Antiretroviral Therapy Guidelines

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: February 22, 2012
WHEN TO START

- October 2011 DHHS Guidelines
- July 2010 IAS-USA Guidelines
- Supporting Evidence Base
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).
Natural History of Untreated HIV Infection

CD4 Cell Count vs. Years

CD4 < 200: High risk for Opportunistic Infection
Initiating Antiretroviral Therapy in Treatment-Naïve Patients

Change in CD4 Threshold in DHHS Guidelines

Source: DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)
DHHS Antiretroviral Therapy Guidelines: October 2011
Initiating Therapy in Treatment-Naïve Patients

Source: DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)
Antiretroviral therapy indicated regardless of CD4 cell count.
## DHHS Antiretroviral Therapy Guidelines: October 2011
### Initiating Therapy in Treatment-Naïve Patients

<table>
<thead>
<tr>
<th>CD4 Cell Count</th>
<th>Recommendation for Antiretroviral Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;350 cells/mm³</td>
<td><strong>Strongly Recommend</strong> Initiating Therapy (AI)</td>
</tr>
</tbody>
</table>
| 350-500 cells/mm³  | **Recommend** Initiating Therapy (A/B-II):  
- 55% of panel voted for strong recommendation (A)  
- 45% of panel voted for moderate recommendation (B) |
| >500 cells/mm³     | **Consider** Initiating Therapy (B/C-III):  
- 50% of panel favor starting antiretroviral therapy (B)  
- 50% of panel view treatment is optional (C)           |

### Initiating Antiretroviral Therapy Regardless of CD4 Cell Count
- History of AIDS-defining illness (AI)
- Pregnancy (AI)
- Hepatitis B virus (HBV) co-infection when treatment of HBV is indicated (AIII)
- HIV associated nephropathy (AII)

Source: DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)
Antiretroviral Treatment of Adult HIV Infection
2010 Recommendations of the International AIDS Society–USA Panel

Melanie A. Thompson, MD
Judith A. Abercrombie, MD
Pedro Cahn, MD
Julio S. G. Montaner, MD
Giuliano Rizzardini, MD
Amalio Telen, MD, PhD
Jose M. Gutierrez, MD, PhD
Holger C. G. Guntner, MD
Scott M. Hammer, MD
Martin S. Hirsch, MD
Donna M. Jacobson, BS
Peter Reiss, MD, PhD
Douglas D. Richman, MD
Paul A. Volberding, MD
Patrick Yeni, MD
Robert T. Schooley, MD

Successful antiretroviral therapy (ART) is associated with dramatic decreases in AIDS-defining conditions and their associated mortality. Expansion of treatment options and evolving knowledge require revision of guidelines for the initiation and long-term management of ART in adults with HIV infection.

Since the 2008 International AIDS Society–USA ART guidelines, new data have emerged regarding timing of therapy, optimal regimen choices, and monitoring. There are also issues of special relevance to circumstances such as pregnancy, hepatitis virus coinfections, kidney disease, cardiovascular disease, and primary HIV infection.

Analyses of clinical trials and epidemiologic cohorts have shed light on the role of ART in mitigating serious non-AIDS events associated with untreated HIV replication. Newer drugs are better understood in terms of efficacy, toxicity, and potential uses. New data also suggest a role for ART in the prevention of HIV transmission.

METHODS
The panel was convened in 1995 to develop evidence-based recommendations for ART for HIV-infected adults in developed-world settings. Members are appointed by the International AIDS Society–USA according to clinical and research expertise. Current panel members do not participate in pharmaceutical marketing or promotional activities (e.g., speakers bureaus, industry satellites) during tenure on the panel. The current panel convened in January 2010 and met weekly in person or by teleconference. Data published or presented in specific scientific meetings since the last report...

**Consider**

*Consider unless patient is an elite controller (HIV RNA < 50 copies/ml) or has stable CD4 cell count and low-level viremia in absence of HAART*

**CD4 Cell Count**

- **500**
  - **Consider**
- **500-**
  - **Recommend**
- **< 500**
  - **Recommend**

Antiretroviral Therapy Recommend regardless of CD4 cell count with following conditions:

- Symptomatic HIV
- Pregnancy
- HIV RNA > 100,000 copies/ml
- Rapid CD4 Decline (> 100/yr)
- Chronic HBV
- Chronic HCV
- Active or High-Risk for CVD
- HIVAN
- Symptomatic Primary HIV
- Age > 60
- High Risk for 2° Transmission

# IAS-USA Antiretroviral Therapy Guidelines: July 2010

## Recommendations for Initiating Therapy in Treatment-Naive Adults

<table>
<thead>
<tr>
<th>Measure</th>
<th>Antiretroviral Therapy Recommendation</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Specific Conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic HIV Disease</td>
<td>Antiretroviral Therapy Recommended Regardless of CD4 cell Count</td>
<td>Ala</td>
</tr>
<tr>
<td>Pregnant women</td>
<td></td>
<td>Ala</td>
</tr>
<tr>
<td>HIV-1 RNA &gt; 100,000 copies/ml</td>
<td></td>
<td>Alla</td>
</tr>
<tr>
<td>Rapid decline in CD4 count, &gt; 100/µl per year</td>
<td></td>
<td>Alla</td>
</tr>
<tr>
<td>Active HBV or HCV coinfection</td>
<td></td>
<td>BIIa, Alla</td>
</tr>
<tr>
<td>Active or high risk for cardiovascular disease</td>
<td></td>
<td>BIIa</td>
</tr>
<tr>
<td>HIV-associated nephropathy</td>
<td></td>
<td>BIIa</td>
</tr>
<tr>
<td>Symptomatic primary HIV infection</td>
<td></td>
<td>BIIa</td>
</tr>
<tr>
<td>High risk for secondary HIV transmission</td>
<td></td>
<td>BIIa</td>
</tr>
<tr>
<td><strong>Asymptomatic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 cell count &lt; 350/µl</td>
<td>Recommended</td>
<td>Ala</td>
</tr>
<tr>
<td>CD4 count 350-500/µl</td>
<td>Recommended</td>
<td>Alla</td>
</tr>
<tr>
<td>CD4 count &gt;500/µl</td>
<td>Consider</td>
<td>CIII</td>
</tr>
</tbody>
</table>

Mounting Evidence supporting Earlier HAART

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Setting</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIPRA HT 001</td>
<td>RCT</td>
<td>Haiti</td>
<td>Deferring ART until CD4&lt;200 associated with higher mortality than starting when CD4 between 200 and 350</td>
</tr>
<tr>
<td>SMART substudy</td>
<td>RCT</td>
<td>Europe, Australia</td>
<td>Deferring ART until CD4&lt;250 associated with higher mortality than starting when CD4 between 350 and 250</td>
</tr>
<tr>
<td>ART-CC</td>
<td>Obs</td>
<td>Europe, North America</td>
<td>Significant increase in risk of AIDS and death when therapy was delayed until patients CD4+ counts fell below 350 cells/mm³ compared to earlier treatment.</td>
</tr>
<tr>
<td>NA-ACCORD</td>
<td>Obs</td>
<td>North America</td>
<td>69% lower mortality in those who initiated in 350-500 range than those who deferred; 94% lower mortality in those who initiated at CD4 &gt; 500 than in those who deferred</td>
</tr>
<tr>
<td>HPTN 052</td>
<td>RCT</td>
<td>Africa, US, Asia, S. America</td>
<td>96% decrease in transmission of HIV in serodiscordant couples when one partner on ART; 41% decrease in AIDS-related events (extra-pulmonary TB) for those on ART</td>
</tr>
</tbody>
</table>

WHAT TO START

- Regimens for ART Naïve Patients
- New, Alternative, and Acceptable Agents
Anti-retroviral drug targets

HIV RNA

HIV DNA

Nucleus

Host Cell

CD4

CCR5

HIV

Entry Inhibitors

Nucleoside RTI

Integrase Inhibitors

Non-Nucleoside RTI

Protease Inhibitors

mRNA

Gag-Pol

Gag

Myr
**Anti-retroviral Therapy in 2012**

**New NNRTI:** Rilpivirine  
Co-formulated with Emtricitabine-Tenofovir as  
**Complera**

---

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

<table>
<thead>
<tr>
<th>NRTI</th>
<th>Dose</th>
<th>Dosage</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rilpivirine</td>
<td>300 mg</td>
<td></td>
<td>Hyperemesis reaction symptoms may include:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>nausea, vomiting, diarrhea, abdominal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>region pain, headache, insomnia,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dyspnea, dyspepsia, design, constipation,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>arthralgia, peripheral neuropathy, paresthesia</td>
</tr>
</tbody>
</table>

---

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

<table>
<thead>
<tr>
<th>NNRTI</th>
<th>Dose</th>
<th>Dosage</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevirapine</td>
<td>200 mg</td>
<td></td>
<td>Rash, headache, altered liver function</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>200 mg</td>
<td>600 mg</td>
<td>Rash, altered liver function, dizziness,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>insomnia, impaired concentration, drowsiness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delavirdine</td>
<td>200 mg</td>
<td></td>
<td>Rash, headache, altered liver function</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>200 mg</td>
<td></td>
<td>Rash, altered liver function, dizziness,</td>
</tr>
<tr>
<td>(EFV)</td>
<td></td>
<td></td>
<td>insomnia, impaired concentration, drowsiness</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>200 mg</td>
<td></td>
<td>Rash, headache, altered liver function</td>
</tr>
</tbody>
</table>

---

**Entry Inhibitors**

- **Enfuvirtide (ENV, Fuzeon®)**: 90 mg/ml, subcutaneously (SQ) 2 times a day (105 mg sq. dissolved in 1.1 ml sterile water)  
  - Store at controlled room temperature

**Combination NRTIs + NNRTI**

<table>
<thead>
<tr>
<th>组合NRTIs + NNRTI</th>
<th>Dosage</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir + Emtricitabine + Rilpivirine (Complera)</td>
<td>TDF 300 mg/FTC 200 mg/ EFV 600 mg</td>
<td>Peripheral neuropathy, headache, nausea, dizziness</td>
</tr>
<tr>
<td>Elvitegravir/ Emtricitabine/Tenofovir/ Rilpivirine (TRUVADA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elvitegravir/ Emtricitabine/Tenofovir/ Rilpivirine (TRITIV)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Integrase Inhibitors**

- **Raltegravir (RAL, Isentress®)**: 400 mg
  - 2 tablets a day  
  - May be taken with or without food

**Protease Inhibitors (PI)**

- **Atazanavir (ATV, Reconstyl®)**: 150 mg, 300 mg  
  - 2 x 200 mg capsules once daily  
  - 2 x 300 mg capsules twice a day  
  - May be taken with or without food

- **Darunavir (DRV, Prezista®)**: 600 mg, 800 mg  
  - 1 x 100 mg tablet twice a day  
  - 2 x 100 mg tablets twice a day  
  - May be taken with food

- **Fosamprenavir (CPV, Lexiva®)**: 700 mg, 2800 mg  
  - 2 x 700 mg tablets twice a day  
  - 1 x 1000 mg tablet once a day  
  - 2 x 1000 mg tablets once a day  
  - May be taken with food

- **Indinavir (IDV, Cordafé®)**: 400 mg, 600 mg  
  - 2 x 400 mg capsules twice a day  
  - 2 x 600 mg capsules twice a day  
  - May be taken with food

- **Lopinavir/Ritonavir (LPV/R, Kaletra®)**: 400 mg/100 mg  
  - 2 x 200 mg pellets once a day  
  - 2 x 300 mg pellets once a day  
  - May be taken with food

- **Nelfinavir (NFV, Viracept®)**: 250 mg, 625 mg  
  - 2 x 250 mg tablets twice a day  
  - 3 x 250 mg tablets 3 times a day  
  - May be taken with food

- **Ritonavir (RTV, Norvi®)**: 100 mg, 200 mg  
  - 2 x 100 mg tablets twice a day  
  - 2 x 200 mg tablets 2 times a day  
  - Take with food

- **Saquinavir (SQV, Invirase®)**: 200 mg, 400 mg  
  - 2 x 200 mg tablets twice a day  
  - 2 x 400 mg tablets 2 times a day  
  - Take with food

- **Tipranavir (TPV, Aptivus®)**: 400 mg  
  - 2 x 200 mg pellets 2 times a day  
  - Take with food

Source: www.nwaetc.org
DHHS Antiretroviral Therapy Guidelines: October 2011
Preferred Regimens for ARV-Naïve Patients

ANTIRETROVIRAL THERAPY: DHHS GUIDELINES

Source: DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)
DHHS Antiretroviral Therapy Guidelines: October 2011
Preferred Regimens for ARV-Naïve Patients

(2) Nucleoside RTI (NRTI) + (2) Nucleoside RTI (NRTI) + (2) Nucleoside RTI (NRTI)

Non-Nucleoside RTI (NNRTI)
Protease Inhibitor
Integrase Inhibitors

OR
BID

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

### Preferred Regimens for ARV-Naïve Patients

<table>
<thead>
<tr>
<th>Class</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI-Based Regimen</td>
<td>Efavirenz-Tenofovir-Emtricitabine (AI)</td>
</tr>
<tr>
<td>PI-Based Regimen</td>
<td>Atazanavir + Ritonavir + Tenofovir-Emtricitabine (AI) Darunavir (qd) + Ritonavir + Tenofovir-Emtricitabine (AI)</td>
</tr>
<tr>
<td>INSTI-Based Regimen</td>
<td>Raltegravir + Tenofovir-Emtricitabine (AI)</td>
</tr>
</tbody>
</table>

Source: DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)
## 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 (<strong>B</strong>I)</td>
</tr>
<tr>
<td></td>
<td>Rilpivirine + Tenofovir-Emtricitabine (<strong>B</strong>I)</td>
</tr>
<tr>
<td></td>
<td>Rilpivirine + Abacavir-Lamivudine (<strong>B</strong>II)</td>
</tr>
<tr>
<td>PI-Based</td>
<td>Atazanavir + Ritonavir + Abacavir-Lamivudine (<strong>B</strong>I)</td>
</tr>
<tr>
<td></td>
<td>Darunavir + Ritonavir + Abacavir-Lamivudine (<strong>B</strong>II)</td>
</tr>
<tr>
<td></td>
<td>Fosamprenavir (1-2x daily) + Ritonavir + Abacavir-Lamivudine (<strong>B</strong>I)</td>
</tr>
<tr>
<td></td>
<td>Fosamprenavir (1-2x daily) + Ritonavir + Tenofovir-Emtricitabine (<strong>B</strong>I)</td>
</tr>
<tr>
<td></td>
<td>Lopinavir-Ritonavir (1-2x daily) + Abacavir-Lamivudine (<strong>B</strong>I)</td>
</tr>
<tr>
<td></td>
<td>Lopinavir-Ritonavir (1-2x daily) + Tenofovir-Emtricitabine (<strong>B</strong>I)</td>
</tr>
<tr>
<td>INSTI-Based</td>
<td>Raltegravir + Abacavir-Lamivudine (<strong>B</strong>II)</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><strong>Effavirenz + Zidovudine-Lamivudine</strong> (CI)</td>
</tr>
<tr>
<td></td>
<td><strong>Nevirapine + Tenofovir-Emtricitabine</strong> (CI)</td>
</tr>
<tr>
<td></td>
<td><strong>Nevirapine + Zidovudine-Lamivudine</strong> (CI)</td>
</tr>
<tr>
<td></td>
<td><strong>Nevirapine + Abacavir-Lamivudine</strong> (CIII)</td>
</tr>
<tr>
<td></td>
<td><strong>Rilpivirine + Zidovudine-Lamivudine</strong> (CIII)</td>
</tr>
<tr>
<td><strong>PI-Based</strong></td>
<td><strong>Atazanavir + Abacavir-Lamivudine</strong> (CI)</td>
</tr>
<tr>
<td></td>
<td><strong>Atazanavir + Zidovudine-Lamivudine</strong> (CI)</td>
</tr>
<tr>
<td></td>
<td><strong>Darunavir + Ritonavir + Zidovudine-Lamivudine</strong> (CIII)</td>
</tr>
<tr>
<td></td>
<td><strong>Fosamprenavir + Ritonavir + Zidovudine-Lamivudine</strong> (CI)</td>
</tr>
<tr>
<td></td>
<td><strong>Lopinavir-Ritonavir + Zidovudine-Lamivudine</strong> (CI)</td>
</tr>
<tr>
<td><strong>INSTI-Based</strong></td>
<td><strong>Raltegravir + Zidovudine-Lamivudine</strong> (CIII)</td>
</tr>
<tr>
<td><strong>CCR5 Antagonist-Based</strong></td>
<td><strong>Maraviroc + Zidovudine-Lamivudine</strong> (CI)</td>
</tr>
<tr>
<td></td>
<td><strong>Maraviroc + Tenofovir-Emtricitabine</strong> (CIII)</td>
</tr>
<tr>
<td></td>
<td><strong>Maraviroc + Abacavir-Lamivudine</strong> (CIII)</td>
</tr>
</tbody>
</table>
SPECIAL POPULATIONS

- Acute HIV Infection
  - Pregnancy
- Opportunistic Infections
  - Tuberculosis
ART in Special Populations: Acute HIV & Pregnancy

Acute HIV Infection

- Benefit unknown for treatment of acute HIV infection; treatment should be considered optional (CIII) except in pregnant women (AI).
- A ritonavir (RTV)-boosted PI-based regimen should be used if therapy is initiated before drug-resistance test results are available (AIII).

Pregnancy

- Antiretroviral therapy (ART) is recommended for all pregnant women, regardless of CD4 count with the goal to prevent perinatal transmission (AI)
- The preferred regimen for pregnant women is Lopinavir/ritonavir (Kaletra) + Zidovudine/Lamivudine (Combivir) twice daily

Source: DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)
ART in Special Populations: OI’s & Tuberculosis

Opportunistic Infections

- In OI’s with no effective therapy (Cryptosporidiosis, Microsporidiosis, PML). Initiate ART as soon as possible (AIII)
- In OI’s with a high potential for IRIS (Cryptococcus, MAC). A short delay may be warranted before initiating ARV treatment (CIII)
- In OI’s known to have better survival with early ART (Pneumocystis pneumonia). ART should not be delayed (AI)

Tuberculosis

<table>
<thead>
<tr>
<th>CD4 Cell Count</th>
<th>Recommendations for TB Therapy and ART</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Start TB therapy immediately (AI)</td>
</tr>
<tr>
<td>&lt; 200 cells/mm³</td>
<td>Initiate ART within 2-4 weeks of starting TB treatment (AI)</td>
</tr>
<tr>
<td>200-500 cells/mm³</td>
<td>Initiate ART within 2-4 weeks, or at least by 8 weeks, after starting TB treatment (AIII)</td>
</tr>
<tr>
<td>&gt; 500 cells/mm³</td>
<td>Initiate ART within 8 weeks of starting TB treatment (BIII)</td>
</tr>
</tbody>
</table>

Source: DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)
When to Start

- DHHS and IAS-USA Guidelines recommend starting ART at or below a CD4 count threshold of 500 cells/mm$^3$. Treatment above this level is considered optional.

What to Start

- Starting regimens should use a dual NRTI backbone of Emtricitabine and Tenofovir (FTC/TDF – Truvada) and a third agent such as Efavirenz, Atazanavir/ritonavir, Darunavir/ritonavir, or Raltegravir
- The role of newly approved agents is constantly evolving

Special Populations

- All pregnant women should start ART to prevent vertical transmission
- ART in the setting of Primary HIV and/or acute OI or TB is complex and evolving based on current evidence