HIV/AIDS Guideline Update and Antiretroviral Drug Interactions

Natalie Perkins, PharmD, AAHIVE
nataliep@elrio.org
AzPA July, 2010

Purpose

• To educate pharmacists on the key changes of the DDHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents
Goals and objectives

- Describe benefits of antiretroviral therapy.
- Identify the optimal time to initiate antiretroviral therapy.
- Select an initial antiretroviral regimen.
- Recognize common drug interactions with antiretrovirals.
- List strategies to improve adherence to antiretroviral therapy.

Accessing the guidelines

DHHS

http://www.aidsinfo.nih.gov

Updated: December 1, 2009
Treatment goals

• Reduce HIV-related morbidity and prolong survival
• Restore and/or preserve immunologic function
• Improve QOL
• Maximally and durably suppress HIV viral load
• Prevent HIV transmission

Achieving treatment goals

• Selection and initiation of ARV regimen
• Maximizing adherence
• Resistance testing
Common abbreviations

• AIDS = Acquired immune deficiency syndrome
• CD4 = CD4+ T Lymphocyte
• HIV = Human immunodeficiency virus
• OI = Opportunistic infection
• VL = Viral load

Common abbreviations

• ARV = Antiretroviral
• ART = Antiretroviral therapy
• INSTI = Integrase inhibitor
• NNRTI = Non-nucleoside reverse transcriptase inhibitor
• NRTI = Nucleos(t)ide analog reverse transcriptase inhibitor
• PI = Protease inhibitor
Fixed-Dose Combinations

Individual Agents

- ZDV
- ABC
- TDF
- EFV
- LPV

Fixed-dose combinations

- Combivir ZDV/3TC
- Epzicom ABC/3TC
- Truvada TDF/FTC
- Atripla EFV/TDF/FTC
- Kaletra LPV/RTV

Rating scheme for recommendations

<table>
<thead>
<tr>
<th>Strength of recommendation</th>
<th>Quality of evidence for recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Strong recommendation for the statement</td>
<td>I: One or more randomized trials with clinical outcomes</td>
</tr>
<tr>
<td>B: Moderate recommendations for the statement</td>
<td>II: One or more well designed, nonrandomized trials or observational cohort studies with LT clinical outcomes</td>
</tr>
<tr>
<td>C: Optional recommendation</td>
<td>III: Expert opinion</td>
</tr>
</tbody>
</table>
CD4 cell

- Major indicator of immune function
- Predictor of disease progression
- Guides decision to start HAART or OI prophylaxis
- Important in determining response to ART
- Monitor at baseline, 4 weeks, Q 3-6 months

HIV RNA/Viral Load

- Determines response to HAART
- GOAL: VL below level of detection
- Monitor at baseline, 2-8 weeks, Q 3-6 months
Drug resistance testing

- Initial testing recommended for all persons with HIV infection (AIII)
  - Genotypic assay preferred (AIII)
- Virologic failure (AII)
- Suboptimal virologic response (AIII)
- Pregnant women (AIII)
- Phenotypic testing (BIII)

Resistance

www.iasusa.org/resistance_mutations

http://hivdb.stanford.edu
HLA-B*5701 screening

- Abacavir (Ziagen, Epzicom, Trizivir)
- Reduce risk of hypersensitivity reaction (HSR) (AI)
- Positive results = allergy (All)
- Counseling and monitoring (CIII)

WARNING CARD
Ziagen® (abacavir sulfate)

- Patients taking ZIAGEN may have a serious allergic reaction (hypersensitivity reaction) that can cause death. If you get a symptom from 2 or more of the following groups while taking ZIAGEN, call your doctor right away to determine if you should stop taking this medicine. Symptom(s)
- Group 1 Fever
- Group 2 Rash
- Group 3 Nausea, vomiting, diarrhea, or abdominal (stomach area) pain
- Group 4 Generally ill feeling, extreme tiredness, or achiness
- Group 5 Shortness of breath, cough, or sore throat
Back of warning card

• If you must stop treatment with EPZICOM because you have had an allergic reaction to abacavir, NEVER take EPZICOM or another abacavir-containing medicine (ZIAGEN® and TRIZIVIR®) again. If you take EPZICOM or another abacavir-containing medicine again after you have had an allergic reaction, WITHIN HOURS you may get life-threatening symptoms that may include very low blood pressure or death.

• Please read the Medication Guide for additional information on EPZICOM.

Coreceptor tropism assays

• CCR5 antagonist
  – Selzentry (maraviroc) (AII)
Indications for initiating ARV

- History of AIDS-defining illness (AI)
- CD4 count <350 (AI)
- Pregnant women (AI)
- Persons with HIV-associated nephropathy (AII)
- Persons coinfected with hepatitis B virus (HBV), when treatment is indicated (AIII)

Indications for initiating ARV

- Patients with CD4 count between 350-500 (A/BII)
  - 55% strong recommendation (A)
  - 45% moderate recommendation (B)
- Patients with CD4 count >500 (B/CIII)
  - 50% favor/optional (B/C)
Conditions favoring more rapid initiation of therapy

- Pregnancy (AI)
- AIDS-defining conditions (AI)
- Acute OIs
- Lower CD4 counts (AI)
- Rapidly declining CD4 counts (AIII)
- Higher VLs (BII)
- HIV associated nephropathy (AII)
- HBV coinfection when treatment for HBV is indicated (AIII)

Support for earlier therapy

- Report from at least one recent cohort study demonstrating survival benefit with initiation of ART at CD4 >500
- Growing awareness that untreated HIV infection may be associated with development of many non-AIDS defining diseases, including CV, kidney, liver, malignancy
Support for earlier therapy

- Greater efficacy, convenience, tolerability, and safety of current ARV
- Increasing evidence that effective ART reduces HIV transmission (BIII)

Consider deferral of ART

- Adherence concerns (AIII)
- Clinical or personal factors
- Comorbidities complicate or prohibit
- Cost
### Why Do Patients Miss Doses?

#### Reasons Given for Missing Antiretroviral Doses (Structured Questionnaire) (%)

<table>
<thead>
<tr>
<th>Reason</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Too busy/simply forgot</td>
<td>52</td>
</tr>
<tr>
<td>Away from home</td>
<td>46</td>
</tr>
<tr>
<td>Change in daily routine</td>
<td>27</td>
</tr>
<tr>
<td>Felt depressed/overwhelmed</td>
<td>19</td>
</tr>
<tr>
<td>Took drug holiday/medication break</td>
<td>20</td>
</tr>
<tr>
<td>Ran out of medication</td>
<td>20</td>
</tr>
<tr>
<td>Too many pills</td>
<td>19</td>
</tr>
<tr>
<td>Worried about becoming “immune”</td>
<td>18</td>
</tr>
<tr>
<td>Felt drug was too toxic</td>
<td>17</td>
</tr>
<tr>
<td>Wanted to avoid side effects</td>
<td>17</td>
</tr>
<tr>
<td>Did not want others to notice</td>
<td>16</td>
</tr>
<tr>
<td>Reminder of HIV infection</td>
<td>15</td>
</tr>
<tr>
<td>Confused about dosage direction</td>
<td>13</td>
</tr>
<tr>
<td>Did not think it was improving health</td>
<td>10</td>
</tr>
<tr>
<td>To make it last longer</td>
<td>9</td>
</tr>
<tr>
<td>Was told the medicine is no good</td>
<td>9</td>
</tr>
</tbody>
</table>

#### Possible interventions
- Simplify dosing schedule
- Decrease pill burden
- Other

---

### Improving adherence

- Support and reinforcement
- Simplified dosing
- Reminders
- Ongoing education
- Trust in PCP

---

## Current ARV Medications

### NRTI
- Abacavir (ABC)
- Didanosine (ddI)
- Emtricitabine (FTC)
- Lamivudine (3TC)
- Stavudine (d4T)
- Tenofovir (TDF)
- Zidovudine (AZT, ZDV)

### NNRTI
- Delavirdine (DLV)
- Efavirenz (EFV)
- Etravirine (ETR)
- Nevirapine (NVP)

### PI
- Atazanavir (ATV)
- Darunavir (DRV)
- Fosamprenavir (FPV)
- Indinavir (IDV)
- Lopinavir (LPV)
- Nelfinavir (NFV)
- Ritonavir (RTV)
- Saquinavir (SQV)
- Tipranavir (TPV)

### Integrase Inhibitor (II)
- Raltegravir (RAL)

### Fusion Inhibitor
- Enfuvirtide (ENF, T-20)

### CCR5 Antagonist
- Maraviroc (MVC)

---

## Initial ART : DHHS Categories

- **Preferred**
  - Randomized controlled trials show optimal efficacy and durability
  - Favorable tolerability and toxicity profiles
- **Alternative**
  - Effective but have potential disadvantages
  - May be the preferred regimen in individual patients
- **Acceptable**
  - Less virologic efficacy, lack of efficacy data, or greater toxicities
- **May be acceptable but more definitive data are needed**
Selecting a treatment regimen

- Initiate therapy with 1 of the following 3 types of regimens (AI)
  1. NNRTI + 2NRTIs OR
  2. PI (preferably boosted) + 2NRTIs OR
  3. INSTI + 2 NRTIs

Selecting a treatment regimen

- Individualization based on
  - Virologic efficacy
  - Pill burden
  - Dosing frequency
  - Drug-drug interaction potential
  - Resistance testing results
  - Comorbid conditions
Initial Treatment: Preferred

NNRTI Option
- Sustiva (efavirenz)*

OR

PI Options
- Reyataz®/Norvir® (atazanavir/r)
- Prezista/Norvir (darunavir/r)

OR

INSTI Options
- Isentress (raltegravir )

NRTI Options
- Truvada (tenofovir + emtricitabine$^{1,2}$)

* Avoid in pregnant women and women with significant pregnancy potential
$^1$ Emtricitabine can be used in place of lamivudine and vice versa
$^2$ Tenofovir + emtricitabine or lamivudine is preferred in patients with HIV/HBV coinfection
$^3$ Atazanavir should not be used in patients that require >20mg omeprazole equivalent QD
$^4$ Atazanavir is generally preferred over atazanavir

Comparing “Preferred” Initial ART

<table>
<thead>
<tr>
<th>Recommended Regimen</th>
<th>Total # of Pills/Day</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atripla</td>
<td>1</td>
<td>QD</td>
</tr>
<tr>
<td>Reyataz + Norvir + Truvada</td>
<td>3</td>
<td>QD</td>
</tr>
<tr>
<td>Prezista + Norvir + Truvada</td>
<td>4</td>
<td>QD</td>
</tr>
<tr>
<td>Isentress + Truvada</td>
<td>3</td>
<td>BID</td>
</tr>
</tbody>
</table>
Preferred regimen for pregnancy

- Kaletra (lopinavir/r) BID +
- Combivir (zidovudine/lamivudine) (AI)

<table>
<thead>
<tr>
<th>Recommended Regimen</th>
<th>Total # of Pills/Day</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaletra + Combivir</td>
<td>6</td>
<td>BID</td>
</tr>
</tbody>
</table>

Alternative regimens

- NNRTI-based (BI)
  - Sustiva + Epzicom or Combivir
  - Viramune + Combivir
- PI-based (BI)
  - Reyataz/Norvir + Epzicom or Combivir
  - Lexiva/Norvir + Epzicom or Combivir or Truvada
  - Kaletra + Epzicom or Combivir or Truvada
  - Invirase/Norvir + Truvada
Initial Treatment: Alternative

**NNRTI Option**
- Sustiva (efavirenz)*
- Viramune (nevirapine)^

**OR**

**PI Options**
- Reyataz\(^3\)/Norvir\(^4\)(atazanavir/r)
- Lexiva/Norvir (fosamprenavir/r)
- Kaletra (lopinavir/r)
- Invirase/Norvir (saquinavir/r)

**NRTI Options**
- Truvada (tenofovir/emtricitabine\(^{1,2}\))
- Epzicom (abacavir\(^5\)/lamivudine)
- Combivir (lamivudine/zidovudine)

---

---

Comparing “Alternative” Initial ART

<table>
<thead>
<tr>
<th>Recommended Regimen</th>
<th>Total # of Pills/Day</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustiva + Epzicom or Combivir</td>
<td>2</td>
<td>QD</td>
</tr>
<tr>
<td>Sustiva + Combivir</td>
<td>3</td>
<td>BID</td>
</tr>
<tr>
<td>Viramune + Combivir</td>
<td>4</td>
<td>BID</td>
</tr>
<tr>
<td>Reyataz/Norvir + Epzicom</td>
<td>3</td>
<td>QD</td>
</tr>
<tr>
<td>Reyataz/Norvir + Combivir</td>
<td>4</td>
<td>BID</td>
</tr>
<tr>
<td>Lexiva/Norvir + Epzicom</td>
<td>4</td>
<td>BID</td>
</tr>
<tr>
<td>Lexiva/Norvir + Combivir</td>
<td>5</td>
<td>BID</td>
</tr>
<tr>
<td>Lexiva/Norvir + Truvada</td>
<td>4</td>
<td>QD</td>
</tr>
<tr>
<td>Kaletra + Epzicom</td>
<td>5</td>
<td>QD</td>
</tr>
<tr>
<td>Kaletra + Combivir</td>
<td>6</td>
<td>BID</td>
</tr>
<tr>
<td>Kaletra + Truvada</td>
<td>5</td>
<td>QD</td>
</tr>
<tr>
<td>Invirase/Norvir + Truvada</td>
<td>7</td>
<td>BID</td>
</tr>
</tbody>
</table>

---

\(^*\) Should not be used in patients with moderate to severe hepatic impairment. NVP should not be started if pre-ARV CD4 >250 in women or >400 in men.

\(^^\) Should not be used for patients who test HLA-B5701 positive, caution if HIV RNA >100,000 copies/mL, or if high risk of cardiovascular disease.
ARVs not recommended

- High rate of early virologic failure
- Inferior virologic efficacy
- High incidence of toxicities
- High pill burden/dosing inconvenience
- Lack of data as initial treatment
- No benefit over standard regimen

ART that should not be offered

- Monotherapy with NRTI (AII)
- Dual-NRTI (AII)
- Triple NRTI (AII)
- Reyataz + Crixivan (AIII)
- Zerit + Videx (didanosine) (AII)
- 2-NNRTI (AII)
- Sustiva (pregnancy) (AIII)
ART that should not be offered

• Emtriva + Epivir (AIII)
• Intelence + unboosted PI (AII)
• Intelence + boosted Reyataz or Lexiva
• Intelence + boosted Aptivus (AII)
• Viramune (BI)
  – Women CD4 >250
  – Men CD4 >400
• Unboosted Prezista, Invirase, Aptivus

NNRTI-based

• Advantages
• Disadvantages
• Adverse drug effects
  – Rash
• Sustiva (efavirenz)
  – Neuropsychiatric, tertogenic
• Viramune (nevirapine)
  – Hepatoxicity
PI-based

• Advantages
• Disadvantages
• Adverse drug effects
  – Hyperlipidemia
  – Insulin resistance and diabetes
  – Lipodystrophy
  – Elevated LFTs
  – Possibility of increased bleeding risk for hemophiliacs

PI ADEs

• Reyataz (atazanavir)
  – Hyperbilirubinemia, PR prolongation, nephrolithiasis
• Prezista (darunavir)
  – Rash, liver toxicity
• Lexiva (fosamprenavir)
  – GI, rash, possible increased risk of MI
• Crixivan (indinavir)
  – Nephrolithiasis, GI
PI ADEs

• Kaletra (lopinavir/ritonavir)
  – GI, PR and QT prolongation, possible increased risk of MI
• Norvir (ritonavir)
  – GI, hepatitis
• Invirase (saquinavir)
  – GI
• Aptivus (tipranavir)
  – Rash, liver toxicity, cases of intracranial hemorrhage

INSTI-based

• Advantages
• Disadvantages
• Adverse drug effects
  – Nausea, headache, diarrhea, CPK elevation
NRTI-based

- Advantages
- Disadvantages
- Adverse drug effects
  - Lactic acidosis and hepatic steatosis (highest incidence with stavudine, then didanosine, lower with tenofovir, abacavir, lamivudine and emtricabine);
  - Lipoatrophy (stavudine)

NRTI ADEs

- Ziagen (abacavir)
  - HSR, rash, possible increased risk of MI
- Videx (didanosine)
  - Peripheral neuropathy, pancreatitis
- Zerit (stavudine)
  - Peripheral neuropathy, pancreatitis
NRTI ADEs

- Viread (tenofovir)
  - Renal impairment, possible decrease in BMD, headache
- Retrovir (zidovudine)
  - bone marrow suppression

Fusion Inhibitor

- Fuzeon (enfuviritide)
  - Injection site reactions
  - HSR
  - Increased risk bacterial pneumonia
CCR5 antagonist

- Selzentry (maraviroc)
  - Drug-drug interactions
  - Abdominal pain
  - Upper respiratory tract infections
  - Cough
  - Hepatotoxicity
  - Musculoskeletal symptoms
  - Rash
  - Orthostatic hypotension

Treatment-experienced

- Treatment goal is to suppress virus below limit of detection (AI)
- Appropriate initial ARV regimens should suppress HIV indefinitely
  - Optimal regimen
  - Adherence
- In patients with suppressed VL <50
  - Assess adherence frequently
  - Simplify regimen
- Patients with ARV failure
  - Assess and address aggressively
ART failure

- Causes of treatment failure include:
  - Drug resistance
  - Suboptimal adherence
  - ARV toxicity and intolerance
  - Pharmacokinetic problems
  - Suboptimal drug potency
  - Provider experience

ART failure

- Virologic failure:
  - HIV RNA >400 copies/mL after 24 weeks or
  - >50 copies/mL after 48 weeks

- Immunologic failure:
  - Failure to achieve and maintain adequate CD4 increase despite virologic suppression
  - Immnomodulator interlekin-2 has not demonstrated clinical benefits (AI)

- Clinical progression:
  - Occurrence of HIV-related events
Management of treatment-experienced patients

• Evaluate remaining ARV options
• Base ARV selection on medication history, resistance testing, expected tolerability, adherence, and future treatment options
• Avoid treatment interruption, which may cause viral rebound, immune decompensation, clinical progression

Regimen simplification

• Changing a suppressive ARV regimen to:
  – Reduce pill burden
  – Reduce dosing frequency
  – Enhance tolerability
  – Decrease food and fluid requirements
• Goals: improve patient’s quality of life, improve ART adherence, avoid long-term toxicities, reduce risk of virologic failure
Drug interactions

- Use of 3 or 4 drug ARV regimens
- Multiple agents to treat/prevent OIs
- Chronic diseases
- Pharmacokinetic
- Pharmacodynamic

- ALL PIs and NNRTIs are metabolized by the CYP3A4 enzyme system
- All PIs can inhibit CYP3A4 enzymes
  - Ritonavir (Norvir)
  - Saquinavir (Invirase)
- NNRTIs
  - Nevirapine (Viramune)
  - Efavirenz (Sustiva)
CYP450

- **Substrate**: metabolized by enzyme
- **Inhibitor**: inhibits metabolism of substrate
- **Inducer**: induces metabolism of substrate through increased production of enzyme
  - Interactions involving induction may be delayed since new enzyme must be synthesized

### Effect of ARVs on Drug Metabolism

- Induced by: RTV, NFV, LPV, EFV, NVP, TPV
- Inhibited by: RTV, NFV, IDV, APV, SQV, ATV, DLV
- Induced by: EFV, NVP
- Inhibited by: RTV
- Induced by: RTV, NFV
- Inhibited by: EFV, DLV
- Induced by: RTV, NFV?
- Inhibited by: ATV
CYP450

- CYP3A4 substrate with narrow margin of safety
- Presence of CYP3A4 inhibitor
  - Prolonged T1/2
  - Toxic drug accumulation
- Ritonavir (Norvir)
  - Inhibitory effect
  - Pharmacokinetic enhancer to increase Cmin and prolong T1/2

Boosting Protease Inhibitors

- Some PI's can be “boosted” by being used in combination with Norvir.
- Norvir slows down the time it takes the body to get rid of other PI’s by interacting with the enzymes responsible for their elimination.
- This allows the PI’s to be present in the body longer.
Drugs that should no be given with PIs

- Simvastatin
- Lovastatin
- Astemizole
- Terfenadine
- Cisapride
- Pimozide
- Bepridil
- St. John’s Wort
- Rifampin
- Rifapentine
- Midazolam
- Triazolam
- Ergot alkaloids

Drug interactions:
Lipid lowering agents

- Simvastatin and lovastatin are CI with PIs
- Pravastatin and fluvastatin least likely to interact
- Atorvastatin at low doses
Drug interactions

- Fluticasone (3A4 substrate)
- Anxiolytics
  - Safest to use glucuronidated benzodiazepines

Drug interactions  OTCs

- St John's Wort
- Acid reducers
  - Traditional antacids
  - H-2 blockers
  - PPIs
Interaction Between Atazanavir + Omeprazole

- N = 48 HIV(-) subjects
- ATV exposures substantially reduced by coadministration with OMP 40 mg
- Not corrected by increased ATV dose or 8 oz cola
- OMP exposures not significantly altered
- Effect of OMP 20 mg (OTC dose) not known
- Do not coadminister

Dosing requirements

- Renal
- Hepatic
- Weight
- Food
More information

- www.aidsinfo.nih.gov
- www.aidsetc.org
- www.clinicalcareoptions.com
- www.aidsinfonet.org
- www.hiv-druginteractions.org
- http://hivinsite.ucsf.edu

Additional Questions

Thanks!