Update: 2012 HIV Treatment Guidelines

Daniel Lee, MD
August 30, 2012

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Learning Objectives

1) Understand when initiation of antiretrovirals is recommended for treatment of adult HIV infection

2) Identify appropriate antiretrovirals for the treatment of adult HIV infection

3) Understand modifications in the timing and choice of antiretrovirals in specific conditions
Antiretroviral Treatment of Adult HIV Infection: 2012 Recommendations of the International Antiviral Society–USA Panel

Melanie A. Thompson, MD; Judith A. Aberg, MD; Jennifer F. Hoy, MBBS, FRACP; Amalio Telenti, MD, PhD; Constance Benson, MD; Pedro Cahn, MD, PhD; Joseph J. Eron Jr, MD; Huldrych F. Günthard, MD; Scott M. Hammer, MD; Peter Reiss, MD, PhD; Douglas D. Richman, MD; Giuliano Rizzardini, MD; David L. Thomas, MD; Donna M. Jacobsen, BS; Paul A. Volberding, MD

IAS–USA Antiretroviral Guidelines

- Authored by 15-member, international (6 countries) panel
  - Members receive no compensation and do not participate in industry promotional activities while on the panel
- Based upon pathogenesis- and evidence-based individualization of therapy
- Primarily for clinicians in highly resourced settings; however, principles are universally applicable
- Reviewed data published or presented 7/10 – 5/12
- Rated on strength of recommendations and quality of evidence
- Focused on when to start therapy; pre-exposure prophylaxis; what to start; patient monitoring; treatment-experienced patients

Rationale for Issuing Revised Guidelines

• Evaluate new data showing all patients may benefit from ART

• Evaluate new data that ART reduces likelihood of HIV transmission

• Consider issues of relevance to persons with hepatic, renal, or cardiovascular comorbidities; opportunistic infections; or at high risk for HIV transmission

When to Start
# Risks and Benefits of Earlier Initiation of ART

**Benefits**

- Prevention of progressive immune dysfunction (reduced immune activation)
- Delayed progression to AIDS and prolonged survival
- Decreased risk of non-AIDS/HIV-related morbidity (HIVAN, malignancies, neurocognitive dysfunction, cardiovascular disease, etc)
- Decreased drug resistance
- Decreased risk for some ARV toxicities
- Decreased HIV transmission

**Risks**

- Reduced quality of life
- Development of drug resistance if adherence is suboptimal
- Limitation in future choices of ART if drug resistance occurs
- Uncertain long-term toxicities and duration of effectiveness for some drugs/regimens
- Possible transmitted drug resistance
Rationale for Recommending ART for All HIV-Infected Adults

- Uncontrolled HIV replication, immune activation and inflammation associated with ‘non-AIDS’ illnesses
  - Cardiovascular, hepatic, renal, malignancies
  - ART and high CD4 associated with decreased disease incidence

- Patients starting ART when CD4 counts are < 350/µL have greater morbidity and mortality than those starting when CD4 counts are < 500/µL

- Increasing evidence of detrimental effects of uncontrolled viremia at CD4 cell counts > 500/µL

When to Start ART: IAS–USA Recommendations 2012

- Patient readiness should be considered when deciding to initiate antiretroviral therapy (ART)
- ART should be offered regardless of CD4 cell count (increasing strength of the recommendation as CD4 decreases)
  - CD4 ≤ 500 cells/µL (AIa)
  - CD4 > 500 cells/µL (BIII)
  - Pregnancy (Ala)
  - Chronic HBV (Ala)
  - HCV (may delay until after HCV treatment if CD4 > 500) (CIII)
  - Age older than 60 (BIIa)
  - HIV-associated nephropathy (Ala)
  - Acute phase of primary HIV infection, regardless of symptoms (BIII)
Initial Regimens in the Treatment-Naive Patient
# Available Antiretroviral Agents

## Nucleoside RTIs
- Zidovudine (ZDV)
- Didanosine (ddl)
- Zalcitabine (ddC)
- Stavudine (d4T)
- Lamivudine (3TC)
- Abacavir (ABC)
- Emtricitabine (FTC)

## Nonnucleos(t)ide RTIs
- Nevirapine (NVP)
- Delavirdine (DLV)
- Efavirenz (EFV)
- Etravirine (ETR)
- Tenofovir DF (TDF)

## Protease Inhibitors
- Saquinavir (SQV)
- Ritonavir (RTV)
- Indinavir (IDV)
- Nelfinavir (NFV)
- Amprenavir (APV)
- Lopinavir/r (LPV/r)
- Atazanavir (ATV)
- Fosamprenavir (Fos-APV)
- Tipranavir (TPV)
- Darunavir (DRV)
- Ritonavir (RTV)
- Cobicistat* (cobi)

## Boosters
- Ritonavir (RTV)
- Cobicistat* (cobi)

## Integrase Inhibitors
- Raltegravir (RAL)
- Dolutegravir*
- Elvitegravir*

## Fusion Inhibitor
- Enfuvirtide (T-20)

## CCR5 Antagonist
- Maraviroc (MVC)

* In expanded access or submitted for regulatory approval

July 20, 2012
Choice of Initial Regimen

Tenofovir/emtricitabine (TDF/FTC)  OR  Abacavir/lamivudine (ABC/3TC)

WITH

Third agent (NNRTI, boosted PI, or InSTI):

• Efavirenz  OR
• Atazanavir/r  OR
• Darunavir/r  OR
• Raltegravir

### Recommended Initial Antiretroviral Regimens*

<table>
<thead>
<tr>
<th>Component</th>
<th>Recommended Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI plus nRTIs</td>
<td>• Efavirenz/tenofovir/emtricitabine (Ala)</td>
</tr>
<tr>
<td></td>
<td>• Efavirenz plus abacavir/lamivudine (Ala) in HLA-B*5701-negative patients with baseline plasma HIV-1 RNA &lt;100,000 copies/mL</td>
</tr>
<tr>
<td>PI/r plus nRTIs</td>
<td>• Darunavir/r plus tenofovir/emtricitabine (Ala)</td>
</tr>
<tr>
<td></td>
<td>• Atazanavir/r plus tenofovir/emtricitabine (Ala)</td>
</tr>
<tr>
<td></td>
<td>• Atazanavir/r plus abacavir/lamivudine (Ala) in patients with plasma HIV-1 RNA &lt;100,000 copies/mL</td>
</tr>
<tr>
<td>InSTI plus nRTIs</td>
<td>• Raltegravir plus tenofovir/emtricitabine (Ala)</td>
</tr>
</tbody>
</table>

* See comments

### Alternative Initial Antiretroviral Regimens*

<table>
<thead>
<tr>
<th>Component</th>
<th>Alternative Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI plus nRTIs</td>
<td>• Nevirapine plus tenofovir/emtricitabine or abacavir/lamivudine (BIIa)</td>
</tr>
<tr>
<td></td>
<td>• Rilpivirine/tenofovir/emtricitabine (or rilpivirine plus abacavir/lamivudine) with baseline plasma HIV-1 RNA &lt; 100,000 copies/mL (BIIa)</td>
</tr>
<tr>
<td>PI/r plus nRTIs</td>
<td>• Darunavir/r plus abacavir/lamivudine (BIII)</td>
</tr>
<tr>
<td></td>
<td>• Lopinavir/r plus tenofovir (BIIa) (or abacavir/lamivudine) (BIIa)</td>
</tr>
<tr>
<td>InSTI plus nRTIs</td>
<td>• Raltegravir plus abacavir/lamivudine (BIIa)</td>
</tr>
<tr>
<td></td>
<td>• <em>Elvitegravir/cobicistat/tenofovir/emtricitabine</em> (BIIb)</td>
</tr>
</tbody>
</table>

* See comment

**Submitted for regulatory approval

## CCR5 Antagonist–Based and nRTI-Sparing Initial Regimens in Special Circumstances Only

<table>
<thead>
<tr>
<th>Component</th>
<th>Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCR5 antagonist plus nRTIs, (NNRTI-, PI-, and InSTI-sparing)</td>
<td>• Maraviroc plus tenofovir/emtricitabine or abacavir/lamivudine (CIII)</td>
</tr>
<tr>
<td>PI/r plus InSTI (nRTI-sparing)</td>
<td>• Darunavir/r plus raltegravir (BIIa)</td>
</tr>
<tr>
<td></td>
<td>• Lopinavir/r plus raltegravir (Bla)</td>
</tr>
</tbody>
</table>

* See comments

Recommendations for Initial Treatment in the Settings of Specific Conditions

- In patients with or at high risk of cardiovascular disease, avoiding use of abacavir, lopinavir/r, or fosamprenavir/r might be considered (BIIa)
- In patients with reduced renal function, tenofovir should be avoided, or if treatment for HBV coinfection is needed, dosing should be adjusted according to the prescribing information (AIIa)
- Given the increased risk of fragility fractures, it may be prudent to avoid tenofovir as part of initial therapy in postmenopausal women (BIIa)

Recommendations for Initial Treatment in the Settings of Specific Conditions (cont’d)

• The recommended initial ART regimen in the setting of rifampin–based tuberculosis treatment is efavirenz plus 2 nRTIs (Ala)

• The recent recommendation for use of a 3-month, once-weekly regimen of isoniazid with rifapentine for treatment of latent TB infection is not recommended for HIV-infected patients receiving ART (BIII).

• The ART regimen for HIV- and HBV–coinfected persons should include tenofovir and emtricitabine or lamivudine as the nRTI background (Ala)

Conclusions
Conclusions I

• Recommendation to begin therapy earlier in asymptomatic persons is informed by
  
  – Increased evidence of the harmful effects of uncontrolled viremia and its associated immune activation and inflammation, even at higher CD4 cell counts
  
  – Evidence that all HIV-infected adults may benefit from ART
  
  – Data showing ART reduces likelihood of transmission

Summary of Selected New Recommendations and Those for Which Strength or Quality of Evidence Has Changed Substantially in 2012

• ART is recommended and should be offered regardless of CD4 cell count (A1a-CIII depending on CD4 cell count and existing conditions).

• ART is recommended and should be offered to persons during the acute phase of primary HIV infection, regardless of symptoms (BIII).

Summary of Selected New Recommendations and Those for Which Strength or Quality of Evidence Has Changed Substantially in 2012 (cont’d)

- ART should be started as soon as possible, preferably within the first 2 weeks of diagnosis, in patients with opportunistic infections (other than cryptococcal and tuberculous meningitis), with attention to drug interactions and the potential for immune reconstitution inflammatory syndrome (IRIS) (Ala).

- The optimal timing of ART initiation in patients with cryptococcal meningitis is less certain, but initiating ART early during cryptococcal treatment may be associated with higher mortality; therefore, ART initiation in patients with cryptococcal meningitis should be managed in consultation with experts (BIII).

ART is recommended in all HIV-infected persons with TB and should be started within weeks of TB treatment when CD4 cell count is below 50/μL and by 8 to 12 weeks for those with higher CD4 cell counts (Ala). The optimal timing for patients with TB meningitis is less certain, but ART should be started within the first 2 to 8 weeks of TB treatment and managed in consultation with experts (BIII).

Abacavir/lamivudine (in patients with HIV-1 RNA levels < 100,000 copies/mL) is now a recommended rather than alternative dual nRTI component of initial ART (Ala).

Summary of Selected New Recommendations and Those for Which Strength or Quality of Evidence Has Changed Substantially in 2012 (cont’d)

- Rilpivirine has been added as an alternative NNRTI component of the initial regimen (B1a).
- Coformulated elvitegravir/cobicistat/tenofovir/emtricitabine has been added as an initial regimen component, pending regulatory approval (B1b). Elvitegravir is an investigational InSTI and cobicistat is an investigational pharmocokinetic booster.
- Given increased risk of fragility fractures in postmenopausal women, it may be prudent to consider avoiding tenofovir as part of initial therapy in this group (BIIa).

The recommended initial ART regimen in the setting of rifampin-based TB therapy is efavirenz plus 2 nRTIs (A1a).

The recent recommendation for use of a 3-month, once-weekly regimen of isoniazid with rifapentine for treatment of latent TB infection is not recommended for HIV-infected patients receiving ART (BIII).

Sustained elevation of plasma HIV-1 RNA between 50 and 200 copies/mL should prompt evaluation of factors leading to failure and consideration for switching of ART (BIII).

• Health care practitioners and health systems should initiate strategies to monitor and improve entry into and retention in care and ART adherence and to incorporate and analyze quality-of-care indicators (CIII).

• Management of multidrug resistance is complex and expert advice should be sought (BII).
Questions?
Case Presentation

Resistance Testing

Craig Ballard, PharmD
August 30, 2012
OS 25 yo male

- 25 yo AA male presents to Owen Clinic May 2010 to establish care
- HIV ab+ 12/2009
- RF: MSM
- Antiretroviral Treatment Naïve
- He is going to school, unemployed, no insurance
- Patient’s partner is on Atripla and undetectable
OS 25 yo male

- CD4 306 and 23% 05/17/2010
- HIV RNA 9,035 cpm

- Meds: none
- Tobacco: 1 cigarette every few months
- EtOH 3-4 drinks monthly
OS Baseline HIV-1 Genotype Resistance Test 05/17/10

<table>
<thead>
<tr>
<th>Drug</th>
<th>Generic Name</th>
<th>Brand Name</th>
<th>GENESEQ™ Drug Resistance Associated Mutations Detected</th>
<th>ASSESSMENT*</th>
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<tbody>
<tr>
<td>Abacavir</td>
<td></td>
<td>Ziagen</td>
<td>None</td>
<td>ABC</td>
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<tr>
<td>Didanosine</td>
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<td>Videx</td>
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<td>ddI</td>
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<tr>
<td>Emtricitabine</td>
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<td>Emtriva</td>
<td>None</td>
<td>FTC</td>
</tr>
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<td>Lamivudine</td>
<td></td>
<td>Epivir</td>
<td>None</td>
<td>3TC</td>
</tr>
<tr>
<td>Stavudine</td>
<td></td>
<td>Zerit</td>
<td>None</td>
<td>d4T</td>
</tr>
<tr>
<td>Tenofovir</td>
<td></td>
<td>Viread</td>
<td>None</td>
<td>TFV</td>
</tr>
<tr>
<td>Zidovudine</td>
<td></td>
<td>Retrovir</td>
<td>None</td>
<td>ZDV</td>
</tr>
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</table>

HIV-1 Subtype: B
## OS Baseline HIV-1 Genotype Resistance Test 05/17/10

<table>
<thead>
<tr>
<th>NNRTI</th>
<th>Initial Drug</th>
<th>Resistance Profile</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delavirdine</td>
<td>Rescriptor</td>
<td>E138E/A</td>
<td>DLV Sensitive</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Sustiva</td>
<td>E138E/A</td>
<td>EFV Sensitive</td>
</tr>
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<td>Etravirine</td>
<td>Intelence</td>
<td>E138E/A, V179V/I, V189V/I</td>
<td>ETR Reduced Susc</td>
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<tr>
<td>Nevirapine</td>
<td>Viramune</td>
<td>E138E/A</td>
<td>NVP Sensitive</td>
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</table>
### OS Baseline HIV-1 Genotype Resistance Test 05/17/10

<table>
<thead>
<tr>
<th>PI</th>
<th>Drug</th>
<th>Genotype</th>
<th>ATV</th>
<th>DRV</th>
<th>AMP</th>
<th>IDV</th>
<th>LPV</th>
<th>NFV</th>
<th>RTV</th>
<th>SQV</th>
<th>TPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atazanavir</td>
<td>Reyataz</td>
<td>None</td>
<td>Sensitive</td>
<td>ATP/r</td>
<td>Sensitive</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reyataz/r</td>
<td>None</td>
<td>Sensitive</td>
<td>DRV/r</td>
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<td></td>
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<td>Prezista/r</td>
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<td>AMP</td>
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<td></td>
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<tr>
<td></td>
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<td>L63S</td>
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<td>AMP/r</td>
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<td>IDV/r</td>
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<tr>
<td></td>
<td>Indinavir</td>
<td>Crixivan/r</td>
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<td>Sensitive</td>
<td>LPV/r</td>
<td>Sensitive</td>
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<td>Lopinavir</td>
<td>Kaletra</td>
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<td>NFV</td>
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<td>RTV</td>
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<tr>
<td></td>
<td>Ritonavir</td>
<td>Norvir</td>
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<td>SQV</td>
<td>Sensitive</td>
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<td></td>
<td>Saquinavir</td>
<td>Invirase</td>
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<td>SQV/r</td>
<td>Sensitive</td>
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<tr>
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<td>TPV/r</td>
<td>Sensitive</td>
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<tr>
<td></td>
<td>Tipranavir</td>
<td>Aptivus/r</td>
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<td>Sensitive</td>
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<td></td>
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</tr>
</tbody>
</table>
Is it reasonable to start a NNRTI based regimen after viewing this genotype?

1. Yes
2. No
If you answered yes, which NNRTI?

1. Efavirenz (EFV)
2. Nevirapine (NVP)
3. Etravirine (ETR)
4. Rilpivirine (RIL)
5. Delavirdine (DLV) (i.e., I really don’t know what an NNRTI is)
OS 25 yo male

Starts Atripla on 06/07/2010

05/17/2010  cd4 306 23%  pVL 9035 cpm
08/06/2010  cd4 443 30%  pVL 142 cpm
10/04/2010  cd4 371 27%  pVL <40 cpm
3/31/2011  cd4 603 28%  pVL <48 cpm
<table>
<thead>
<tr>
<th>Date</th>
<th>Values</th>
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<tbody>
<tr>
<td>05/17/2010</td>
<td>nd</td>
</tr>
<tr>
<td>08/06/2010</td>
<td>Tchol 330 TG 812</td>
</tr>
<tr>
<td>10/04/2010</td>
<td>Tchol 286 TG 607</td>
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<tr>
<td></td>
<td>HDL 32</td>
</tr>
<tr>
<td></td>
<td>LDL invalid</td>
</tr>
</tbody>
</table>

BMI 25.5
OS 25 yo male

- Primary Care Provider wants to change Atripla because of dyslipidemia
- Patient wants to maintain a single tablet regimen and doesn’t want a more complicated regimen
Would you change the antiretroviral regimen to Complera or Stribild?

1. Yes
2. No
3. Maybe
4. STRI-B-what?!!?
<table>
<thead>
<tr>
<th>NNRTI</th>
<th>DDCT</th>
<th>Change</th>
<th>Class</th>
<th>Resistance</th>
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</thead>
<tbody>
<tr>
<td>Delavirdine</td>
<td>Rescriptor</td>
<td>E138E/A</td>
<td>DLV</td>
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<tr>
<td>Efavirenz</td>
<td>Sustiva</td>
<td>E138E/A</td>
<td>EFV</td>
<td>Sensitive</td>
</tr>
<tr>
<td>Etravirine</td>
<td>Intelence</td>
<td>E138E/A, V179V/I, V189V/I</td>
<td>ETR</td>
<td>Reduced Susc</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Viramune</td>
<td>E138E/A</td>
<td>NVP</td>
<td>Sensitive</td>
</tr>
</tbody>
</table>
Baseline Genotype 5/17/2010

Results:

**NNRTI:** E138E/A, V179V/I, V189V/I  
**PI:** G16E, L63S  

Tropism testing reveals R5 utilizing virus

hivdb.stanford.edu

Stanford’s db states:

- **(June 2010)** E138A is a polymorphism that has been recently added to the list of mutations associated with decreased ETR response in the DUET studies.

- **(August 2012)** E138A is a polymorphism that may contribute to reduced ETR and RPV susceptibility in combination with other NNRTI-resistance mutations.
Baseline Genotype 5/17/2010

Results:
PI: G16E, L63S

Tropism testing reveals R5 utilizing virus

hivdb.stanford.edu Stanford’s db states:

(June 2010) V179I is a common polymorphism which occurs more commonly in NNRTI-treated isolates. However, it does not reduce NNRTI susceptibility.

(August 2012) V179I is a common polymorphism is often selected by ETR and RPV salvage therapy. It has not been shown to reduce NNRTI susceptibility.
Questions?