Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

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### Rating Scheme for Recommendations

<table>
<thead>
<tr>
<th>Rating of Recommendation</th>
<th>Rating of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Strong Recommendation</td>
<td>I = Data from randomized controlled trials</td>
</tr>
<tr>
<td>B: Moderate Recommendation</td>
<td>II = Data from well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes</td>
</tr>
<tr>
<td>C: Optional Recommendation</td>
<td>III = Expert opinion</td>
</tr>
</tbody>
</table>

Source: 2012 DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)
WHEN TO START

- March 2012 DHHS Guidelines
- Supporting Evidence Base
Natural History of Untreated HIV Infection

CD4 Cell Count

Year 1  1  2  3  4  5  6  7  8  9  10  11  12  13  14  15

CD4 < 200: High risk for Opportunistic Infection
ANTIRETROVIRAL THERAPY: DHHS GUIDELINES

Initiating Antiretroviral Therapy in Treatment-Naïve Patients
Change in CD4 Threshold in DHHS Guidelines

CD4 Cell Count

- 2003: 200
- 2007: 350
- 2009: 500

[Graph showing changes in CD4 cell count threshold from 2003 to 2009.]
Initiating Antiretroviral Therapy in Treatment-Naïve Patients
Change in CD4 Threshold in DHHS Guidelines

CD4 Cell Count

- 2003: 200
- 2007: 350
- 2009: 500
- 2012: 1000

ANTIRETROVIRAL THERAPY: DHHS GUIDELINES
DHHS Antiretroviral Therapy Guidelines: October 2011
Initiating Therapy in Treatment-Naïve Patients

- **Consider**: CD4 cell count between 350 and 500
  - Favor: 50% of panel
  - Optional: 50% of panel

- **Recommend**: CD4 cell count below 350
  - Strong: 55% of panel
  - Moderate: 45% of panel

- **Strongly Recommend**: CD4 cell count below 350
  - Strong: 55% of panel

Source: 2011 DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)
DHHS Antiretroviral Therapy Guidelines: March 2012
Initiating Therapy in Treatment-Naïve Patients

Source: 2012 DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)
DHHS Antiretroviral Therapy Guidelines: October 2011
Initiating Therapy in Treatment-Naïve Patients

Antiretroviral therapy indicated regardless of CD4 cell count

Source: 2011 DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)
### Initiating Antiretroviral Therapy Regardless of CD4 Count*

<table>
<thead>
<tr>
<th>Strong Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical AIDS</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Chronic HBV</td>
</tr>
<tr>
<td>HIVAN</td>
</tr>
<tr>
<td><strong>AI</strong></td>
</tr>
<tr>
<td><strong>AI</strong></td>
</tr>
<tr>
<td><strong>AII</strong></td>
</tr>
<tr>
<td><strong>AII</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 50</td>
</tr>
<tr>
<td><strong>BIII</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic HCV</td>
</tr>
<tr>
<td><strong>BII</strong></td>
</tr>
</tbody>
</table>

*ART should be offered to patients who are at risk of transmitting HIV to sexual partners

- **AI** Heterosexuals
- **AIII** other groups

Source: 2012 DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)
## 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>Partners</td>
<td>Obs</td>
<td>Africa</td>
<td>92% drop in transmission of HIV when index pt on ART</td>
</tr>
<tr>
<td>HPTN 052</td>
<td>RCT</td>
<td>Africa, Asia, S. America 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 (treatment threshold 350 cells/mm³)</td>
</tr>
</tbody>
</table>
DHHS Antiretroviral Therapy Guidelines: March 2012
Initiating Therapy in Treatment-Naïve Patients
Factors Affecting Decision on When to Initiate Therapy

Earlier Therapy
- More effective regimens
- More convenient regimens
- Better tolerated therapy
- Less long-term toxicity
- Better immune recovery
- Lower rates of resistance
- More treatment options
- Concerns for uncontrolled viremia
- Decrease HIV transmission

Later Therapy
- Lack of RCT data supporting early Rx
- Potential drug toxicity
- Drug and monitoring cost
- Potential negative impact on QOL
START (Strategic Timing of ART) Insight Network: international recruiting

**Study Design**

**Protocol**
- N = 4000
- Randomized 1:1
- 237 study sites in 36 countries
- Antiretroviral naïve
- Age ≥ 18 years
- CD4 ≥ 500 cells/mm$^3$ x 2 within 60 d
- No prior AIDS condition
- No Malignancy, hemodialysis, CV event

**Early ART**
Initiate immediately on Randomization (n = 2,000)

**Deferred ART**
Defer until CD4 < 350 cells/mm$^3$ or AIDS (n = 2,000)

- Current (7/12) enrollment = 2709 (68%)
- Anticipated Duration ~ 6 years

Source: http://insight.ccbr.umn.edu/start/
WHAT TO START

Regimens for Antiretroviral-Naïve Patients

- New, Alternative, Acceptable Regimens
- Changes to Perinatal ART Guidelines
Anti-retroviral drug targets

- HIV RNA
- HIV DNA
- Nucleus
- Host Cell
- CD4
- CCR5
- Entry Inhibitors
- Non-Nucleoside RTI
- Nucleoside RTI
- Integrase Inhibitors
- Protease Inhibitors
- mRNA
- Gag-Pol
- Gag
- Myr
- HIV RNA
- HIV DNA
- HIV
Anti-retroviral Therapy in 2012

New NNRTI: Rilpivirine
Co-formulated with Emtricitabine-Tenofovir as Complera
DHHS Antiretroviral Therapy Guidelines: March 2012
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: 2012 DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)
(2) Nucleoside RTI (NRTI) + Non-Nucleoside RTI (NNRTI) + Protease Inhibitor OR (2) Nucleoside RTI (NRTI) + Non-Nucleoside RTI (NNRTI) + Integrase Inhibitors

Source: DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)
### DHHS Antiretroviral Therapy Guidelines: March 2012

#### Preferred Regimens for ARV-Naïve Patients

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

Source: 2012 DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)
### DHHS Antiretroviral Therapy Guidelines: March 2012
#### 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: 2012 DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)
### DHHS Antiretroviral Therapy Guidelines: March 2012

Acceptable Regimens for ARV-Naïve Patients

<table>
<thead>
<tr>
<th>Class</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI-Based</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>PI-Based</td>
<td>Atazanavir + Abacavir-Lamivudine (CI)</td>
</tr>
<tr>
<td></td>
<td>Atazanavir + Zidovudine-Lamivudine (CI)</td>
</tr>
<tr>
<td></td>
<td>Atazanavir + Ritonavir + 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 (CIII)</td>
</tr>
<tr>
<td>INSTI-Based</td>
<td>Raltegravir + Zidovudine-Lamivudine (CIII)</td>
</tr>
<tr>
<td>CCR5 Antagonist-Based</td>
<td>Maraviro + Zidovudine-Lamivudine (CI)</td>
</tr>
<tr>
<td></td>
<td>Maraviro + Tenofovir-Emtricitabine (CIII)</td>
</tr>
<tr>
<td></td>
<td>Maraviro + Abacavir-Lamivudine (CIII)</td>
</tr>
</tbody>
</table>

Source: 2012 DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)
### DHHS Antiretroviral Therapy Guidelines: March 2012

Regimens may be Acceptable but should be used with Caution

<table>
<thead>
<tr>
<th>Class</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI-Based</td>
<td>Saquinavir + Ritonavir + Tenofovir-Emtricitabine (CI)</td>
</tr>
<tr>
<td></td>
<td>Saquinavir + Ritonavir + Abacavir-Lamivudine (CIII)</td>
</tr>
<tr>
<td></td>
<td>Saquinavir + Ritonavir + Zidovudine-Lamivudine (CIII)</td>
</tr>
</tbody>
</table>

Source: 2012 DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)
Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States

Downloaded from http://aidsinfo.nih.gov/guidelines on 8/2/2012 EST.
Visit the AIDSinfo website to access the most up-to-date guideline.
Register for e-mail notification of guideline updates at http://aidsinfo.nih.gov/news.
Pre-Conception

- ART recommended for HIV+ partner in sero-discordant couples (AI for CD4 < 550 cells/mm³, BIII for CD4 >550 cells/mm³)
- Maximal viral suppression recommended before conception (AIII)
- Peri-conception PrEP for HIV- partners may reduce risk (CIII)
- Testing for Hepatitis C and Tuberculosis is recommended (CIII)

Intra-Partum

- Intravenous AZT (Zidovudine) no longer required for HIV+ women receiving combination ART who have HIV RNA <400 copies/mL (BII)

Post-Partum

- ART for exposed infants should include AZT (Zidovudine) x 6 weeks with option of adding NVP (Nevirapine) (1st dose 0-48 hrs, 2nd dose 48 hours after 1st, 3rd dose 96 hrs after 2nd (AI)

Source: 2012 DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)
What to Start

• ddI (Didanosine) and d4T (Stavudine): alternative → use in special circumstances

• ATZ/r (Atazanavir): alternative → preferred

• DRV/r (Darunavir): insufficient data → alternative

• RAL (Raltegravir): insufficient data → use in special circumstances

• EFV (Efavirenz): “Because the risk of neural tube defects is restricted to the first 5-6 weeks and pregnancy is rarely diagnosed before 4-6 weeks of pregnancy and unnecessary ARV drug changes during pregnancy may be associated with loss of virologic control and increased risk of perinatal transmission, EFV may be continued in pregnant women receiving an EFV-based regimen who present for care in the 1st trimester, provided there is virologic suppression on the regimen”

Source: 2012 DHHS Antiretroviral Therapy Guidelines. (aidsinfo.nih.gov)
Antiretroviral Therapy Guidelines - Summary

When to Start

- DHHS and IAS-USA Guidelines recommend ART for all HIV-infected individuals; strength of recommendations differs at different CD4 levels

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

- ATZ/r is now a preferred agent, Efavirenz can be used in pregnancy beyond 6th week gestation, Raltegravir in pregnancy is discussed by not endorsed…more data needed
Questions?