
Protease Inhibitors (PI)

- **Atazanavir (ATV) Reyataz®**
  - 400mg QD or 300mg/r
- **Darunavir (DRV) Prezista®**
  - N= 800/r QD  E=600mg/r BID
- **Fosamprenavir (FPV) Lexiva®**
  - 700mg BID (variable)
- **Indinivir (IDV) Crixivan®**
  - 800mg/r BID
- **Ritonavir (RTV) Norvir®**
  - 100mg-200mg as “booster”
- **Lopinavir/ritonavir (LPV/r) Kaletra®**
  - 400mg/100mg BID
- **Nelfinavir (NFV) Viracept®**
  - 1250mg po BID
- **Saquinavir (SQV) Invirase®**
  - 500mg/r BID
- **Tipranavir (TPV) Aptivus®**
  - 500mg/r BID
Elevated Lipids
(Cholesterol and Triglycerides)

- Occurs with EFV and PI’s
- May increase risk for coronary heart disease
- Treat through or stop medication
  - “statins” (e.g. atorvastatin)
  - Fibrate (e.g. fenofibrate or gemfibrozil)
- Prevention
  - Stop Smoking
  - Diet and exercise
  - Fish Oil
Entry Inhibitors

- **Enfuvirtide (T-20, ENF) Fuzeon®**
  - 90mg SQ q12H $$$$
  - Injection site reactions

- **Maraviroc (MVC) Selzentry®**
  - Requires trophic assay {Trofile™}
  - Treatment experienced or Naïve
  - Dose dependent on CYP interactions
    - Strong inhibitor = 150mg po BID (PI/r)
    - Strong inducer = 600mg po BID (EFV)
Integrase Strand Transfer Inhibitor (INSTI)

- Raltegravir (RAL) *Isentress®* HA, NV, ↑CPK
- UGT1A1 Glucuronidation

Drug interaction
- Rifampin ↑RAL dose to 800mg po BID
Drug Interactions

- **Protease Inhibitors**
  - Amiodarone
  - Antiarrhythmics
  - Ergot Alkaloids
  - Fluticasone
  - Midazolam, Triazolam

- **ATV/r**
  - Proton Pump Inhibitors

- **Proton Pump Inhibitors**
  - Quinidine
  - Rifampin
  - St. John’s Wort
  - Simvastain, Lovastatin

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Drug Interactions

- Non-Nucleoside Reverse Transcriptase Inhibitors
  - Ergot Alkaloids
  - Midazolam, Triazolam
  - Methadone
  - Rifampin
  - St. John’s Wort
NRTI Drug Interactions

- Gancyclovir/Valgancyclovir-ddI
- Ribavirin- ddI, AZT, D4T
- Methadone-monitor
- Didanosine –d4T, TDF
- Allopurinol-ddI
- Protease Inhibitors
Perinatal Implications

- Guidelines updated May 24, 2010

- With universal prenatal HIV counseling and testing, ARV prophylaxis, scheduled cesarean section delivery, and avoidance of breastfeeding, perinatal HIV infection has diminished to <2% in the United States and Europe.
Use of ARVs during Pregnancy: General Principles

- Initial evaluation should include (AIII)
  - Assessment of HIV disease status
  - Recommendations regarding initiating ART or altering the current ARV regimen

- ARV prophylaxis for ALL pregnant HIV-infected women, regardless of VL or CD4 count (AI)

- Discuss known benefits and potential risks of ARVs during pregnancy (AIII)
Use of ARVs during Pregnancy: General Principles (2)

- Resistance testing: for all women whose HIV RNA is detectable (e.g., >500-1,000 copies/mL), before starting or modifying therapy (AI)
  - Prior to starting ARV therapy or prophylaxis
  - For women with suboptimal VL suppression or rebound

- ZVD should be included in regimen unless (AIII)
  - There is severe toxicity
  - Documented resistance
  - The women is already on a fully suppressive regimen
Still true

Administer AZT…

- During Pregnancy
- During labor and delivery
- The infant for the 1\textsuperscript{st} six weeks of life
Recommendations

- If mom is tx naïve- start HAART in 2nd trimester
- If mom is experienced continue current regimen unless she is on EFV
- Goal is VL <48 copies/ml
- If VL >1000 copies/ml at 36-38 weeks C-Section advised
References

- www.CDC.gov/HIV
- www.Medscape.com/hiv-aidshome
- www.Hopkins-aids.edu
- http:AIDSinfo.nih.gov
- Netaccess/Micromedix
- www.aidsetc.org
- www.lexi.com