Initial Anti-Retroviral Therapy

Christian B. Ramers, MD, MPH
Medical Director, NW AETC ECHO
Assistant Professor of Medicine & Global Health, University of Washington

Presentation Prepared by:
Christian B. Ramers, MD, MPH and David Spach, MD
Last Updated: March 6, 2012
Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

October 14, 2011

Developed by the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC)

How to Cite the Adult and Adolescent Guidelines:


It is emphasized that concepts relevant to HIV management evolve rapidly. The Panel has a mechanism to update recommendations on a regular basis, and the most recent information is available on the AIDSinfo Web site (http://aidsinfo.nih.gov/).
SELECTING AMONG ‘PREFERRED’ REGIMENS
Anti-retroviral drug targets

- HIV RNA
- HIV DNA
- HIV mRNA
- Gag
- Gag-Pol
- Myr
- Non-Nucleoside RTI
- Entry Inhibitors
- Nucleoside RTI
- Integrate Inhibitors
- Protease Inhibitors

Host Cell

Nucleus

HIV

CD4

CCR5

Entry

Inhibitors
## Anti-retroviral Therapy in 2012

### Nucleos(t)ide Reverse Transcriptase Inhibitors (NRTI)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Frequency</th>
<th>Formulations</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abacavir</strong></td>
<td>300 mg</td>
<td>1x300 mg t.i.d.</td>
<td>300 mg tablets</td>
<td>Hypersensitivity reaction symptoms may include fever, rash, mucositis, nausea, vomiting, diarhea, respiratory difficulties</td>
</tr>
<tr>
<td><strong>Didanosine</strong></td>
<td>250 mg</td>
<td>1x250 mg t.i.d.</td>
<td>250 mg capsules</td>
<td>Peripheral neuropathy, pancreatitis, nausea, diarrhea</td>
</tr>
<tr>
<td><strong>Emtricitabine</strong></td>
<td>200 mg</td>
<td>1x200 mg t.i.d.</td>
<td>200 mg tablets</td>
<td>Headaches, fatigue, nausea</td>
</tr>
<tr>
<td><strong>Lamivudine</strong></td>
<td>150 mg</td>
<td>1x150 mg t.i.d.</td>
<td>150 mg tablets</td>
<td>Headaches, fatigue, nausea</td>
</tr>
<tr>
<td><strong>Stavudine</strong></td>
<td>30 mg</td>
<td>1x40 mg q.d.</td>
<td>40 mg capsules</td>
<td>Peripheral neuropathy, altered liver function</td>
</tr>
<tr>
<td><strong>Tenofovir EF</strong></td>
<td>300 mg</td>
<td>1x300 mg t.i.d.</td>
<td>300 mg tablets</td>
<td>Renal insufficiency (rare), nausea, upset stomach</td>
</tr>
<tr>
<td><strong>Zidovudine</strong></td>
<td>100 mg</td>
<td>1x300 mg t.i.d.</td>
<td>300 mg tablets</td>
<td>Anemia, neutropenia, headache, nausea, body aches, insomnia</td>
</tr>
</tbody>
</table>

### Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Frequency</th>
<th>Formulations</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Delavirdine</strong></td>
<td>200 mg</td>
<td>2x100 mg t.i.d.</td>
<td>200 mg tablets</td>
<td>Rash, headache, altered liver function</td>
</tr>
<tr>
<td><strong>Efavirenz</strong></td>
<td>200 mg</td>
<td>1x200 mg t.i.d.</td>
<td>200 mg capsules</td>
<td>Rash, altered liver function, dizziness, insomnia, impaired concentration, drowsiness</td>
</tr>
<tr>
<td><strong>Etravirine</strong></td>
<td>100 mg</td>
<td>2x100 mg t.i.d.</td>
<td>100 mg capsules</td>
<td>Nausea, headache, weight loss, transaminitis, hypersensitivity reaction, rashes</td>
</tr>
<tr>
<td><strong>Nevirapine</strong></td>
<td>200 mg</td>
<td>1x300 mg t.i.d.</td>
<td>200 mg tablets</td>
<td>Rash, headache, altered liver function</td>
</tr>
</tbody>
</table>

### New NNRTI: Rilpivirine

Co-formulated with Emtricitabine-Tenofovir as Complera

Source: www.nwaetc.org
ANTIRETROVIRAL THERAPY: DHHS GUIDELINES

DHHS Antiretroviral Therapy Guidelines: October 2011
Preferred Regimens for ARV-Naïve Patients

Backbone

(2) Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Third Agent

Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)

or

Protease Inhibitor (PI) (ritonavir-boosted)

or

Integrase Strand Transfer Inhibitor (INSTI)

Source: DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)
Key Factors Influencing First-line Regimen

**Host**
- Age, Sex, Family Plans
- Meds/Co-morbidities
- Occupation/Lifestyle
- Predicted Adherence
- HLA-B*5701
- Patient Preference

**Virus**
- Baseline Viral Load
- Tropism (CCR5, CXCR4)
- Transmitted Resistance

**ARV**
- Efficacy, Tolerability
- Long-term safety
- Drug-Drug interactions
- Pharmacokinetics
- Pill burden, cost
### DHHS Antiretroviral Therapy Guidelines: October 2011
**Preferred Regimens for ARV-Naïve Patients: Pill Burden**

<table>
<thead>
<tr>
<th>Class</th>
<th>Therapy</th>
<th>Pill Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI-Based</td>
<td>Efavirenz-Tenofovir-Emtricitabine</td>
<td>![Pill Burden Icon]</td>
</tr>
<tr>
<td>PI-Based</td>
<td>Ritonavir + Atazanavir + Tenofovir-Emtricitabine</td>
<td>![Pill Burden Icon]</td>
</tr>
<tr>
<td></td>
<td>Darunavir + Ritonavir + Tenofovir-Emtricitabine</td>
<td>![Pill Burden Icon]</td>
</tr>
<tr>
<td>INSTI-Based</td>
<td>Raltegravir + Tenofovir-Emtricitabine</td>
<td>![Pill Burden Icon]</td>
</tr>
</tbody>
</table>

Efavirenz-based Regimens (Atripla)

Advantages
- Long history as Gold Standard
- Never lost head-to-head trial
- Only preferred One Pill QD
- Appropriate for TB co-infection

Disadvantages
- Low genetic resistance barrier
- Higher risk of NRTI resistance with NNRTI failure
- CNS adverse effects
- 1\textsuperscript{st} trimester teratogenicity
- Potential drug-drug interactions

Atazanavir/ritonavir-based Regimens

Advantages
- Equivalent to EFV at 96 weeks\(^1\)
- Favorable lipid effects\(^2,3\)
- Low resistance risk at failure\(^1-3\)
- 3 pills QD, only 100 mg ritonavir

Disadvantages
- Impaired absorption with acid-reducing agents
- Unconjugated hyperbilirubinemia in 4-9% of patients\(^4\)
- Food requirements for dosing
- No co-formulations available
- Requires 100 mg ritonavir

---

Darunavir/ritonavir-based Regimens

Advantages
- Most potent PI
- Favorable lipid effects\(^1,2\)
- Low resistance risk at failure\(^1,2\)
- 4 pills QD, only 100 mg ritonavir

Disadvantages
- Rash in ~6% of patients; caution for use in sulfa-allergic patients\(^3\)
- No co-formulations available
- No head-to-head comparisons with other recommended agents
- Requires 100 mg ritonavir

\(^3\) Darunavir [package insert]. November 2011.
Raltegravir-based Regimens

**Advantages**
- Comparable to EFV at 4-year follow-up, regardless of baseline CD4/VL
- Very well-tolerated
- Few drug interactions
- Favorable Lipid profile
- Greater CD4+ increase than EFV

**Disadvantages**
- Requires BID dosing
- Low genetic barrier to resistance
- Risk of NRTI resistance with failure
- No co-formulations w/ other classes
- Potential for skin reactions
- Little data except with FTC/TDF

---

CONSIDERING INDIVIDUAL PATIENT FACTORS
Patient Factors: HIV VL > 100,000

Do all agents perform equally well?

- **Efavirenz** (EFV) – equivalent at all VL strata\(^1,2\)
- **Atazanavir** (ATZ/r) – similar efficacy to EFV\(^2\) and LPV/r\(^3\)
- **Darunavir** (DRV/r) – superior to LPV/r\(^4\)
- **Raltegravir** (RAL)– similar to EFV\(^5\)
- **Truvada** (FTC/TDF) – superior to Epzicom (ABC/3TC)\(^2\)

- **Epzicom** (ABC/3TC) – more virologic failures
- **Complera** (FTC/TDF/RPV) – more virologic failures

---

Patient Factors: Adherence Concerns

- **Efavirenz** (EFV) and **Raltegravir** (RAL) both have a lower genetic barrier to resistance.
- Long half-life of **Efavirenz** (EFV) makes it vulnerable to drug resistance due to shorter half-life of other agents in **Atripla** (FTC/TDF/EFV).
- **Protease Inhibitors** (**Atazanavir**, ATZ/r and **Darunavir** DRV/r) have a high genetic barrier to resistance and low incidence of drug resistance even on failure.
Patient Factors: Viral Hepatitis

Hepatitis B

- Emtricitabine (FTC), Tenofovir (TDF), Lamivudine (3TC) all have activity against Hepatitis B. Preferred to use either FTC/TDF, 3TC/TDF, or 3TC/Entecavir in context of ART
- Caution at discontinuation or regimen switch regarding rebound of HBV if any active agents are removed

Hepatitis C

- Drug-induced liver injury more common, but can’t specify individual agents (except NVP, d4T, ddI, RTV)
- ART has overlapping toxicity and many drug-drug interactions with new HCV Protease Inhibitors; AVOID ddI, d4T, ZDV; Truvada (FTC/TDF) + Raltegravir probably has least interactions
Patient Factors: CV disease or Hyperlipidemia

How will ART affect my patient’s lipids?

- Protease Inhibitors generally increase lipids but **Atazanavir** (ATZ/r) and **Darunavir** (DRV/r) have mild effects compared to **Lopinavir** (LPV/r)\(^3, 4\)

- **Efavirenz** (EFV) adversely affected cholesterol more than **Atazanavir** (ATZ/r)\(^2\) and **Raltegravir** (RAL)\(^1\)

- **Raltegravir** (RAL) appears to be neutral with respect to lipid changes\(^1\)

- Concern for **Abacavir** (ABC)-related cardiovascular risk

---

Patient Factors: Renal Function

- Some ARV’s require renal dose adjustment making fixed dose combinations (Truvada FTC/TDF, Epzicom ABC/3TC) problematic
- Tenofovir (TDF) has been associated with declining renal function over time in some patients\(^1\), perhaps made worse in presence of boosted PI’s\(^2, 3\).
- Cumulative exposure to Atazanavir (ATZ/r) was associated with reversible renal dysfunction\(^4\)

Must have a candid discussion regarding future plans to initiate pregnancy

- **Efavirenz** (EFV, Atripla, FTC/TDF/EFV) felt to be teratogenic in 1st Trimester
- Limited data on **Raltegravir** (RAL) and Darunavir (DRV) in pregnancy
- **Combivir** (AZT/3TC) + **Lopinavir** (LPV/r) preferred agent in pregnancy, however **Truvada** (FTC/TDF) + **Atazanavir** (ATZ/r) acceptable
Patient Factors: Dyspepsia/GERD

- Use of acid-reducing agents is associated with reduction of **Atazanavir** (ATZ/r) and **Rilpivirine** (RPV) concentration.
- Can theoretically be overcome by stepping down to H2-antagonists and/or dosing antacid 12 hrs apart from **Atazanavir** (ATZ/r) dose.
- **Raltegravir** (RAL) concentrations may be increased by concurrent use of proton-pump inhibitors.
Patient Factors: Psychiatric Disease

- **Efavirenz** (EFV) associated with neuropsychiatric side effects such as dizziness, vivid dreams,
- **Atripla** (FTC/TDF/EFV) thus not a great choice for patients significant mental health diagnoses:
  - bipolar disorder
  - Severe PTSD
  - Schizophrenia
- **Complera** (FTC/TDF/RPV) has less neuropsychiatric effects, but more virologic failures than Atripla (FTC/TDF/RPV) and currently not a ‘preferred’ agent
WHEN IS IT APPROPRIATE NOT TO USE A ‘PREFERRED’ REGIMEN?
## DHHS Antiretroviral Therapy Guidelines: October 2011
### Alternative Regimens for ARV-Naïve Patients

<table>
<thead>
<tr>
<th>Class</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI-Based</td>
<td>Efavirenz + Abacavir-Lamivudine (BI)</td>
</tr>
<tr>
<td></td>
<td>Rilpivirine + Tenofovir-Emtricitabine (BI)</td>
</tr>
<tr>
<td></td>
<td>Rilpivirine + Abacavir-Lamivudine (BIII)</td>
</tr>
<tr>
<td>PI-Based</td>
<td>Atazanavir + Ritonavir + Abacavir-Lamivudine (BI)</td>
</tr>
<tr>
<td></td>
<td>Darunavir + Ritonavir + Abacavir-Lamivudine (BIII)</td>
</tr>
<tr>
<td></td>
<td>Fosamprenavir (1-2x daily) + Ritonavir + Abacavir-Lamivudine (BI)</td>
</tr>
<tr>
<td></td>
<td>Fosamprenavir (1-2x daily) + Ritonavir + Tenofovir-Emtricitabine (BI)</td>
</tr>
<tr>
<td></td>
<td>Lopinavir-Ritonavir (1-2x daily) + Abacavir-Lamivudine (BI)</td>
</tr>
<tr>
<td></td>
<td>Lopinavir-Ritonavir (1-2x daily) + Tenofovir-Emtricitabine (BI)</td>
</tr>
<tr>
<td>INSTI-Based</td>
<td>Raltegravir + Abacavir-Lamivudine (BIII)</td>
</tr>
</tbody>
</table>

Source: DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)
### DHHS Antiretroviral Therapy Guidelines: October 2011

Acceptable Regimens for ARV-Naïve Patients

<table>
<thead>
<tr>
<th>Class</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NNRTI-Based</strong></td>
<td>Efavirenz + Zidovudine-Lamivudine (CI)</td>
</tr>
<tr>
<td></td>
<td>Nevirapine + Tenofovir-Emtricitabine (CI)</td>
</tr>
<tr>
<td></td>
<td>Nevirapine + Zidovudine-Lamivudine (CI)</td>
</tr>
<tr>
<td></td>
<td>Nevirapine + Abacavir-Lamivudine (CIII)</td>
</tr>
<tr>
<td></td>
<td>Rilpivirine + Zidovudine-Lamivudine (CIII)</td>
</tr>
<tr>
<td><strong>PI-Based</strong></td>
<td>Atazanavir + Abacavir-Lamivudine (CI)</td>
</tr>
<tr>
<td></td>
<td>Atazanavir + Zidovudine-Lamivudine (CI)</td>
</tr>
<tr>
<td></td>
<td>Darunavir + Ritonavir + Zidovudine-Lamivudine (CIII)</td>
</tr>
<tr>
<td></td>
<td>Fosamprenavir + Ritonavir + Zidovudine-Lamivudine (CI)</td>
</tr>
<tr>
<td></td>
<td>Lopinavir-Ritonavir + Zidovudine-Lamivudine (CI)</td>
</tr>
<tr>
<td><strong>INSTI-Based</strong></td>
<td>Raltegravir + Zidovudine-Lamivudine (CIII)</td>
</tr>
<tr>
<td><strong>CCR5 Antagonist-Based</strong></td>
<td>Maraviroc + Zidovudine-Lamivudine (CI)</td>
</tr>
<tr>
<td></td>
<td>Maraviroc + Tenofovir-Emtricitabine (CIII)</td>
</tr>
<tr>
<td></td>
<td>Maraviroc + Abacavir-Lamivudine (CIII)</td>
</tr>
</tbody>
</table>

Source: DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)
Summary: Selecting an Initial ART Regimen

- Four ‘preferred’ regimens all have extensive safety and efficacy experience through many clinical trials.
- ‘Third agents’ (Efavirenz, Atazanavir, Darunavir, and Raltegravir) have advantages and disadvantages that must be discussed with the patient.
- Patient-level factors (e.g. childbearing potential, co-infections, co-morbidities, medlist) should be considered when selecting the ideal ART regimen.
- Occasionally an Alternative regimen may be appropriate.
- Respect the patient’s opinion as it will affect adherence.