Pharmacotherapy of HIV Management for Clinicians

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Virginia Commonwealth University Medical Center

Global Summary of the AIDS Epidemic—December 2008

Number of people living with HIV in 2008:

<table>
<thead>
<tr>
<th>Total</th>
<th>33.8 million (31.1 million-36.5 million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>33.3 million (32.1 million-34.3 million)</td>
</tr>
<tr>
<td>Women</td>
<td>15.8 million (13.9 million-17.7 million)</td>
</tr>
<tr>
<td>Children under 15 years</td>
<td>2.1 million (1.2 million-2.9 million)</td>
</tr>
</tbody>
</table>

People newly infected with HIV in 2008:

<table>
<thead>
<tr>
<th>Total</th>
<th>2.7 million (2.4 million-3.0 million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>2.3 million (2.1 million-2.5 million)</td>
</tr>
<tr>
<td>Children under 15 years</td>
<td>430,000 (340,000-510,000)</td>
</tr>
</tbody>
</table>

AIDS-related deaths in 2008:

<table>
<thead>
<tr>
<th>Total</th>
<th>2.0 million (1.7 million-2.4 million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td>1.7 million (1.4 million-2.1 million)</td>
</tr>
<tr>
<td>Children under 15 years</td>
<td>260,000 (190,000-410,000)</td>
</tr>
</tbody>
</table>

Global Summary of the AIDS Epidemic—December 2008

<table>
<thead>
<tr>
<th>Region</th>
<th>Adults &amp; adolescents living with HIV/AIDS</th>
<th>Adults &amp; adolescents newly infected</th>
<th>AIDS-related deaths a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Saharan Africa</td>
<td>22.2 million</td>
<td>2.9 million</td>
<td>1.4 million</td>
</tr>
<tr>
<td>South East Asia</td>
<td>3.9 million</td>
<td>39,000</td>
<td>67,000</td>
</tr>
<tr>
<td>Pacific</td>
<td>17.4 million</td>
<td>17,000</td>
<td>64,000</td>
</tr>
<tr>
<td>Latin America</td>
<td>2.9 million</td>
<td>3,000</td>
<td>2,000</td>
</tr>
<tr>
<td>Caribbean</td>
<td>1.4 million</td>
<td>1,000</td>
<td>1,000</td>
</tr>
<tr>
<td>Eastern Europe &amp; Central Asia</td>
<td>0.9 million</td>
<td>110,000</td>
<td>87,000</td>
</tr>
<tr>
<td>Europe</td>
<td>1.1 million</td>
<td>54,000</td>
<td>21,000</td>
</tr>
<tr>
<td>North America</td>
<td>1.0 million</td>
<td>54,000</td>
<td>12,000</td>
</tr>
<tr>
<td>Middle East &amp; North Africa</td>
<td>0.1 million</td>
<td>10,000</td>
<td>5,000</td>
</tr>
<tr>
<td>Total</td>
<td>33.8 million</td>
<td>31.1 million</td>
<td>26.6 million</td>
</tr>
</tbody>
</table>
HIV Prevalence


Estimated Number of Life-Years Added Due to Antiretroviral Therapy

When to start HAART?
Indications for Initiating Antiretroviral Therapy

- History of an AIDS-defining illness or CD4 count < 350 cells/mm³
- Regardless of CD4 count
  - Pregnancy
  - HIV-associated nephropathy
  - Hepatitis B virus (HBV) coinfection (when HBV treatment is indicated)

Indications for Initiating Antiretroviral Therapy

- CD4 counts between 350 and 500 cells/mm³
  - Panel was divided
    • 55% with AII rating
    • 45% with BII rating
- CD4 counts > 500 cells/mm³
  - Panel was divided
    • 50% with BIII
    • 50% with CIII

When to Start HAART?

- Graphs showing outcomes of different CD4 counts and viral loads over time.
**When to Start HAART?**

**Determinants of a First-AIDS-defining Malignancy**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cumulative Exposure</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 cell count, &lt; 200 cells/mm³</td>
<td>1.36 (1.21-1.54)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma HIV RNA level, &gt; 500 copies/mL</td>
<td>1.27 (1.13-1.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ARV exposure</td>
<td>0.92 (0.91-0.93)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Determinants of a First Non-AIDS-defining Malignancy**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cumulative Exposure</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 cell count, &lt; 500 cells/mm³</td>
<td>1.13 (1.03-1.24)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Plasma HIV RNA level, &gt; 500 copies/mL</td>
<td>1.03 (0.94-1.13)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ARV exposure</td>
<td>0.90 (0.81-0.98)</td>
<td>&lt;0.07</td>
</tr>
</tbody>
</table>
When to Start HAART?
Impact of CD4 cell count at 36 months

Only 43% of patients with Baseline CD4 < 200 cells/mm³ will achieve > 500 cells/mm³ at 36 months.

- Baseline CD4
- 36-Month CD4

When to Start HAART?

Early treatment of uncomplicated human immunodeficiency virus type 1 (HIV-1) infection results in lower mortality and improved long-term survival compared with delayed ART. To assess the long-term outcomes of HIV-1-infected patients treated with early ART, the antiretroviral therapy cohort collaboration (ART-CC) conducted a study in sub-Saharan Africa and the United States. The study included patients with baseline CD4 counts of 200 cells/mm³ or fewer who started ART within 1 year of diagnosis. The primary endpoint was the proportion of patients achieving a CD4 count of > 500 cells/mm³ at 36 months. The results showed that 43% of patients with baseline CD4 counts < 200 cells/mm³ achieved > 500 cells/mm³ at 36 months. This finding highlights the importance of early ART initiation to achieve optimal outcomes in HIV-1-infected patients.
WHICH HAART TO START?

Pharmacologic Agents

ARV Mechanism of Action
ARV Mechanism of Action

Preferred HAART Regimens


ART Components for Treatment Naïve Patients

Which HAART to Start?

- AIDS Clinical Trials Group A5202
  - Phase 3B, 96-week study
  - Initial once-daily ARV treatment regimens
    - Abacavir 600 mg/lamivudine 300 mg, or
    - Tenofovir 300 mg/emtricitabine 200 mg with
    - Atazanavir 300 mg/ritonavir 100 mg or
    - Efavirenz 600 mg
  - 1858 eligible patients
  - 797 patients with baseline HIV PCR > 100,000 copies/mL

Which HAART to Start?
Individual Tailoring

- Comorbid conditions
- Baseline genotypic analysis
  - Ranges between 6-16%
  - Cost-effective
- Pharmacogenomic analysis
- Adherence
- Drug Interactions
- Resistance prediction
- Expected toxicities

Measurements of Resistance

- Genotypic test
  - Detection of HIV genetic mutations predominating at the time of sample
  - Significance of mutations not evaluated
  - Difficult to perform if HIV <1000 copies
  - $360-480/test
Pharmacogenomic Analysis

- Abacavir hypersensitivity reaction
  - Incidence: 5-8% patients
  - Onset: within 6 weeks of therapy
  - Early discontinuation of therapy
- HLA-B*5701 screening
  - 100% Negative Predictive Value
  - 47.9% Positive Predictive Value
  - True hypersensitivity reactions: 2.7%


Which HAART to Start?
Individual Tailoring

- Comorbid conditions
- Baseline genotypic analysis
  - Ranges between 6-16%
  - Cost-effective
- Pharmacogenomic analysis
- Adherence
- Drug Interactions
- Resistance prediction
- Expected toxicities

Patient Case

- 56 yo AAM presents for initial evaluation
- PMH:
  - HTN
  - Obesity (138kg)
- SH:
  - Tobacco (+)
  - Occasional EtOH
- Medications:
  - Amlodipine/benazapril 10mg/40mg
  - Followed by PCP with poor control
Patient Case

<table>
<thead>
<tr>
<th>LFTs</th>
<th>AST 22</th>
<th>ALT 21</th>
<th>ALP 111</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>HDL 33</td>
<td>LDL 103</td>
<td>TG 101</td>
</tr>
<tr>
<td>Surrogate markers</td>
<td>CO2</td>
<td>261 (9%) cells/mL</td>
<td>HIV RCR 150,000 copies/mL</td>
</tr>
<tr>
<td>Baseline Genotype</td>
<td>NRTIs None reported</td>
<td>NNRTIs None reported</td>
<td>PI's L63P</td>
</tr>
</tbody>
</table>

3.5 107 24 21 1.13 96
5.6 12.3 107
UA: ptn (-); glucose (-)
HLA-B*5701 Negative

Preferred HAART Regimens

Which HAART to Start?
Individual Tailoring

- Comorbid conditions
- Baseline genotypic analysis
  – Ranges between 6-16%
  – Cost-effective
- Pharmacogenomic analysis
- Adherence
- Drug Interactions
- Resistance prediction
- Expected toxicities
Which HAART to Start?

- A. Efavirenz
- B. Atazanavir/ritonavir
- C. Darunavir/ritonavir
- D. Raltegravir

Patient Case

<table>
<thead>
<tr>
<th>LFTs</th>
<th>AST 17</th>
<th>ALT 17</th>
<th>ALP 123</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>HDL 42</td>
<td>LDL 112</td>
<td>TG 180</td>
</tr>
<tr>
<td>Surrogate markers</td>
<td>CD4 392 (14) cells/mm³</td>
<td>HIV PCR &lt;50 copies/mL</td>
<td></td>
</tr>
</tbody>
</table>

WHICH HAART TO START FOR THE PATIENT WITH RESISTANCE?
Goals of Therapy in the Resistant Patient

- Defined Goals
  - To achieve plasma HIV PCR below assay detection

Patient Case: Multidrug Resistance

- 46yo WM with HIV diagnosed in 1983
  - PMH:
    - Kaposi’s sarcoma
    - COPD
    - Peripheral neuropathy
  - Prior HAART includes:
    - All NRTIs with ? HSR to abacavir
    - Efavirenz and Nevirapine
    - Fosamprenavir/ritonavir (most recent HAART) 2005-2008
    - Saquinavir
    - Full dose ritonavir in 1996
- HIV PCR= 135,000 copies/mL
- CD4=120 (10%) cells/mm³
Which HAART to Start for the Patient with Resistance?

- Comorbid conditions
- Baseline genotypic analysis
  - Ranges between 6-16%
  - Cost-effective
- Pharmacogenomic analysis
- Adherence
- Drug Interactions
- Resistance prediction
- Expected toxicities
- Assessment of treatment failure
  - Adherence issues
  - Medication intolerance
  - Pharmacokinetic issues
  - Food/fasting requirements
  - Drug-drug interactions
  - Suspected drug resistance
  - Genotypic analysis
  - Phenotypic analysis
  - Virologic suppression
  - Immunologic failure

Genotypic Analysis

Measurements of Resistance

- Phenotypic test
  - Growth properties of HIV in the presence of antiretroviral agents
    - IC 50, 90, 95%
    - Difficult to perform if HIV <1000 copies
    - $900/test
Which HAART to Start for the Patient with Resistance?

A. Etravirine  
B. Darunavir/ritonavir  
C. Enfuvirtide  
D. Maraviroc  
E. Raltegravir  
F. Tipranavir

ARV Mechanism of Action

Maraviroc (Selzentry)

- CCR5 tropism must be tested prior to initiation
- Maraviroc 150-600 mg bid
- Adverse reactions
  - Cough/Pyrexia
  - URIs
  - Musculoskeletal symptoms
  - Abdominal pain
  - Dizziness
  - Cardiac ischemia
  - Rash
    - Systemic allergic rxn reaction +/- hepatitis
    - Black Box Warning

CCR5 Antagonist: Maraviroc (Selzentry)
CCR5 Antagonist Maraviroc (Selzentry)

Baseline characteristics:
- CD4 = 191 cells/mm³
- HIV PCR = 71,891 copies/mL

* P <0.001 versus placebo and OBT

ARV Mechanism of Action

Integrase Inhibitor: Raltegravir (Isentress)

- Novel MOA
- Dosage: 400 mg bid
- Elimination:
  - Metabolism: glucuronidation via UDGT
- Minimal drug interactions
- Adverse events
  - Nausea
  - Headache
  - CPK elevation (6%)
**Raltegravir (Isentress) Phase III Clinical Trial**

<table>
<thead>
<tr>
<th>Benchmark I, II</th>
<th>Raltegravir 400 mg bid</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>(N=462)</td>
<td>(N=237)</td>
</tr>
<tr>
<td>Viral Load (copies/mL)</td>
<td>44,668</td>
<td>39,810</td>
</tr>
<tr>
<td>CD4 Cell count (cells/mm³)</td>
<td>151</td>
<td>158</td>
</tr>
<tr>
<td>Efficacy at Week 48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 400 copies/mL</td>
<td>73.1</td>
<td>37.4</td>
</tr>
<tr>
<td>&lt; 50 copies/mL</td>
<td>62.8</td>
<td>33.2</td>
</tr>
<tr>
<td>CD4 Change (cells/mm³)</td>
<td>109</td>
<td>45</td>
</tr>
</tbody>
</table>

**ARV Mechanism of Action**

**NNRTI: Etravirine (Intelence)**

- **Indication:** Treatment resistant HIV
- **Dosage:** 200 mg bid
- **Elimination:**
  - Metabolism
    - CYP 3A4, 2C9, 2C19
    - Glucuronidation
- **Drug Interactions:**
  - CYP 3A4 induction
  - CYP 2C9/19 inhibition
- **Adverse events:**
  - Rash
**Patient Case:**

**Multidrug Resistance**

- 46yo WM with HIV diagnosed in 1983
  - PMH:
    - Kaposi’s sarcoma
    - COPD
    - Peripheral neuropathy
  - Prior HAART includes:
    - All NRTIs with 7 HSR to abacavir
    - Efavirenz and Nevirapine
    - Fosamprenavir/ritonavir (most recent HAART) 2005-2008
    - Saquinavir
    - Full dose ritonavir in 1996
  - HIV PCR = 135,000 copies/mL
  - CD4 = 120 (10%) cells/mm³

**Raltegravir-Etravirine Drug-Drug Interactions**
Patient Case: Multidrug Resistance

- Raltegravir 800 mg AM/400 mg PM
- Etravirine 200 mg twice daily
- Tenofovir 300 mg/Emtricitabine 200 mg once daily

Follow-up | CD4 count (cells/mm³) | HIV PCR (copies/mL)
--- | --- | ---
Baseline | 120 (15%) | 135,000
Four weeks | 285 (15%) | 200
Four months | 268 (16%) | < 48
Eight months | 272 (17%) | < 48
Eleven months | 306 (17%) | 59
Fifteen months | 324 (18%) | 56.1
Nineteen months | 240 (15%) | < 48


*Raltegravir C_{trough} lower than the IC 95 (14.6 ng/mL)
### Raltegravir

**Drug-Drug Interactions**

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>Raltegravir Drug Schedule</th>
<th>Ratio 90% Confidence Interval of Raltegravir Exposure to Drug-Drug Interaction</th>
<th>$\Delta$ Efficacy</th>
<th>$\Delta$ CD4</th>
<th>$\Delta$ Viral Load</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir</td>
<td>5 mg bid + 300 mg daily</td>
<td>0.9 (0.8, 1.1)</td>
<td>0.4%</td>
<td>0.7%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>200 mg daily</td>
<td>0.95 (0.87, 1.04)</td>
<td>0.5%</td>
<td>1.2%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Stavudine</td>
<td>400 mg daily, 800 mg qid</td>
<td>0.98 (0.89, 1.08)</td>
<td>0.4%</td>
<td>0.7%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>400 mg daily</td>
<td>1.01 (1.0, 1.02)</td>
<td>0.4%</td>
<td>0.7%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>150 mg daily</td>
<td>1.01 (1.0, 1.02)</td>
<td>0.4%</td>
<td>0.7%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Abacavir</td>
<td>600 mg daily</td>
<td>0.98 (0.89, 1.08)</td>
<td>0.4%</td>
<td>0.7%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

**Future Antiretrovirals**

- **Rilpivirine**
  - NNRTI
  - 96-week, Phase II data
  - Dosage=25 mg
  - Drug-drug interaction with acid suppression

- **Elvitegravir**
  - Integrase inhibitor
  - Significant CYP interactions (CYP 3A4)
  - Pharmacokinetic enhancement with ritonavir
HAART and Adverse Events

Hypersensitivity: Rash

IMPORTANT DRUG WARNING

August 2009

Dear Healthcare Professional

Fiumara Pharmacies, in cooperation with the U.S. Food and Drug Administration, would like to inform healthcare professionals that severe rash reactions (hypersensitivity reactions), including severe skin reactions (toxic epidermal necrolysis) and Stevens-Johnson syndrome, have been reported following the use of tacrolimus.

Specifically, the existing warning and precaution regarding Stevens-Johnson Syndrome has been updated to include this information.

Fiumara Pharmacies, Inc.

1717 15th Street, Suite 200
Denver, CO 80202

Phone: 1-800-528-3800

www.fiumarapharmacies.com

IMPORTANT DRUG WARNING

Severe, potentially life-threatening rash reactions (hypersensitivity reactions), including Stevens-Johnson Syndrome, have been reported following the use of tacrolimus.

8.5 Severe Skin and Hypersensitivity Reactions

Severe, potentially life-threatening, and fatal skin reactions have been reported. These include cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme.

If you have any questions or concerns regarding this information, please contact your healthcare provider.
Hypersensitivity: Rash

• Etravirine
  – Clinical trial data: 14-20%
  – Higher incidence in females
  – Onset: 11-14 days
  – Duration: 12-16 days
  – Discontinuation rate: 2%

• Protease Inhibitors
  – Atazanavir* (20%)
  – Darunavir* (7%, clinical trials 16%)
  – Fosamprenavir* (19%)
  – Lopinavir/ritonavir (clinical trials 7%)
  – Tipranavir* (10% adults; 21% pediatrics)

*Sulfonamides

HAART and Adverse Events
**Nephrotoxicity**

- Nephrolithiasis
  - Indinavir
  - Atazanavir
- Acute interstitial nephritis
  - Atazanavir

**HAART and Adverse Events**

- Veterans Affairs Database
  - Retrospective data
  - Cardiovascular mortality
- Myocardial infarction (D:A:D study group)
  - Prospective study
  - 11 international cohorts
  - N=23,437 patients
HAART and Adverse Events
Risk of Myocardial Infarction with Exposure to Antiretroviral Therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted Model</th>
<th>Adjusted Model 1</th>
<th>Adjusted Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed to protease inhibitors (per additional year)</td>
<td>1.17 (1.13-1.22)</td>
<td>&lt;0.001</td>
<td>1.18 (1.13-1.23)</td>
</tr>
<tr>
<td>Exposed to nonnucleoside reverse transcriptase inhibitors (per additional year)</td>
<td>1.07 (1.04-1.11)</td>
<td>0.09</td>
<td>1.05 (1.02-1.08)</td>
</tr>
</tbody>
</table>

+ Adjusted model:
- Gender
- Cohort
- HIV transmission group
- Incarcerated group
- Age
- BMI
- Family history
- Smoking status
- CV history
- Calendar year

++ Adjusted model:
- Diabetes mellitus
- Hypertension
- Dyslipidemia

HAART and Adverse Events
Risk of Myocardial Infarction with Exposure to Antiretroviral Therapy

November 2009

Dear Healthcare Professional:

LDV/HIV-1 RTV tablets: Tablets and Oral Suspension:
Myocardial Infarction and Myocardial Injury

Please refer to the data presented at the 19th Conference on Retroviruses and Opportunistic Infections (CROI 2012) relating to a potential association between LDV/HIV-1 RTV tablets and Oral Suspension and myocardial infarction in HIV-infected adults.

Active Ingredient: 120 mg Piroxicam. 5 mg Ketoprofen.


HAART and Adverse Events
Risk of Myocardial Infarction with Exposure to Antiretroviral Therapy

• NRTI risk
  – Zidovudine
  – Didanosine
  – Stavudine
  – Lamivudine
  – Abacavir

HAART and Adverse Events
Risk of Myocardial Infarction with Exposure to Antiretroviral Therapy

• NRTI risk
  – Zidovudine
  – Didanosine
  – Stavudine
  – Lamivudine
  – Abacavir
HAART and Adverse Events
Risk of Myocardial Infarction with Exposure to Antiretroviral Therapy

Risk of MI associated with prolonged exposure to antiretroviral therapy (ART) and after 3-5 years of suppression.

<table>
<thead>
<tr>
<th>ART</th>
<th>JOV</th>
<th>EV</th>
<th>ATV</th>
<th>FTC</th>
<th>ABC</th>
<th>LPV</th>
<th>ATV</th>
<th>NVP</th>
<th>ABC</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>1.04</td>
<td>1.03</td>
<td>1.03</td>
<td>1.03</td>
<td>1.03</td>
<td>1.03</td>
<td>1.03</td>
<td>1.03</td>
<td>1.03</td>
</tr>
</tbody>
</table>

HAART and Adverse Events
Risk of Myocardial Infarction with Exposure to Antiretroviral Therapy

<table>
<thead>
<tr>
<th>Risk score variables</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>45</td>
</tr>
<tr>
<td>Male</td>
<td>yes</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>160 mg/dL</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>35 mg/dL</td>
</tr>
<tr>
<td>Smoker</td>
<td>yes</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>125 mmHg</td>
</tr>
</tbody>
</table>

The risk score calculation is based on the criteria in the equation. For the risk score, additional factors such as APPT, triglycerides, use of protease inhibitors, and a statin are incorporated into the equation to calculate a risk score that approximates the statin benefit score.

Questions