Switching ARV Regimens: Managing Toxicity and Improving Tolerability; Switches & Class-Sparing Approaches

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Faculty and Planning Committee Disclosures

Please consult your program book.

Off-Label Disclosure

The following off-label/investigational uses will be discussed in this presentation:

• none
Learning Objectives

Upon completion of this presentation, learners should be better able to:

• Describe the efficacy of class sparing strategies in treatment naïve and experienced patients
• Discuss the risks and benefits of switching ARV therapy in patients receiving suppressive ARV therapy
• Devise and modify ARV regimens in treatment-experienced patients
Outline

• Class sparing approaches
• Recent “switch” studies
• How to assess potential risks and benefits of switching ARV regimens in treatment-experienced patients
Case 1

- 53 yo man with HIV (CD4 nadir 250 in 1996, current CD4 700, VL < 40 copies/mL) requests treatment “simplification”
  - Comorbidities:
    - osteopenia with metatarsal stress fractures, on Ca, Vit D, alendronate recently started after fractures healed
    - Hyperlipidemia, on atorvastatin and fenofibrate
    - Obesity, on disability for stress fractures in metatarsal bones
  - Current regimen: maraviroc, atazanavir/r, TDF/FTC, nevirapine
ARV History

• 1996 – 1999:
  – D4T, 3TC, indinavir. Had virologic failure but no GT available

• 1999 – 2006:
  – DDI, nevirapine, lopinavir/ritonavir

• 2006 – 2008: Treatment Interruption

• 2008:
  – R5 virus, enrolled in MVC study, started on maraviroc 150 mg BID, r/ATZ 400 mg QD, NVP 400 mg QD, TDF/FTC one QD

• Since 2008:
  – Excellent adherence and virologic suppression since 2008; chronic diarrhea for which he takes imodium
What would you start him on?

A. maraviroc, rilpivirine, dolutegravir
B. maraviroc, etravirine, raltegravir
C. check HLA B5701, if negative, start on abacavir/lamivudine, rilpivirine, dolutegravir
D. Something else
What would you start him on?

A. maraviroc, rilpivirine, dolutegravir
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C. check HLA B5701, if negative, start on abacavir/lamivudine, rilpivirine, dolutegravir
D. Something else

Outcome: pt starts on regimen A, has maintained suppression after 6 mos, and loves his new regimen. Fenofibrate has been discontinued with good control of lipids
**DHHS Guidelines 2015: What to Start**

<table>
<thead>
<tr>
<th>NNRTI</th>
<th>Recommended regimens</th>
<th>Alternative regimens*</th>
</tr>
</thead>
</table>
|       |                      | • EFV/TDF/FTC  
|       |                      | • RPV/TDF/FTC  |

<table>
<thead>
<tr>
<th>Boosted PI</th>
<th>Recommended regimens</th>
<th>Alternative regimens*</th>
</tr>
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</table>
|            | • DRV/RTV + TDF/FTC  | • ATV + RTV or COBI + TDF/FTC  
|            |                      | • DRV + RTV or COBI + ABC/3TC  
|            |                      | • DRV/COBI + TDF/FTC  |

<table>
<thead>
<tr>
<th>INSTI</th>
<th>Recommended regimens</th>
<th>Alternative regimens*</th>
</tr>
</thead>
</table>
|       | • DTG + ABC/3TC  
|       | • DTG + TDF/FTC  
|       | • EVG/COBI/TDF/FTC  
|       | • RAL + TDF/FTC  |

DHHS Guidelines, April 8, 2015

*DRV/r + RAL AND LPV/r + 3TC for pts who cannot take TDF or ABC  
For pts with VL < 100K:  ATV/r or EFV + ABC/3TC; RPV/TDF/FTC  
For pts who are HLA-B*5701 positive, avoid abacavir
## Current options for NRTI sparing regimens: IAS-USA guidelines 2014

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Caveats</th>
</tr>
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<tbody>
<tr>
<td>Raltegravir plus darunavir/r</td>
<td>Raltegravir given BID, DRV/r QD; Inferior results with CD4 &lt; 200 and HIV PCR &gt; 100,000</td>
</tr>
<tr>
<td>Lopinavir/r plus lamivudine</td>
<td>Single study&lt;br&gt;LPV/r not standard first line PI/r in US</td>
</tr>
<tr>
<td>Lopinavir/r plus raltegravir</td>
<td>BID dosing for both PI/r and RAL&lt;br&gt;LPV/r not standard first line PI/r in US</td>
</tr>
</tbody>
</table>

Gunthard HF et al, JAMA 2014; 312:410 - 25
NRTI-sparing in treatment-naïve

- 3TC + LPV/r (GARDEL): encouraging results
- Studies with DRV/r + RAL (NEAT-1): equivocal results
- MVC + DRV/r (MODERN): poor results, leading to early trial discontinuation
GARDEL: Study Design

• Randomized, international, open label phase III study
• Included ARV naïve adults (HIV-1 RNA > 1000 copies/mL; no IAS defined NRTI or PI resistance)
• Randomized to LPV/r 400 mg/100 mg BID + 3TC (n=217) vs LPV/r 400 mg/100 mg BID + investigator-selected 2NRTI fixed dose combination (n=209)
• Primary endpoint: HIV RNA < 50 copies/mL (ITT) at week 48
• Approximately 80% from Latin America

GARDEL: Results

• For primary endpoint, 2D combo non-inferior to 3D combo at wk 48 (VL < 50 2D 88% vs 3D 83%)
• Similar results for pts with baseline VL > 100K
• 10 discontinuations in 3D vs 1 in 2D arm
• Drugs used reflect availability in developing world
• ?what would results be with DRV/r or DOL with either 3TC or FTC?

NEAT 001/ANRS 143: DRV/r + RAL vs. DRV/r + TDF/FTC in ARV Naïve Pts

• Randomized, open label phase 3 study
  – 805 ARV-naïve patients randomized in 15 European countries

• Primary (composite) endpoint:
  – Virologic: change of rx prior to week 32 because of inadequate response OR VL > 50 copies/mL after week 32
  – Clinical: Death, new AIDS-defining events, new non-AIDS defining events

RAL + DRV/RTV Noninferior to TDF/FTC + DRV/RTV at 96 Wks

• Similar numbers of pts with PDVF (RAL: n = 66; TDF/FTC: n = 52)
• No pts with resistance in TDF/FTC arm vs 5 with integrase mutations and 1 with K65R

Primary endpoint at W96 by baseline characteristics

Overall analysis: RAL + DRV/r non inferior to TDF/FTC + DRV/r

<table>
<thead>
<tr>
<th>Overall</th>
<th>n = 805</th>
<th>-1.1</th>
<th>8.6</th>
<th>17.4 %</th>
<th>13.7 %</th>
</tr>
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<tbody>
<tr>
<td>Baseline HIV-1 RNA</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>&lt; 100,000 c/ml</td>
<td>n = 530</td>
<td>-3.9</td>
<td>3.5</td>
<td>7 %</td>
<td>7 %</td>
</tr>
<tr>
<td>≥ 100,000 c/ml</td>
<td>n = 275</td>
<td>-0.05</td>
<td>19.3</td>
<td>36 %</td>
<td>27 %</td>
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<tr>
<td>Baseline CD4+</td>
<td></td>
<td></td>
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<tr>
<td>&lt; 200/mm³</td>
<td>n = 123</td>
<td>-3.4</td>
<td>6.3</td>
<td>39.0 %</td>
<td>21.3 %</td>
</tr>
<tr>
<td>≥ 200/mm³</td>
<td>n = 682</td>
<td>4.7</td>
<td>30.8</td>
<td>13.6 %</td>
<td>12.2 %</td>
</tr>
</tbody>
</table>

Difference in estimated proportion (95% CI) RAL - TDF/FTC; adjusted

* Test for homogeneity
Switching ART in suppressed patients: potential benefits

• Convenience
  – Stigma
  – Pill burden
  – Lack of food restrictions

• Tolerability
  – Lipid sparing, cardiovascular risk
  – Psychiatric comorbidities/suicidality
  – Renal and bone disease

• Drug-drug interactions

• Cost

DHHS Guidelines, May 1, 2014
Switching ART in suppressed patients: potential risks

- New toxicities
- Some newer agents may be less potent
- Continuing partially active or inactive agents may lead to “functional monotherapy”
- Food requirements
- Drug interactions

DHHS Guidelines, May 1, 2014
Case 2

- 37 yo male, intermittent meth use, depression, CD4 nadir 50, EGFR 80, no other comorbidities
- ARV history
  - 1998 – 2003: AZT, 3TC, NVP
  - 2003 – present: TDF, FTC, ATZ/r
- Current CD4 300, has VL blips from time to time in 200 – 300 copies/mL range, never high enough to genotype
- He insists on switching to STR, insists he will be 100% adherent
- You prescribe EVG/COBI/FTC/TDF
- After 6 mos, CD4 is 200, HIV PCR is 2500
# HIV Genotype*

*No PI mutations

<table>
<thead>
<tr>
<th>Drug</th>
<th>GenoSure PRIme*</th>
<th>Assessment*</th>
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<tbody>
<tr>
<td><strong>NRTI</strong></td>
<td>Drug Resistance Associated Mutations Detected</td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>M41L, K65K/R, M184V, T215F</td>
<td>ABC</td>
</tr>
<tr>
<td>Didanosine</td>
<td>M41L, K65K/R, M184V, T215F</td>
<td>ddl</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>M41L, K65K/R, M184V, T215F</td>
<td>FTC</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>M41L, K65K/R, M184V, T215F</td>
<td>3TC</td>
</tr>
<tr>
<td>Stavudine</td>
<td>M41L, K65K/R, T215F</td>
<td>d4T</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>M41L, K65K/R, T215F</td>
<td>TFV</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>M41L, T215F</td>
<td>ZDV</td>
</tr>
</tbody>
</table>

| **NNRTI**       | Drug Resistance Associated Mutations Detected          |             |
| Efavirenz       | K103R, V179D, Y181C                                   | EFV         |
| Etiravirine     | V179D, Y181C                                          | ETR         |
| Nevirapine      | K103R, V179D, Y181C                                   | NVP         |
| Rilpivirine     | K103R, V179D, Y181C                                   | RPV         |

| **INI**         | Drug Resistance Associated Mutations Detected          |             |
| Dolutegravir    | E92Q                                                     | DTG         |
| Elvitegravir    | E92Q                                                     | EVG         |
| Raltegravir     | E92Q                                                     | RAL         |

*ACTHIV 2015: A State-of-the-Science Conference for Frontline Health Professionals*
Encouraging adherence, what regimen do you suggest??

A. TDF/FTC, ATZ/r
B. TDF/FTC, DRV/r
C. Continue EVG/COBI/TDF/FTC
D. TDF/FTC, DRV/r, dolutegravir 50 mg qd
E. TDF/FTC, DRV/r, dolutegravir 50 mg BID
Encouraging adherence, what regimen do you suggest??

A. TDF/FTC, ATZ/r
B. TDF/FTC, DRV/r
C. Continue EVG/COBI/TDF/FTC
D. TDF/FTC, DRV/r, dolutegravir 50 mg qd
E. TDF/FTC, DRV/r, dolutegravir 50 mg BID

Outcome: you switch him back to choice A, and he continues to blip in 200 – 400 copies/mL range
Recent switch studies: what have we learned?

• From PI/r based ART to RAL
  – SWITCHMRK and Spiral Studies
• From PI/r based ART to TDF/FTC/RPV
  – Spirit Study
• From TDF/FTC/EVG/COBI to:
  – STRATEGY – NNRTI
  – STRATEGY – PI
SWITCHMRK vs. Spiral: Conflicting Results
switch studies to RAL from r/PI based ART in suppressed pts

SWITCHMRK (double blind)
• Suppressed pts on 2n + LPV/r randomized switch to 2n/RAL vs continue 2n/LPV/r
• After 24 weeks switch NOT noninferior
• Duration of previous suppression on LPV/r 2n: 6 months
• Most failures in patients on multiple prior regimens

SPIRAL (open label)
• Suppressed pts on 2n/PI/r randomized switch to 2n/RAL vs. continue 2n/PI/r
• After 48 weeks noninferior
• Duration of previous suppression on PI/r + 2n: 6 years

STRATEGY Trials: switch to EVG/COBI/TDF/FTC in Suppressed Pts

- STRATEGY NNRTI: randomize 2:1 switch to EVG/COBI/TDF/FTC qd vs continue TDF/FTC NNRTI in suppressed patients
- STRATEGY PI: randomize 2:1 switch to EVG/COBI/TDF/FTC vs. continue TDF/FTC/PI/r in suppressed pts
- Approximately 330 pts randomized in each study
- Primary endpoint: HIV RNA < 50 copies/mL at wk 48

STRATEGY-NNRTI: Change to EVG/COBI Noninferior to Stable NNRTIs at Wk 48

- Results for primary endpoint: 93% achieved HIV VL < 50 copies/mL in switch group vs 88% in no switch group
- Regimens: EFV, 78%; NVP, 17%; RPV, 4%; ETR, < 1%; 74% on EFV/TDF/FTC; 91% on first regimen
- Results similar across all baseline virologic and demographic subgroups
- 3 pts with VF in switch arm vs 1 in no switch arm
- 5 in switch arm vs 1 in the NNRTI arm discontinued due to AE
- Similar results in STRATEGY-PI study

Canadian National Cohort: Switching After Suppression Associated With Risk of VF

- Retrospective analysis of factors associated with VF among suppressed pts who switched (N = 2807)
  - Initiated first-line ART with ≥ 3 agents between 1/1/2005 and 6/30/2012
- In multivariate model
  - Switching ART associated with increased risk of VF ($P < .001$)
  - Females and pts with IDU history at increased risk of VF with switch ($P < .001$)
- Would be interesting to speculate who was advocating the switch: patient or provider?

Efavirenz as initial therapy and increased risk for suicidal ideation

- Review of 4 ACTG studies in ARV naïve patients
- Compared 3241 pts starting EFV vs 2091 pts starting non EFV-based ART
- Average duration f/u 96 mos
- First suicidal ideation OR attempted OR completed suicide in each group:
  - 8.08 events per 1000 PY in EFV group (47 events)
  - 3.66 events per 1000 PY in EFV-free group (5 events)

Rather than d/c TDF/FTC/EFV, what about reducing EFV dose to minimize toxicity?
ENCORE1: EFV 400 vs 600 mg QD + TDF/FTC in Treatment-Naive Pts

• Randomized, double-blind, noninferiority study performed in Europe, Asia, Central America
• Primary endpoint: HIV-1 RNA < 200 c/mL at Wk 96
• ART naive pts randomized to EFV 400 mg/d plus TDF/FTC (n = 321) vs EFV 600 mg/d plus TDF/FTC (n = 309)
• Primary endpoint: HIV RNA<200 copies/mL at week 48
• % suppressed at wk 48: 94% EFV 400 mg vs 92% EFV 600 mg

ENCORE1: EFV 400 vs 600 mg QD + TDF/FTC in Treatment-Naïve Patients

• Mean change in CD4+ cell count from BL greater with 400-mg vs 600-mg EFV ($P = .03$)

• Rate of EFV-related AEs lower with 400-mg vs 600-mg dose: 37.7% vs 47.9% ($P = .01$)

• Trend toward lower rate of discontinuation for EFV-related AEs with 400-mg vs 600-mg dose: 8.3% vs 15.5% ($P = .07$)

• Frequency of treatment emergent NNRTI resistance similar in both arms

Conclusions

• Most NRTI sparing regimens in treatment-naïve patients have suboptimal outcomes
• Selected patients with HIV can have treatment simplification with excellent outcomes
• Multiple prior ARV regimens and poor patient adherence may affect efficacy of switch regimens
Thank you for your attention!!