When to Rock the Boat
Switching Antiretroviral Therapy for Metabolic Complications

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Objectives

• Understand **rationale** for switching antiretroviral therapy (ART) for metabolic complications

• Be familiar with **clinical trial data** and **treatment guidelines** regarding switching ART

• Be aware of potential **risks and benefits** of switching ART
Rocking the boat…

1. *Lit.* to do something to move a boat from side to side, causing it to rock. (Often in a negative sense.) *Sit down and stop rocking the boat. You'll turn it over!*

2. *Fig.* to cause trouble where none is welcome; to disturb a situation that is otherwise stable and *satisfactory.* (Often negative.) *Look, Tom, everything is going fine here. Don't rock the boat! You can depend on Tom to mess things up by rocking the boat.*
Is the situation *really* “stable and satisfactory?”

*Sometimes rocking the boat is a good idea...*
Outline

• Background/historical perspective
• Review of metabolic complications
• Switching nucleoside reverse transcriptase inhibitors (NRTIs)
• Switching protease inhibitors (PIs)
• Caveats and **cautions**
• Conclusions and applications
DECLINING MORBIDITY AND MORTALITY AMONG PATIENTS WITH ADVANCED HUMAN IMMUNODEFICIENCY VIRUS INFECTION

FRANK J. PALELLA, JR., M.D., KATHLEEN M. DELANEY, M.S., ANNE C. MOORMAN, B.S.N., M.P.H.,
MARK O. LOVELESS, M.D., JACK FUHRER, M.D., GLEN A. SATTEL, PH.D., DIANE J. ASCHMAN, R.P.H., M.S.,
SCOTT D. HOLMBERG, M.D., M.P.H., AND THE HIV OUTPATIENT STUDY INVESTIGATORS*
• Metabolic effects of PI-based ART
  – Dyslipidemia
  – Insulin resistance
  – Abdominal obesity ("lipodystrophy")

The patient expressed concern about continuing indinavir therapy because of the changes in his physical appearance and the potential risk of long-term cardiovascular disease.
Early ART switch studies

- **1998-99: Switch PI (>90% IDV or NFV) to NVP**
  - 3 months:
    - Improved face/arm “Acquired HIV-associated Lipodystrophy”
    - “tendency toward” improved cholesterol, triglycerides at 3 months
  - 1 year:
    - **Decreased total cholesterol, triglycerides** from baseline in NVP group; not statistically different from PI group
    - **No difference in body fat**


HIV protease inhibitor substitution in patients with lipodystrophy: a randomized, controlled, open-label, multicentre study

Andrew Carr\(^a\), Jeff Hudson\(^b\), John Chuah\(^c\), Simon Mallal\(^d\),
Matthew Law\(^e\), Jennifer Hoy\(^e\), Nicholas Doong\(^f\), Martyn French\(^d\),
Don Smith\(^e\) and David A. Cooper\(^a,e\) for the PIILR study group

*AIDS* 2001, 15:1811–1822

Protease Inhibitor Induced Lipodystrophy Reversal (PIILR)

N=81 randomized: continue ART with PI or **switch PI to ABC + NVP + adeovir + hydroxyurea**

Decreased total body fat, total cholesterol, triglycerides
What are ART-associated metabolic complications?

• Fat redistribution
  – Lipoatrophy and lipo hypertrophy

• Dyslipidemia
  – Hypercholesterolemia
  – Hypertriglyceridemia
  – Low HDL cholesterol

• Insulin resistance/type 2 diabetes mellitus

• Metabolic syndrome (increased in HIV?)

• *Increased cardiovascular risk*
European AIDS Clinical Society (EACS) guidelines on the prevention and management of metabolic diseases in HIV*

<table>
<thead>
<tr>
<th>Metabolic impact of drugs</th>
<th>NNRTI</th>
<th>NRTI</th>
<th>PI</th>
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<tbody>
<tr>
<td>Less</td>
<td>NVP</td>
<td>3TC / FTC</td>
<td>ATV/r</td>
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<tr>
<td></td>
<td>EFV</td>
<td>ABC</td>
<td>SQV/r</td>
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<td>ddI</td>
<td>LPV/r</td>
<td>IDV/r</td>
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<td></td>
<td>d4T</td>
<td>fAPV/r</td>
<td>TPV/r</td>
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<td>DRV/r</td>
<td>RTV (full dose)</td>
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*Limited data from use of fusion inhibitors (enfuvirtide), integrase inhibitors (raltegravir), and CCR5 inhibitors (maraviroc) suggest these drugs to have little metabolic impact, but length of experience for some of these is limited.
Conceptual model of ART metabolic complications

Switching NRTIs for metabolic complications
NRTI-associated lipoatrophy

Grinspoon and Carr. NEJM 2005; 352: 48-62
What is lipoatrophy?

NRTI switch studies
Change in limb fat over time

Switch d4T/ZDV to ABC
Switch d4T+PI to ZDV+ABC
Switch d4T to ZDV or ABC
Switch d4T+PI/NNRTI to ZDV+ABC
Continue d4T/ZDV
Switch from PI/NNRTI to ABC

Modified from: Sutinen Curr Opin Infect Dis 2005. 18: 25-33
NRTI switch for lipoatrophy
Mitochondrial Toxicity Study (MITOX)

• Moderate-severe peripheral lipoatrophy
  - HIV RNA <400 x 3 months; on d4T or ZDV ≥ 8 weeks

Outcome = change in limb fat by DEXA at 24 weeks

MITOX extension study- continued to 104 weeks

NRTI switch for lipoatrophy

MITOX Extension Study

At 24 weeks, improved limb fat by DEXA in ABC group; no subjective improvement.

At 104 weeks, continued improvement in ABC group; trend in 24 week switch group; no subjective improvement.

NRTI switch for lipoatrophy
Randomized Abacavir versus Viread Evaluation (RAVE)

• 105 subjects with moderate-severe lipoatrophy
  ➢ Randomization: switch d4T/ZDV to ABC or TDF
  ➢ Primary endpoint: DEXA limb fat at 48 weeks

48-week mean limb fat increases:

- TDF = 329g (p=0.01)
- ABC = 483g (p=0.0001)

NRTI switch for lipoatrophy
Randomized Abacavir versus Viread Evaluation (RAVE)

NRTI switch studies
Change in limb fat over time

Modified from: Sutinen *Curr Opin Infect Dis* 2005. 18: 25-33
NRTI switch studies
Simplification With Easier Emtricitabine Tenofovir (SWEET)

- Randomized, open-label trial
  - Continue CBV vs. switch to TDV
  - N=234 (100 with DEXA)
  - Primary outcome= hemoglobin
  - 6 subjects had VL increase >50 copies over 48 weeks
- Improved total cholesterol and triglycerides in switch arm at week 24

NRTI switch studies
Simplification With Easier Emtricitabine Tenofovir (SWEET)

NRTI switch studies
Change in limb fat over time

Modified from: Sutinen Curr Opin Infect Dis 2005. 18: 25-33
How Much Fat Loss Is Needed for Lipoatrophy to Become Clinically Evident?

Daniel Podzamczer, Elena Ferrer, Esteban Martínez, Luis del Rio, Joaquín Rosales, Jordi Curto, Esteban Ribera, Pilar Barrufet, Josep M. Llibre, and Miquel Aranda for the ABCDE Study Team
NRTI switch studies
Switch to NRTI-sparing ART (ANRS NoNuke)

- Randomized, open-label
  - N=100 with stable ART, self-reported lipoatrophy
- Continue NRTIs vs. switch to PI+NNRTI
  - ~70% baseline ZDV or d4T
- 96 week change in thigh SAT (by CT scan)

- NRTI-sparing:
  - Increased LDLc (and HDLc) in at week 96
  - Increased triglycerides at week 48

NRTI switch studies
Switch to ABC or NRTI-sparing ART (ACTG A5110)

Subjects had significant improvement in body image self-perception, but did not correlate with fat measurements by CT imaging

NRTI switch studies

Summary

• **Switch d4T or ZDV to ABC or TDF for lipoatrophy**
  - Virologically safe in selected patients
    - Fully suppressed/adherent at time of switch
    - Minimal underlying resistance/few prior regimens
  - ~200-500g limb fat gain at 1 year
  - >1kg at 2 years
  - Earlier the better; better late than never
  - Subjective improvement may take several years
  - **Be aware of ABC HSR and TDF renal toxicity**
    - Check HLA-B57*01, baseline CrCl before considering switch
    - New drug interactions (e.g. TDF and ATV)
    - Cardiovascular risk with ABC?

• **Switching d4T or ZDV to TDF (or ABC) improves lipids**
  - Probably improves insulin resistance

• **Question in clinic:** *Is there a compelling reason why this patient should remain on d4T or ZDV?*

• **NRTI-sparing regimens?** Lipid trade-off; not ready for prime time…yet

• **Switching a PI alone** does *not* affect lipoatrophy
Switching PIs for metabolic complications
PI switch for metabolic complications
Nevirapine EFavirenz Abacavir (NEFA) Study

- RCT of PI switch to NNRTI or ABC (N=460)
  - Primary endpoint= virologic failure
    - ABC>NNRTI ($P=0.1$)
  - 24-month metabolic substudy (n=90)
  - Improved lipids with NNRTI switch
    - HDLc and TC/HDLc
    - Less benefit with lipodystrophy
  - Triglycerides decreased at 12 months, not 24 months
  - No improvement in lipodystrophy

PI switch for metabolic complications

- Non-randomized study of PI-switch to (un-boosted) ATV for dyslipidemia
  - Improved TG, TC, non-HDL cholesterol; no change in HDLc or LDLc

- Switch to Another Protease Inhibitor (SWAN) study
  - RCT, open-label (N>400)
  - Stable PI regimens
  - Switch to ATV or ATVr (if TDF) vs. no switch
  - Less virologic failure with ATV

PI switch for metabolic complications
LPVr switch to ATVr (ATAZIP)

• Randomized, open-label, 48-week non-inferiority trial
  ➢ Continue LPVr vs. switch to ATVr
  ➢ N=248
  ➢ Outcome= treatment failure

• Median baseline lipids:
  ➢ Triglycerides ~180 mg/dL
  ➢ Total cholesterol ~200 mg/dL
  ➢ LDLc ~110 mg/dL

PI switch for metabolic complications

Better to switch or treat lipids?

- PI switch to NVP or EFV vs. adding pravastatin or bezafibrate
  - Randomized, open label trial
  - N=130 on 1st HAART; NNRTI naïve; mixed hyperlipidemia
  - Adding lipid-lowering drug more effective than switching (p<0.01)

PI switch for metabolic complications

**SWITCHMRK 1 and 2 (Merck protocols 032/033)**

- 2 randomized, double-blind, multicenter, non-inferiority trials
  - Total N > 650 switched from LPVr to RAL

- Decreased total and non-HDLc (12-15%), triglycerides (41-43%) with RAL switch

- Fewer RAL switch subjects had 24 week HIV RNA < 50
  - 81/88% vs. 87/94%
  - Differences -6.6 (-14.4, 1.2) and -5.8 (-12.2, 0.2)
  - Non-inferiority cutoff: lower CI of 12

- RAL switch arms did not meet non-inferiority for virologic outcome
  - 84% RAL failures on > 1st regimen; 66% virologic failure on prior regimen

CROI 2009. Montreal, Canada. Abstract 70aLB
PI switch for metabolic complications

Summary

• Safe in selected patients
  ➢ No NRTI-only regimens

• Little evidence for improved abdominal/visceral fat

• Significant improvements in lipids
  ➢ PI to NNRTI: HDLc and triglycerides
  ➢ PI to ATV/ATVr: Total, non-HDLc, triglycerides
  ➢ LPVr to RAL*: Total, non-HDLc, triglycerides (↓40%)

*Caution: RAL switch arm less likely to remain undetectable at 24 weeks. Greatest risk in those with prior ART failures

• Don’t forget other interventions (e.g. diet/exercise, lipid-lowering drugs, smoking cessation)
• No DRVr switch data yet…
• No cardiovascular outcomes data yet…
### Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Associated ARVs</th>
<th>Onset/Clinical Manifestation</th>
<th>Estimated Frequency</th>
<th>Risk Factors</th>
<th>Prevention/Monitoring</th>
<th>Management</th>
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<tbody>
<tr>
<td>Lipodystrophy</td>
<td>Lipoatrophy: NRTIs (d4T &gt; ZDV &gt; TDF, ABC, 3TC, FTC), especially when combined with EFV [33]</td>
<td>Onset: gradual; months after initiation of therapy</td>
<td>High: exact frequency uncertain and dependent on regimen; increases with duration on offending agents</td>
<td>Both lipoatrophy &amp; lipo hypertrophy: low baseline body mass index</td>
<td>• Lipoatrophy: avoid thymidine analogs (esp. when combined with EFV), or switch from ZDV or d4T to ABC or TDF</td>
<td>• Switch from thymidine analogs to TDF or ABC; may slow or halt progression; however, may not fully reverse effects</td>
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<td>Lipo hypertrophy: Abdominal fat gain seen with PI- or NNRTI-based regimens &amp; with thymidine analogs (e.g., d4T, ZDV)</td>
<td>Symptoms:</td>
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<td>• Lipo hypertrophy: pretreatment diet/exercise program may reduce incidence and extent</td>
<td>• Injectable poly-L-lactic acid or other injectable fillers for treatment of facial lipo hypertrophy</td>
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<td>• Lipo hypertrophy: Abdominal</td>
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<td>• Liposuction for dorsocervical fat pad enlargement (recurrence common)</td>
<td>Lipohypertrophy:</td>
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<td>fat gain seen with PI- or</td>
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<td>• Diet/exercise</td>
<td>• Recombinant human growth hormone, under investigation</td>
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European AIDS Clinical Society (EACS) guidelines on the prevention and management of metabolic diseases in HIV*

<table>
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<th>Estimate of IHD in next 10 years*</th>
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<tr>
<td>IHD risk &lt; 10%</td>
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<tr>
<td>IHD risk 10–20%</td>
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<tr>
<td>IHD &gt;20%, prior CVD, type II diabetes, type I diabetes with microalbuminuria</td>
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- Encourage lifestyle changes (diet, exercise, cessation of smoking), reduce visceral fat, reduce insulin resistance and treat hypertension

| LDL-c cut-off level: 5 mmol/L (190 mg/dL) [5–4 mmol/L (190 – 155 mg/dL)] |
| LDL-c cut-off level: 4 mmol/L (155 mg/dL) [4–3 mmol/L (155 – 115 mg/dL)] |
| LDL-c cut-off level: 3 mmol/L (115 mg/dL) [3–2 mmol/L (115 – 80 mg/dL)] |

**Consider modifying ART, if:**
(i) LDL-c is above cut-off, (ii) ART thought to contribute to ↑ LDL-c level, (iii) if possible without compromising HIV suppression

- Strongly consider modifying ART, if:
  (ii) LDL-c is above cut-off, (iii) ART thought to contribute to ↑ LDL-c level, (iii) if possible without compromising HIV suppression

If lifestyle changes, with or without modification of ART, do not result in sufficient lowering of LDL-c to below target level, use of lipid-lowering medication should be considered (see Table 4).

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1 LDL-c cut-off levels [units: mmol/L (mg/dL)] are higher than in guidelines for the general population (more stringent levels where some experts would consider intervention also indicated in parentheses below). In cases where LDL-c cannot be reliably calculated because of high triglyceride levels, the non-HDL-c target level should be used which is 0.8 mmol/L (30 mg/dL) higher than the corresponding LDL-c target.

2 Options for ART modification include: (1) replacing PI( r) by NNRTI, or by another PI( r) known to cause less metabolic disturbance (see Fig. 2); (2) replacing d4T or ZDV by TDF. In patients with >20% 10-year risk or with prior CVD, the risk of CVD events and cardiac death will usually be higher than risk of progression to AIDS or death and in such patients, a strategy to reduce risk of CVD by switching ART is hence most appropriate.

3 Use Framingham equation (see www.cphiv.dk/tools.aspx).
ART switch for metabolic complications
Summary and application

• **Who is a candidate for switching?**
  - Consistently undetectable HIV RNA; good adherence
  - Few prior regimens/resistance mutations
  - Willing to switch

• **Definitely** rock the boat…
  - On *thymidine analogue NRTI* (ZDV or d4T) with lipoatrophy, hypercholesterol, DM
    - Switch to ABC or TDF; consider NRTI-sparing regimen
  - On *older PI* (NFV, IDV, LPVr) with dyslipidemia, DM, high ($\geq 20\%$ 10-year) CV risk
    - Consider switch to newer PI (ATVr, DRVr), minimize RTV, alternate classes

• **Consider** rocking the boat…
  - *Anyone* on d4T or ZDV
    - Consider switch to ABC or TDF
  - *Anyone* on an older PI
    - Consider switch to newer PI, minimize RTV, alternate classes

• **Don’t** rock the boat…
  - Salvage regimen (extensive prior ART; known resistance)
  - HIV/AIDS disease-related risk $>$ CV risk
  - Patient wants to continue after discussion of risks/benefits
Questions?

Successful long-term ART

Metabolic complications