Structured Treatment Interruption in HIV Positive Patients

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HIV Rotation
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Objectives

- To become re-acquainted with the basics of HAART for HIV infection
- To list reasons why a patient may want to interrupt HAART
- To describe the appropriateness of structured treatment interruption based on the findings of the SMART study
HAART

- Highly Active Anti-Retroviral Therapy
- Often involves the use of 3 or more anti-retrovirals (ARVs) acting at different stages of the HIV life cycle (i.e., PIs, NNRTIs, NRTIs, etc)
- Combination therapy provides potent viral suppression leading to good immune system recovery
- Life-long use
- HIV now considered a chronic disease
Figure A: Prognosis According to CD4 Cell Count and Viral Load in the Pre-HAART and HAART Eras

Pre-HAART era

HAART era


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

<table>
<thead>
<tr>
<th>Protease inhibitors “PIs”</th>
<th>Non-nucleoside reverse transcriptase inhibitors “NNRTIs”</th>
<th>Nucleoside reverse transcriptase inhibitors “NRTIs”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir/r</td>
<td>Efavirenz (EFV)</td>
<td>Abacavir (ABC)</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>Nevirapine (NVP)</td>
<td>Lamivudine (3TC)</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>*Etravirine (TMC 125)</td>
<td>Zidovudine (AZT)</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td></td>
<td>Stavudine (d4T)</td>
</tr>
<tr>
<td>*Darunavir/r (TMC 114)</td>
<td></td>
<td>Didanosine (ddl)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*Tenofovir (TDF)</td>
</tr>
</tbody>
</table>
Other agents

- Enfuvirtide (fusion inhibitor)
- Maraviroc, vicriviroc (CCR5 receptor antagonists)
- MK-0518 (integrase inhibitor)
To Construct an Antiretroviral Regimen, Select 1 Component from Column A + 1 from Column B

<table>
<thead>
<tr>
<th>Column A (NNRTI or PI Options – in alphabetical order)</th>
<th>Column B (Dual-NRTI Options – in alphabetical order)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preferred Components</strong></td>
<td>Preferred Components</td>
</tr>
<tr>
<td>NNRTI – efavirenz¹ (AII)</td>
<td>tenofovir/emtricitabine³ (co-formulated) (AII); or</td>
</tr>
<tr>
<td></td>
<td>zidovudine/lamivudine³ (co-formulated) (AII)</td>
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<tr>
<td>FFV + rilpivirine or rilpivirine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Alternative to Preferred Components</strong></td>
<td>Alternative to Preferred Components</td>
</tr>
<tr>
<td>NNRTI – nevirapine² (BII)</td>
<td>abacavir/lamivudine³ (co-formulated) (BII)</td>
</tr>
<tr>
<td></td>
<td>didanosine + (emtricitabine or lamivudine) (BII)</td>
</tr>
<tr>
<td>atazanavir + ritonavir (AIII)</td>
<td></td>
</tr>
<tr>
<td>fosamprenavir + ritonavir (2x/day) (AII)</td>
<td></td>
</tr>
<tr>
<td>lopinavir/ritonavir² (2x/day) (AII)</td>
<td></td>
</tr>
<tr>
<td>(co-formulated)</td>
<td></td>
</tr>
<tr>
<td>atazanavir⁵ (BII)</td>
<td></td>
</tr>
<tr>
<td>fosamprenavir (BII)</td>
<td></td>
</tr>
<tr>
<td>fosamprenavir + ritonavir (1x/day) (BII)</td>
<td></td>
</tr>
<tr>
<td>lopinavir/ritonavir (1x/day) (BII)</td>
<td></td>
</tr>
<tr>
<td>(co-formulated)</td>
<td></td>
</tr>
</tbody>
</table>
WHEN TO TREAT: Indications for Antiretroviral Therapy

Panel’s Recommendations (Table 5):

- Antiretroviral therapy is recommended for all patients with history of an AIDS-defining illness or severe symptoms of HIV infection regardless of CD4\(^+\) T cell count (AI).
- Antiretroviral therapy is also recommended for asymptomatic patients with <200 CD4\(^+\) T cells/mm\(^3\) (AI).
- Asymptomatic patients with CD4\(^+\) T cell counts of 201–350 cells/mm\(^3\) should be offered treatment (BII).
- For asymptomatic patients with CD4\(^+\) T cell count of >350 cells/mm\(^3\) and plasma HIV RNA >100,000 copies/mL most experienced clinicians defer therapy but some clinicians may consider initiating treatment (CII).
- Therapy should be deferred for patients with CD4\(^+\) T cell counts of >350 cells/mm\(^3\) and plasma HIV RNA <100,000 copies/mL (DII).
Adverse Effects

- NRTI backbone
  - Nausea
  - Peripheral neuropathy (often “d” drugs)
  - Lactic acidosis
  - Hepatic steatosis
  - Pancreatitis
  - Lipodystrophy (d4T)
  - Renal insufficiency (TDF)
  - Hypersensitivity (ABC)
  - Bone marrow suppression, headache, insomnia (AZT)
Adverse Effects

- **NNRTIs**
  - Rash $\rightarrow$ Stevens-Johnson syndrome (esp. NVP)
  - $\uparrow$ liver transaminases $\rightarrow$ hepatitis, hepatic necrosis
  - CNS effects with EFV (insomnia, abnormal dreams, dizziness, confusion, abnormal thinking, hallucinations...)
  - Teratogenesis (EFV)
  - ++ potential for drug interactions
Adverse Effects

- **PIs**
  - N/V/D
  - ↑ liver transaminases
  - Hyperlipidemia (esp. ↑ TG)
  - Hyperglycemia
  - Fat maldistribution
  - Hyperbilirubinemia (atazanavir, indinavir)
  - Nephrolithiasis (indinavir)
  - Oral paresthesia (ritonavir)
  - Intracranial hemorrhage (tipranavir)
  - ++ potential for drug interactions
Potential reasons for interruption

- Adverse events!
- Pill burden and necessity of adherence
- Resistance
- Cost
Question:

- Can we safely interrupt ARV treatment???
“CD4+ Count-Guided Interruption of Antiretroviral Treatment”\textsuperscript{4}

The SMART study group. NEJM 2006;335:2283-96

- Enrolment began January 2, 2002
- 318 sites in 33 countries → incl. TGH!
- Ambitious target of 6000 patients
- Follow-up planned for 6+ years
Background

- Despite ↓ morbidity and mortality with HAART, its effectiveness is limited by adverse events (metabolic and cardiovascular complications), problems with adherence, and viral resistance (incl. multi-drug resistance)

- Lifelong treatment
Purpose

- To study a treatment-sparing strategy in hopes of providing the benefits of ARV therapy while minimizing the adverse events and other risks of long-term use.
Intervention

- 5472 patients randomized:
  - Drug conservation arm: episodic drug tx based on CD4 count; start tx if <250, and stop when >350
  - Viral suppression arm: uninterrupted tx with goal of maximal and continuous suppression of HIV replication (standard care)
Inclusion criteria

- >13 years of age (median age 43)
- Not pregnant/breastfeeding
- Eligible whether or not they had received or were currently receiving ARVs (84% on tx at baseline)
- Willing to initiate, modify or stop ARVs according to the guidelines
Case example: CC

- 44 yo ♂ diagnosed at age 38
- Sexual transmission (homosexual)
- At dx: CD4=620, VL=115 795
- Started treatment during seroconversion illness → EFV and Combivir (AZT/3TC)
- Numbness in fingertips, mild lipoatrophy, bad dreams
- ++ interested in stopping treatment
- Enrolled in SMART July 2005; CD4 800, VL <50
- Randomized to discontinue medications
Case example: RC

- 42 yo ♂ diagnosed at age 28
- Sexual transmission (heterosexual)
- ARV history: AZT, AZT/3TC study (impotence, fatigue, h/a, nausea, anemia); ddI; ddC and saquinavir; EFV, d4T, nelfinavir 1998-present
- Has experienced opportunistic infections (OIs) including disseminated zoster
- Tingling extremities, significant abdominal obesity and buffalo hump, ++ vivid dreams (requires sleeping pill), dyslipidemia (TC 13.48, TG 11.45 prior to lipid tx)
- Enrolled in SMART July 2005; CD4 1001, VL <50
- Randomized to continue HAART
Demographics

- Similar at baseline, incl. CV risk factors
- Women (27%), hepatitis B and C co-infection, various races (white 56%, black 29%, other 15%)
- Median CD4 = 597
- VL < 400 in 72% of patients
- Median 6 years since first ARVs
- 24% had prior AIDS-related illness
Monitoring and follow-up

- Scheduled visits @ 1 mo and 2 mos, q2mos thereafter for 1\textsuperscript{st} year, then q4mos in 2\textsuperscript{nd} and subsequent years
- More frequent if clinical care required
- Independent data and safety board to review interim analyses at least yearly
- STOPPED EARLY: mean follow-up only 16 mos; 26\% of pts followed > 2 years
Endpoints

- **Primary**
  - New or recurrent opportunistic disease\textsuperscript{5,6} or death from any cause

- **Secondary**
  - Death from any cause
  - Serious opportunistic disease\textsuperscript{7}
  - Major cardiovascular, renal, or hepatic disease\textsuperscript{6}
  - Grade 4 adverse events\textsuperscript{8} (not incl. opportunistic disease) or death from any cause
Results

- Median duration of 1\textsuperscript{st} interruption = 17 mos
- N=343 stopped ARVs a 2\textsuperscript{nd} time
- N=62 stopped ARVs ≥3 times
- CD4 count ↓ 87 cells/mm\(^3\) per month x 2 mos, then ↓ at lower rate (drug conservation group)
- CD4 count was 206 cells/mm\(^3\) lower in drug conservation group
- Within 2 mos, patients with VL ≤ 400 copies/mL ↓ from 72% to 6%
CD4 count changes

![Graph showing CD4 count changes over time with error bars and patient distribution numbers.](image)

No. of Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
<th>28</th>
<th>32</th>
<th>36</th>
<th>40</th>
<th>44</th>
</tr>
</thead>
<tbody>
<tr>
<td>DC</td>
<td>2720</td>
<td>2002</td>
<td>1561</td>
<td>1240</td>
<td>1024</td>
<td>672</td>
<td>604</td>
<td>524</td>
<td>447</td>
<td>370</td>
<td>269</td>
<td>157</td>
</tr>
<tr>
<td>VS</td>
<td>2752</td>
<td>1925</td>
<td>1547</td>
<td>1216</td>
<td>1021</td>
<td>872</td>
<td>638</td>
<td>540</td>
<td>460</td>
<td>367</td>
<td>261</td>
<td>150</td>
</tr>
</tbody>
</table>
% patients with VL \leq 400^6
Results

- After reinitiation of ARVs, time to VL $\leq 400$ copies/mL was 3.1 mos
- CD4 count $\uparrow$ 166 cells/mm$^3$ within 8 mos
## Results

<table>
<thead>
<tr>
<th></th>
<th>Drug conservation (DC) group</th>
<th>Viral suppression (VS) group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received ARVs (% time)</td>
<td>33.4%</td>
<td>93.7%</td>
</tr>
<tr>
<td>CD4 count ≥ 350 (% time)</td>
<td>67.9%</td>
<td>92.7%</td>
</tr>
<tr>
<td>CD4 count &lt; 250 (% time)</td>
<td>8.6%</td>
<td>1.8%</td>
</tr>
<tr>
<td>VL ≤ 400 copies/mL (% time)</td>
<td>28.8%</td>
<td>72.3%</td>
</tr>
</tbody>
</table>
# Results

<table>
<thead>
<tr>
<th>End Point</th>
<th>Drug Conservation Group (N=2720)</th>
<th>Viral Suppression Group (N=2752)</th>
<th>Hazard Ratio for Drug Conservation Group vs. Viral Suppression Group (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Participants with Event</td>
<td>Event Rate (per 100 Person-Yr)</td>
<td>No. of Participants with Event</td>
<td>Event Rate (per 100 Person-Yr)</td>
</tr>
<tr>
<td>Primary end point</td>
<td>120</td>
<td>3.3</td>
<td>47</td>
<td>1.3</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>55</td>
<td>1.5</td>
<td>30</td>
<td>0.8</td>
</tr>
<tr>
<td>Opportunistic disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious</td>
<td>13</td>
<td>0.4</td>
<td>2</td>
<td>0.1</td>
</tr>
<tr>
<td>Nonserious</td>
<td>63</td>
<td>1.7</td>
<td>18</td>
<td>0.5</td>
</tr>
<tr>
<td>Major cardiovascular, renal, or hepatic disease</td>
<td>65</td>
<td>1.8</td>
<td>39</td>
<td>1.1</td>
</tr>
<tr>
<td>Fatal or nonfatal cardiovascular disease</td>
<td>48</td>
<td>1.3</td>
<td>31</td>
<td>0.8</td>
</tr>
<tr>
<td>Fatal or nonfatal renal disease</td>
<td>9</td>
<td>0.2</td>
<td>2</td>
<td>0.1</td>
</tr>
<tr>
<td>Fatal or nonfatal liver disease</td>
<td>10</td>
<td>0.3</td>
<td>7</td>
<td>0.2</td>
</tr>
<tr>
<td>Grade 4 event</td>
<td>173</td>
<td>5.0</td>
<td>148</td>
<td>4.2</td>
</tr>
<tr>
<td>Grade 4 event or death from any cause</td>
<td>205</td>
<td>5.9</td>
<td>164</td>
<td>4.7</td>
</tr>
</tbody>
</table>

* Numbers of individual events of each type do not sum to the total number because some participants had more than one event. End-point definitions are listed in the Supplementary Appendix. Grade 4 events were determined on the basis of toxicity grades developed by the Division of AIDS of the NIAID. CI denotes confidence interval.
Results

- Hazard ratio (HR) for primary endpoint (opportunistic disease of death from any cause) = 2.6 (95% CI 1.9-3.7; P<0.001)

- Most common individual events
  - DC group: death from any cause (39%), esophageal candidiasis (20%), and PCP (7%)
  - VS group: death from any cause (57%) and esophageal candidiasis (15%)
Results

- Number of deaths = 85
- Only 8% due to opportunistic disease
- Common causes of death outside of opportunistic disease:
  - Cancer (DC>VS)
  - CVD (DC>VS)
  - Substance abuse
  - Accident, violence, or suicide
  - Unknown for 18 patients (15 DC, 3 VS)
Results

- Sensitivity analysis on primary endpoint:
  - New opportunistic disease (OD) or death from any cause HR = 2.6 (95% CI 1.8-3.7, P < 0.001)
  - Fatal and non-fatal cases of OD (excl. deaths from other causes) HR = 3.6 (2.2-5.9, P < 0.001)
  - All reported cases of ODs and deaths irrespective of classification after review by endpoint review committee HR = 2.5 (1.9-33, P < 0.001)

  (Note: HR reported for DC group vs VS group)
Results

- Secondary endpoints (DC group vs VS group)
  - Death from any cause: HR=1.8 (95% CI 1.2-2.9)
  - Serious opportunistic disease: HR=6.6 (1.5-29.1)
  - Major CV, renal, or hepatic disease: HR=1.7 (1.1-2.5)
  - Grade 4 event or death from any cause: HR=1.3 (1.0-1.6)
Clinical Application

- Continuous use of ARVs is superior to episodic use guided by the CD4 count thresholds used in the SMART study.
- SMART strategy is deleterious → even patients with “good” CD4 counts are at risk for bad clinical events if not on treatment (outside of ODs as well).
- Lack of benefit of interruption on major adverse events.
Clinical Application

- Interruption strategies should be viewed with net clinical risk unless proven otherwise in properly powered studies.
Study limitations

- Overall, very well done!
- Follow-up missing for 73 patients at the close of the study (32 in interruption group, 41 in suppression group)
- Unblinded, but endpoint review committee unaware of treatment assignments
- Equal treatment of groups?
- Concomitant diseases and medications unknown, including use of OI treatment and prophylaxis
Unanswered questions

- Is it possible to safely interrupt treatment at higher CD4 thresholds?

- Smaller studies have attempted to answer some of them → Staccato⁹ (n=284) deferred treatment until CD4 < 350; compared to continuous tx, more oral and vaginal candidiasis
Case examples

- **Mr CC:**
  - Discontinued meds (EFV/Combivir) July 2005 as per SMART randomization; very pleased about this
  - Study closed January 2006; CD4 count 912, VL still <50
  - Did not resume medications upon study closure
Case examples

Mr. RC:
- Long ARV history; randomized to continue medications in July 2005 as per SMART study
- Remains on d4T, nelfinavir, EFV (since 1998)
- Lipids controlled on pravastatin and fenofibrate (TG 2.5 recently vs 11.45 in 2002)
- Difficulty with weight loss despite exercise
References


2. Integrase article


4. The SMART study group. CD4+ Count-Guided Interruption of Antiretroviral Treatment. NEJM 2006;255:2283-96.


6. Supplementary web-only appendix for SMART study available through fulltext article at [www.nejm.org](http://www.nejm.org)

