Simplifying Antiretroviral Therapy Regimens: It’s not so simple...

Jonathan Colasanti, MD, MSPH
Division of Infectious Diseases
Emory University School of Medicine
Disclosures

• No Financial Disclosures
• Parts of this talk are adapted from Clinical Care Options (HIV) webinar: Evolving Switch Strategies for Virologically Suppressed HIV-Infected Patients
Objectives

1. Understand the rationale for guideline based ART switch strategies in virologically suppressed HIV patients and become familiar with trial data guiding these decisions

2. Identify patients who are the best candidates for undertaking an ART switch

3. Develop strong working knowledge of pros/cons for each potential switch scenario
Summary of cases

1. **Case 1:** 45 y.o. Jamaican woman on TDF/FTC/ATV/r now with jaundice

1. **Case 2:** 50 y.o. AA gentleman on TDF/FTC/LPV/r with hypertriglyceridemia and GI intolerance

1. **Case 3:** 53 y.o. Peruvian woman with newly diagnosed TB is on TDF/FTC/LPV/r

1. **Case 4:** 50 y.o. Caucasian on AZT/TDF/FTC/DRV/r with HTN, DM, worsening CKD and virologic failure.
BACKGROUND ON SWITCH STRATEGIES
Regimen Switching In the Setting of Virologic Suppression (Last updated May 1, 2014; last reviewed May 1, 2014)

With use of currently available antiretroviral therapy (ART), most HIV-infected patients are able to achieve sustained HIV viral suppression. Furthermore, advances in treatment and better understanding about drug resistance make it possible to consider switching an effective regimen to an alternative regimen in some situations (see below). When contemplating such a switch, clinicians must consider several key principles to maintain viral suppression while addressing concerns with the current treatment.
Reasons to switch

• Simplify regimen
  – dosing frequency / pill burden
• Enhance tolerability and decrease toxicities
• Minimize or address drug interactions
• Pregnancy (anticipated or ongoing)
• Reduce costs
  – To patient
  – To healthcare system

Panel on Antiretroviral Guidelines for Adults and Adolescents. DHHS. H13-16.
Cardinal Principle: Maintain Viral Suppression

• Review full ART history:
  – Drugs
  – Adverse effects
  – Virologic response
  – Resistance profiles
    • Archived mutations
    • Infer mutations based on prior failed regimens

• Increase intensity of monitoring for 3 months
  – Adherence, tolerability, viral suppression, laboratory monitoring
Potential Drawbacks of Switching

“If it ain’t broke, don’t fix it”

• Risk of new toxicities
• Emergence of archived resistance
• STRs don’t allow for dosage adjustments
• Errors
  – MD, pharmacy, patient
  – Difficult follow-up
• Potential increase in cost
Case 1

45 y.o. woman with HIV/AIDS diagnosed 3 years prior (2012) started on TDF/FTC/ATV/r prior to initial genotype result

- Baseline: CD4 116/8%; VL 103,500; HLA-B*5701 negative
- Genotype: WT

Medical / Surgical History

- Cerebral Toxoplasmosis
- Adjustment disorder: no MDD, no suicidality
# Case 1 Labs

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV-1 RNA (copies/mL)</strong></td>
<td>103,500</td>
<td>&lt; 40</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td><strong>CD4 T cell count (cells/µL)</strong></td>
<td>116 / 8%</td>
<td>242/10%</td>
<td>311/10%</td>
<td>260/11%</td>
<td>207/12%</td>
<td>208/12%</td>
</tr>
<tr>
<td><strong>HIV Genotyping</strong></td>
<td>WT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ART Regimen</strong></td>
<td>TDF/FTC/ATV/r</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GFR > 70  
AST 16, ALT 17, AP 109, **T bili 7.2 (direct 0.6)**  
TC 162, TG 79, LDL 111, HDL 35  
HepBsAb (-) sAg (-) cAb (-): immunized

- Jaundice notable. Friends asking why eyes are yellow  
- Patient wants to switch regimens
What do you switch to?

A. TDF/FTC/EFV
B. TDF/FTC/EVG/Cobi
C. TDF/FTC/RPV
D. ABC/3TC/DTG
STRATEGY-PI

Switch from PI based regimen to Stribild

- RCT, open label switch study: patients virologically suppressed ≥ 6months on PI/r + TDF/FTC regimen
- Primary endpoint: HIV-1 RNA <50 copies/mL at wk 48

HIV-1 RNA < 50 c/mL, ≤ 2 previous regimens, no resistance to FTC or TDF and CrCl ≥ 70 mL/min (N = 433)

Switch to EVG/COBI/TDF/FTC QD (n = 293)

Remain on PI/r + TDF/FTC (n = 140)

ATV 37%, DRV 43%, Lop 16%, FPV 4%

STRATEGY-PI
PI/r ➔ EVG/COB/TDF/FTC

Details from the Study

- EFV 78%, NVP 17%, RPV 4%, ETV < 1%
- Plasma HIV-1 RNA > 50 copies/ml
  - Switch = 3 (1%)
  - NNRTI = 1 (1%)
- Discontinued drug but last VL <50 copies/mL
  - Switch = 11(4%)
  - NNRTI = 13 (9%)
- Discontinued study due to AE or death
  - Switch = 5 (2%)
  - NNRTI = 1 (1%)
- No drug resistance in patients with virologic failure
- Patients switch from EFV had higher treatment satisfaction scores at week 24 and fewer neuropsychiatric symptoms at week 48 compared to baseline

Would you switch our patient to ABC/3TC/DTG?

A. Yes
B. No
C. I don’t know
Why not switch all patients to ABC/3TC/DTG?

**ACTG 5202**
ABC/3TC had worse lipid profile than TDF/FTC, whether used with EFV or ATV/r
- Higher TC, LDL and TG

- Daar E et al. CROI 2010. Abstract 59LB
- Sax et al. Abacavir/lamivudine versus tenofovir/emtricitabine as part of combinations regimens for initial treatment of HIV: Final Results. JID 2011 204:1191-201
Case 2

50 y.o. gentleman with HIV/AIDS (dx in 2003), chronic hepatitis B, and HTN currently virologically suppressed on TDF/FTC/LPV/r. Presents with new hypertriglyceridemia and complains of vague ongoing abd bloating and diarrhea

- Baseline: CD4 85/6%, VL 320,000, HLA-B*5701 negative
- ART History:
  - TDF/FTC/LPV/r (9/2008 → present)

Medical / Surgical History
- Elevated Cr baseline 1.3 – 1.5 (GFR 58 – 75)
- Dyslipidemia
- MDD
## Case 2 Labs

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA (copies/mL)</td>
<td>320,000</td>
<td>&lt; 50</td>
<td>ND</td>
<td>251</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>CD4 T cell count (cells/µL)</td>
<td>85/6%</td>
<td>53/12%</td>
<td>244/18%</td>
<td>344/20%</td>
<td>353/22%</td>
<td>444/25%</td>
</tr>
<tr>
<td>HIV Genotyping</td>
<td>NONE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART Regimen</td>
<td>AZT/3TC/LPV/r</td>
<td></td>
<td></td>
<td>9/2008 TDF/FTC/LPV/r</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**GFR ~ 55-60**

AST 41, ALT 37, AP 59, T bili 0.6
TC 262, TG 1039, LDL 93, HDL 41

- Patient requesting simpler regimen / something that won’t upset his stomach
What do you switch to?

A. TDF/FTC/DRV/r
B. TDF/FTC/RAL
C. TDF/FTC/RPV
D. ABC/3TC/ATV/r
SPIRIT
PI/r to Rilpivirine

- RCT, open label switch trial
- Primary endpoint: maintenance of HIV-1 RNA < 50copies/mL at week 24

Pts with HIV-1 RNA < 50 copies/mL on stable RTV-boosted PI + 2 NRTIs for ≥ 6 mos, no previous NNRTI use (N = 476)

Switch to RPV/TDF/FTC
Continue RTV-Boosted PI* + 2 NRTIs

Continue RPV/TDF/FTC
Switch to RPV/TDF/FTC

*PIs: ATV/RTV, 37%; LPV/RTV, 33%; DRV/RTV, 20%; FPV/RTV, 8%; SQV/RTV, 2%

Palella, F. et al. AIDS 2014. 28:335-344
**SPIRIT: Analysis**

<table>
<thead>
<tr>
<th></th>
<th>Immediate Switch to RPV/TDF/FTC (D1 to W24) N = 317</th>
<th>PI/r + 2 NRTIs (D1 to W24) n = 159</th>
<th>Delayed Switch to RPV/TDF/FTC (W24 to W48) n = 159</th>
<th>Immediate RPV/TDF/FTC D1 to W48 n = 317</th>
</tr>
</thead>
<tbody>
<tr>
<td>VS, % HIV-1 RNA &lt;50 copies/mL</td>
<td>93.7%</td>
<td>89.9%</td>
<td>92.1%</td>
<td>89.3%</td>
</tr>
</tbody>
</table>

**A Few More Points**

- 24 had K103N while treatment naïve. 18 in immediate switch arm and none with VF
- No difference in the pretreatment HIV-1 RNA of ≥100,000 or <100,000 groups

Palella, F. et al. *AIDS* 2014. 28:335-344
SPIRIT

A big “FAT” bonus

- Improved lipid profiles with RPV/FTC/TDF switch at 24 and 48 weeks

Palella, F. et al. *AIDS* 2014. 28:335-344
Interim Summary

- Patient currently virally suppressed with no history of virologic failure
  - Wants to switch due to medication side effects or to make dosing easier (decrease pill burden or number of times/day)

- Evidence for
  - NNRTI → TDF/FTC/EVG/Cobi
  - PI/r → TDF/FTC/RPV
  - PI/r → TDF/FTC/EVG/Cobi
Case 3
53 y.o. woman with HIV/AIDS diagnosed 15 years prior, currently on TDF/FTC/LPV/r with undetectable VL and CD4 of 378/19%. Presents with new diagnosis of pulmonary Tuberculosis

Medical / Surgical History
  – HTN
  – DM poorly adherent to therapy (A1C 7.5)
Case 3

- **Baseline HIV data:** CD4 75/5%; VL 170,000; HLA-B*5701 negative

- **ART History:**
  - AZT/3TC/EFV x 5 years (~ 2002 – 2007)
    - Genotype: D67N, K70R, K103N
  - TDF/FTC/LPV/r 2008 - current

- **Current labs:** CBC, CMP within normal limits, TC 220, TG 320, LDL 118, HDL 45

- You decide to start patient on RIPE for tuberculosis therapy...
Case 3

What do you do with ART?

A. Continue TDF/FTC/LPV/r
B. Change to TDF/FTC/EFV
C. Change to TDF/FTC/EVG/Cobi
D. Change to TDF/FTC/RAL
SWITCHMRK Trials
LPV/r → RAL

- RCT, double-blinded, multicenter switch trial
  - OK if previous virologic failure as long as currently suppressed for time specified
- Primary endpoint: maintenance of HIV-1 RNA < 50 copies/mL at week 24

HIV-1 RNA < 50 c/mL on LPV/r-based ART for >3mos (+ at least 2 NRTIs)
(N = 702)

Switch to RAL 400mg BID + continue baseline NRTIs

Continue LPV/r BID + continue baseline NRTIs

Stratified by duration of LPV/r, age, race, sex, region, hepatitis B and C

SWITCHMRK: Analysis

- Study terminated at wk 24 because RAL did not meet noninferiority, BUT....

<table>
<thead>
<tr>
<th>Category</th>
<th>Study</th>
<th>Raltegravir</th>
<th>Lopinavir-r</th>
<th>Treatment difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>%*</td>
<td>n/N</td>
<td>%*</td>
</tr>
<tr>
<td>All Patients</td>
<td>Combined</td>
<td>293/347</td>
<td>319/352</td>
<td>-6.2% (-11.2 to -1.3)</td>
</tr>
<tr>
<td>Patients On LPV/r as first regimen</td>
<td>Combined</td>
<td>112/128</td>
<td>117/130</td>
<td>-2.5% (-10.6 to 5.4)</td>
</tr>
<tr>
<td>Previous Virologic failure</td>
<td>Combined</td>
<td>85/111</td>
<td>113/123</td>
<td>-15.3% (-25 to -6)</td>
</tr>
</tbody>
</table>


* The percentages were rounded
SPIRAL
PI/r $\rightarrow$ RAL

• RCT, open-labeled, multicenter switch trial
  – OK if previous virologic failure as long as currently suppressed for time specified
  – Median duration of virologic suppression prior to switch: 6.6 yrs

• Primary endpoint: maintenance of HIV-1 RNA < 50 copies/mL at week 48

HIV-1 RNA < 50 c/mL on LPV/r-based ART for > 6 mos (N = 273)

- Continue PI/r* based cART n = 134
  *LPR/r 44%; ATV/r 35%; other 21%

- Switch to RAL 400mg BID + continue other baseline ART n = 139

Stratified by use of lipid lowering therapy

**SPIRAL: Analysis**

- Raltegravir switch group non-inferior to boosted PI

<table>
<thead>
<tr>
<th>Maintained Viral Suppression at Week 48</th>
<th>Raltegravir</th>
<th>PI/r</th>
<th>Treatment difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>%</td>
<td>n/N</td>
</tr>
<tr>
<td>All patients</td>
<td>127/142</td>
<td>90</td>
<td>122/140</td>
</tr>
<tr>
<td>Patients with prior VF</td>
<td>50/55</td>
<td>91</td>
<td>40/48</td>
</tr>
<tr>
<td>Patients with prior VF or suboptimal therapy</td>
<td>70/79</td>
<td>89</td>
<td>54/65</td>
</tr>
</tbody>
</table>

- Improved lipids with Raltegravir

NRTI SPARING REGIMENS: ARE THEY AN OPTION?
Why consider NRTI sparing regimens?

• Avoid long term toxicities:
  – Cardiovascular
  – Kidney
  – Bone

• D:A:D: cardiovascular risk with abacavir

• EuroSIDA: progression to CKD

• D:A:D: declining GFR with tenofovir

• Increased BMD with TDF → RAL switch

57 yo Caucasian gentleman with HIV/AIDS (dx 2000), HTN, DM, CAD.

- **Baseline HIV data:** CD4 120; VL 65,000; genotype WT, HLA-B*5701 positive

**ART History:**

- **2004 – 2008:** TDF/FTC/EFV
  - Poorly adherent w/ VF
  - **Genotype M184V, K103N.**

- **2009 – present:** AZT/TDF/FTC/DRV/r
  - Adherent now and VS for 18 months
  - HBsAg negative, HBsAb positive
**GARDEL**

**Dual ART (single NRTI) versus Triple ART**

- RCT, open-labeled
- Primary endpoint: proportion of patients with HIV-1 RNA < 50 copies/mL at week 48

**ART-naïve patients, VL ≥ 1000 copies/mL; no NRTI or PI resistance; HBsAg negative (N = 428)**

- LPV/RTV 400/100mg BID + 3TC 150mg BID
  - N=217

- LPV/RTV 400/100mg BID + 3TC or FTC + Investigator selected NRTI as FDC*
  - N=209

*ZDV/3TC 54%; TDF/FTC 37%; ABC/3TC 9%

- Dual ART noninferior to triple ART at week 48
- CD4 count increases equivalent
- Grade 2/3 adverse events more frequent in triple ART arm (88 v 65)
- 22 patients not virally suppressed at week 48
  - 2 had m184v – both in dual ART arm

Other supporting nucleoside sparing data in naïve Populations

• PROGRESS: 96 wk randomized pilot
  – RAL/LPV/r Vs. TDF/FTC/LPV/r
  – 206 patients randomized
  – Wk 96 response: **RAL 66% vs LPV/r 69%**
  – Comparable safety

• ACTG 5262 (Phase 2b)
  – DRV/r once daily + RAL 400mg twice daily
  – 112 ART naïve patients
  – **84% virologically suppressed at wk 24**
  – Failure associated with baseline VL > 100,000 copies/mL

In patients with VF: LPV/r + NRTIs vs LPV/r + RAL

- RCT, open-labeled
- Primary endpoint: proportion of patients with HIV-1 RNA < 200 copies/mL at week 48

Patients with VF on first-line regimen of 2NRTI + NNRTI (N = 541)

Stratified by HIV-1 RNA around 100,000 copies/mL

LPV/RTV 400/100mg BID + 2 – 3 NRTIs
N=271

LPV/RTV 400/100mg BID + Raltegravir 400mg BID
N=270

SECOND-LINE Results

• RAL non-inferior to the NRTIs
• New mutations in those with VF
  – RAL: 17%
  – Control: 14%

Any difference with newer generation Protease Inhibitors?

- NEAT Trial:
  - Randomized treatment naïve patients to DRV/r + RAL or TDF/FTC/RAL
  - Overall non-inferior
  - But higher rates VF with low CD4

<table>
<thead>
<tr>
<th>CD4 T Cells</th>
<th>RAL + DRV/r</th>
<th>TDF/FTC/RAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 200 cells/µL</td>
<td><strong>43.2%</strong></td>
<td>20.9%</td>
</tr>
<tr>
<td>≥ 200 cells/µL</td>
<td>13.7%</td>
<td>12.3%</td>
</tr>
</tbody>
</table>

Case 4 overview

50 y.o. man with h/o VF (m184V, K103N)

• HTN, DM and worsening CKD (Cr 1.2 – 2.4)
• Hemoglobin 9
• Currently on AZT/TDF/FTC/DRV/r and virologically suppressed x 18 months
Switch to which regimen?

A. AZT/3TC/DRV/r
B. ABC/3TC/DTG
C. TDF/FTC/RAL
D. LPV/r + RAL
Dropping NRTIs Altogether? The story of boosted PI monotherapy

- Some achieved non-inferiority, others didn’t
- Large variability with regard to prior therapy
  - Virologic failure, amount of time virally suppressed
- Patients on PI/r monotherapy who failed virologically tended to not acquire resistance and re-suppressed with addition of NRTI

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Therapy</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>KalMo</td>
<td>96-week, open label, randomized trial; Patients on cART* ≥ 6 months and VL &lt; 80 copies/mL prior to randomization</td>
<td>60</td>
<td>LPV/r versus cART</td>
<td>Endpoint: VL &lt; 80 copies/mL LPV/r: 80.0% cART: 86.6%</td>
</tr>
<tr>
<td>Nunes EP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MONOI</td>
<td>96-week, randomized, open-label, non-inferiority trial; Patients on cART with VL &lt; 400 copies/mL ≥ 18 months and screening VL &lt; 50 copies/mL prior to randomization</td>
<td>225</td>
<td>DRV/r versus cART</td>
<td>Endpoint: VL &lt; 50 copies/mL DRV/r: 88% cART: 86%</td>
</tr>
<tr>
<td>Valantin MA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OK04</td>
<td>96-week, randomized, open-label, non-inferiority trial; Patients on cART with VL &lt; 50 copies/mL ≥ 6 months prior to randomization</td>
<td>205</td>
<td>LPV/r versus cART</td>
<td>Endpoint: VL &lt; 50 copies/mL LPV/r: 77% cART: 78%</td>
</tr>
<tr>
<td>Arribas JR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MONET</td>
<td>144-week, randomized, open-label, non-inferiority trial; Patients on cART for ≥ 6 months with screening VL &lt; 50 copies/mL prior to randomization</td>
<td>256</td>
<td>DRV/r versus cART</td>
<td>Endpoint: VL &lt; 50 copies/mL DRV/r: 72% cART: 78%</td>
</tr>
<tr>
<td>Arribas JR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MODAT</td>
<td>48-week, randomized, open-label, non-inferiority trial, interim analysis; Patients on cART for ≥ 48 weeks with viral suppression for ≥ 24 weeks prior to randomization</td>
<td>103</td>
<td>ATV/r versus cART</td>
<td>Endpoint: Efficacy, where treatment failure was considered virologic failure or discontinuation for any reason ATV/r: 73% cART: 85%</td>
</tr>
<tr>
<td>Castagna A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Colasanti J et al. AIDS. 2014 Apr 24;28(7):943-7
Conclusions

• Possibilities exist even for patients on older/complex/toxic regimens with prior VF
• After a switch, ensure follow up and maintenance of viral suppression
  – Allows for re-broadening of regimen
• Patients with well documented ART history, and longer duration of viral suppression are probably best suited for any reductive approach

Select patients carefully!
References


References


• Palella, F. et al. Simplification to rilpivirine/emtricitabine/tenofovir disoproxil fumarate from ritonavir-boosted protease inhibitor antiretroviral therapy in a randomized trial HIV-1 RNA-suppressed participants. *AIDS* 2014. 28:335-344


References


• Cahn P et al. Dual therapy with lopinavir and ritonavir plus lamivudine versus triple therapy with lopinavir and ritonavir plus two nucleoside reverse transcriptase inhibitors in antiretroviral-therapy-naïve adults with HIV-1 infection: 48 week results of the randomized, open-label, non-inferiority GARDEL trial. *Lancet Infect Dis*. 2014; 14: 572-80
References


