Switching ART Regimens

Thughtfully and Safely

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Objective

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

– Identify the rationale and pitfalls of switching HIV therapy in those with suppressed viremia
Reasons to consider switch:

- Reduce pill burden and dosing frequency to improve adherence
- Enhance tolerability and decrease short- or long-term toxicity
- Change food or fluid requirements
- Minimize or address drug interaction concerns
- Allow for the optimal use of ART during pregnancy or should pregnancy occur
- Reduce costs
When to Switch Antiretroviral Therapies?

• When we SHOULD:
  – Virologic Failure
  – Toxicity, Poor Tolerability
  – Co-Morbidities
  – Drug-Drug Interactions
  – Pregnancy

• When we MAY:
  – Simplification
  – Cost
When to Switch Antiretroviral Therapies?

• When we SHOULD:
  – Virologic Failure
  – Toxicity, Poor Tolerability
  – Co-Morbidities
  – Drug-Drug Interactions
  – Pregnancy

• When we MAY:
  – Simplification
  – Cost
Potential drawbacks

– New toxicities
– May not work
– Previous resistance can come back to haunt you
– Potential for pharmacy/patient error
– Can be more expensive
– “If it ain’t broke, don’t fix it”
Principles of ART Switching

• **Cardinal principle:** Maintain viral suppression without compromising future treatment options.

• Need to know ARV history:
  - Virologic responses
  - Resistance testing (if available)
  - Past Adverse Events

• Consult with HIV specialist regarding regimen switch if patient has history of resistance to ≥1 drug classes.

• Monitor tolerability, viral suppression, and laboratory changes during the first 3 months after regimen switch.

Maintaining viremia with standard issue ART

Keeping viremia suppressed is easier than getting viremia suppressed

![Graph showing plasma HIV RNA over time. The graph shows a sharp increase followed by a gradual decrease, with two pairs of boots representing the initial viremia and the suppressed state.]
Maintaining viremia with standard issue ART

BUT, still need adequately potent regimen to keep viremia suppressed
Switching in Success - I

- 65 yo man on diagnosed with HIV in 2005
- Started on Atazanavir/Ritonavir\(^{PI}\) + Abacavir/3TC\(^{NRTI}\) when entered an ACTG clinical trial. No baseline resistance.
- Baseline HIV RNA = 88,000 copies/mL → Undetectable
- CD4 cell count was 213 → 735
- Feels well
- Comorbidities:
  - Obesity: BMI = 45 (considering bariatric surgery)
  - Hypertension: enalapril + amlodipine
  - Dyslipidemia: Total = 182, LDL = 132, HDL = 35 on atorvastatin 10 mg
    - HbA1C = 6.5%
- eGFR > 60
- Has private insurance
Switching in Success - I

65 yo man on Atazanavir/Ritonavir\textsuperscript{Pl} + Abacavir/3TC\textsuperscript{NRTI} $\rightarrow$ Undetectable, CD4 735, Obese, HTN, pre-DM, dyslipidemia

Should the patients be advised to:

1. Stay on current ART
2. Switch to Atazanavir/Cobicistat + Abacavir/3TC
3. Switch to Dolutegravir/Abacavir/3TC
4. Switch to Elvitegravir/Cobicistat/TAF/FTC
5. Switch to Rilpivirine/TAF/FTC
6. Switch to Dolutegravir + TAF/FTC
7. Switch to something else
TAF – A new prodrug of Tenofovir (TFV)

OAT, organic anion transporter; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.

TFV (tenofovir) is metabolized in the GI tract as TAF (tenofovir alafenamide) and TDF (tenofovir disoproxil fumarate).

300 mg PRO DRUG TAF (tenofovir alafenamide) 25 mg

TAF 25 mg results in 80-90% lower TFV plasma levels.

Switch from TDF-Based Regimen to E/C/F/TAF in Virologically-Suppressed Adults

Randomized, active-controlled, open-label study:

- All patients had HIV-1 RNA < 50 copies/mL for ≥ 96 wks on stable TDF-based regimen
- Required to have eGFR > 50 mL/min

Switch to E/C/F/TAF: Virologic outcome

Virologic Outcome

Switch to E/C/F/TAF associated with:

- Significant improvements kidney function markers
- Significant improvements in spine and hip BMD
- Significant reductions osteopenia/osteoporosis
- Significant increases in fasting lipids

BMD = bone mineral density.
Virologic Outcome by Prior Treatment Regimens at Week 96

E/C/F/TAF was statistically superior in efficacy to a TDF-based regimen at Week 96

DeJesus E, et al. ASM 2016. Boston MA. #087LB
Changes in Spine and Hip BMD through Week 96

Switching to E/C/F/TAF from a regimen containing FTC/TDF + 3rd agent resulted in progressive recovery in spine and hip BMD over 96 weeks.

DeJesus E, et al. ASM 2016. Boston MA. #087LB
STRIIVING Study: Switch to ABC/Dolutegravir/3TC in Virologically Suppressed HIV Patients

Phase 3 (Open-Label)

Stable suppression with PI/r, NNRTI, or INI + 2 NRTIs
HIV RNA <50 copies/mL
HLA-B*5701 negative

Randomization 1:1

<table>
<thead>
<tr>
<th>Week 0</th>
<th>24</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABC/Dolutegravir/3TC (n=275)</td>
<td>Continue Current ART (n=278)</td>
<td>ABC/Dolutegravir/3TC (n=244)</td>
</tr>
</tbody>
</table>

Primary Endpoint
HIV RNA <50 copies/mL

Non-inferiority margin: 10%.

Analyses:
Early switch: week 0 to 24 and 0 to 48
Late switch: week 24 to 48

STRIIVING Study: Switch to ABC/Dolutegravir/3TC in Virologically Suppressed HIV Patients

- Early switch to ABC/dolutegravir/3TC met the non-inferiority criteria versus current ART regimen
  - Maintained through week 48
  - No protocol-defined virologic failures
- Safety following early switch
  - Numerically more discontinuations due to adverse events from week 0 to 24 (4% versus 0%)
    - Mostly due to low-grade adverse events
    - No further discontinuations after wk24
  - Small, non-progressive increase in serum creatinine
  - No differences in lipid profiles compared with current ART

Side Note: Effects on Creatinine Tubular Transporter: COBI and Dolutegravir Inhibit Creatinine Secretion

Cation Transport Pathway

Blood (Basolateral) | Urine (Apical)

Creatinine

OCT2 = organic cation transporter 2.
MATE1 = multidrug and toxin extrusion transporter 1.

SPIRIT:
From PI/r + 2 NRTIs to RPV/TDF/FTC

Multicenter, randomized, open-label switch study
– Primary endpoint: maintenance of VL < 50 c/mL at Wk 24 (FDA snapshot analysis)

Pts with VL < 50 c/mL on stable ritonavir-boosted PI + 2 NRTIs for ≥ 6 mos, no previous NNRTI use (N = 476)

Randomized 2:1

Wk 24
Primary endpoint

Wk 48

Rilpivirine/Tenofovir/Emtricitabine (n = 317)

Ritonavir-Boosted PI* + 2 NRTIs (n = 159)

Rilpivirine/ Tenofovir/Emtricitabine (n = 159)

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

SPIRIT: Virologic Suppression at Weeks 24 and 48

- Switch to RPV/TDF/FTC noninferior to maintaining boosted-PI regimen
- 23/24 subjects with pre-existing K103N maintained virologic suppression at Week 24
- Significant reductions in TC, LDL, TG, HDL, TC:HDL ratio among RPV/TDF/FTC switch pts
SPIRIT: Pre-Treatment Viral Load and Outcomes

Switching in Success - I

65 yo man on Atazanavir/Ritonavir\(\text{PI}\) + Abacavir/3TC\(\text{NRTI}\) → Undetectable, CD4 735, Obsese, HTN, pre-DM, dyslipidemia

Options

• Stay on current ART
• Switch to:
  – Atazanavir/Cobicistat + Abacavir/3TC
  – Dolutegravir/Abacavir/3TC
  – Elvitegravir/Cobicistat/TAF/FTC
  – Rilpivirine/TAF/FTC
  – Dolutegravir + TAF/FTC
  – Something else
Switching in Success - I

65 yo man on Atazanavir/Ritonavir\textsuperscript{PI} + Abacavir/3TC\textsuperscript{NRTI} \rightarrow
Undetectable, CD4 735, Obese, HTN, pre-DM, dyslipidemia

Options

• Stay on current ART
• Switch to:
  – Atazanavir/Cobicistat + Abacavir/3TC \hspace{1em} [Not ideal]
  – Dolutegravir/Abacavir/3TC \hspace{1em} [OK, if HLA-B*5701 neg and have to not worry about ABC & CVD]
  – Elvitegravir/Cobicistat/TAF/FTC \hspace{1em} [OK, unlikely to change lipids]
  – Rilpivirine/TAF/FTC \hspace{1em} [OK, if adherent, takes w food & no acid blockers]
  – Dolutegravir + TAF/FTC \hspace{1em} [OK]
  – Something else
Switching in Success - II

- 34 yo woman on diagnosed with HIV in 2002
- Started Efavirenz $^\text{NNRTI}$ /Tenofovir DF/FTC $^\text{NRTI}$. No baseline resistance.
- Baseline HIV RNA = 33,000 copies/mL $\rightarrow$ Undetectable
- CD4 cell count was 350 $\rightarrow$ 1,100
- Feels well
- Comorbidities:
  - Osteopenia: DEXA t-score = 1.8 hip; 2.3 spine
- eGFR > 60
- Lipids with HDL = 80
- Likes taking a single pill
Switching in Success - II

34 yo woman on Efavirenz $^{NNRTI}$/Tenofovir DF/FTC $^{NRTI} \rightarrow$ Undetectable, CD4 1,100, Osteopenia

Should the patient be advised to:

1. Stay on current ART
2. Switch to Dolutegravir/Abacavir/3TC
3. Switch to Elvitegravir/Cobicistat/TAF/FTC
4. Switch to Rilpivirine/TAF/FTC
5. Switch to Dolutegravir + TAF/FTC
6. Switch to something else
START Study: Efavirenz Use and the Risk of Suicidal Behavior

- In a prior study, efavirenz was associated with suicidal behavior
- ART regimens in the START study were selected by the investigators
  - Efavirenz-based ART was commonly used
- Analyses conducted for the incidence of suicidal behavior
  - All START patients: immediate versus deferred ART groups
  - Patients with or without efavirenz use pre-specified
    - Efavirenz used less in those with a psychiatric diagnosis versus without (40% versus 77%)
  - Among those with and without pre-specified efavirenz, censored at follow-up at time of ART start in the deferred group

### Number With Suicidal Behavior

<table>
<thead>
<tr>
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<th>Immediate ART</th>
<th>Deferred ART</th>
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<tr>
<td>Overall</td>
<td>27</td>
<td>24</td>
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<tr>
<td>Suicidal ideation</td>
<td>10</td>
<td>6</td>
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<tr>
<td>Suicidal attempt</td>
<td>17</td>
<td>13</td>
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<tr>
<td>Completed suicide</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Self-injurious ideation</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Intentional self-injury</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Immediate ART arm excluded patients who never started ART or had event prior to ART initiation. Deferred ART arm follow-up censored at ART initiation. Excess risk associated with EFV was greater for those with a psychiatric diagnosis at baseline.

Virologic Outcome by Prior Treatment Regimens at Week 96

E/C/F/TAF was statistically superior in efficacy to a TDF-based regimen at Week 96

DeJesus E, et al. ASM 2016. Boston MA. #087LB
Changes in Spine and Hip BMD through Week 96

Switching to E/C/F/TAF from a regimen containing FTC/TDF + 3rd agent resulted in progressive recovery in spine and hip BMD over 96 weeks.

BUT: Was there less of a difference for those switching from EFV??

DeJesus E, et al. ASM 2016. Boston MA. #087LB
STRATEGY-NNRTI (NNRTI→E/C/F/TDF): Efavirenz Subgroup Patient-Reported Outcomes

HIV Symptom Index

- Vivid Dreams
- Insomnia
- Anxiety
- Dizziness

<table>
<thead>
<tr>
<th></th>
<th>BL W48</th>
<th></th>
<th>BL W48</th>
<th></th>
<th>BL W48</th>
<th></th>
<th>BL W48</th>
<th></th>
<th>BL W48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vivid Dreams</td>
<td>61%</td>
<td>35%</td>
<td>64%</td>
<td>64%</td>
<td>53%</td>
<td>*</td>
<td>48%</td>
<td>47%</td>
<td>46%</td>
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<tr>
<td>Insomnia</td>
<td>75</td>
<td>40%</td>
<td>84</td>
<td>209</td>
<td>103</td>
<td>222</td>
<td>71</td>
<td>208</td>
<td>40</td>
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<tr>
<td>Anxiety</td>
<td>224</td>
<td>101</td>
<td>224</td>
<td>56</td>
<td>56</td>
<td>87</td>
<td>48</td>
<td>41</td>
<td>40</td>
</tr>
<tr>
<td>Dizziness</td>
<td>136</td>
<td>**</td>
<td>119</td>
<td>*</td>
<td>103</td>
<td>*</td>
<td>40</td>
<td>34</td>
<td>40</td>
</tr>
<tr>
<td>Baseline E/C/F/TDF</td>
<td>224</td>
<td>101</td>
<td>224</td>
<td>56</td>
<td>56</td>
<td>87</td>
<td>48</td>
<td>41</td>
<td>40</td>
</tr>
<tr>
<td>Baseline NNRTI + FTC/TDF</td>
<td>212</td>
<td>87</td>
<td>209</td>
<td>41</td>
<td>208</td>
<td>40</td>
<td>34</td>
<td>87</td>
<td>40</td>
</tr>
<tr>
<td>Week 48 E/C/F/TDF</td>
<td>75</td>
<td>40%</td>
<td>84</td>
<td>209</td>
<td>103</td>
<td>222</td>
<td>71</td>
<td>208</td>
<td>40</td>
</tr>
<tr>
<td>Week 48 NNRTI + FTC/TDF</td>
<td>64</td>
<td>64%</td>
<td>53%</td>
<td>*</td>
<td>48%</td>
<td>47%</td>
<td>46%</td>
<td>*</td>
<td>40%</td>
</tr>
</tbody>
</table>

- Subjects who switched to E/C/F/TDF from EFV + FTC/TDF had:
  - Lower rates of neuropsychiatric symptoms at Week 48 compared with baseline.
  - Higher treatment satisfaction scores at Week 24 (mean: 21 vs 14, \( P < .001 \))

* \( P < .01 \) & ** \( P < .001 \) (comparison with baseline within treatment group). Decreases noted at Wk 4 & sustained through Wk 48.

\( P < .001 \), vivid dreams & \( P < .01 \), dizziness (comparison of changes from baseline at week 48 between treatment group).

\(^{^\wedge}\) HIV Treatment Satisfaction questionnaire, score range: -30 to 30

Switching in Success - II

34 yo woman on Efavirenz NNRTI / Tenofovir DF/FTC NRTI → Undetectable, CD4 1,100, Osteopenia

Options

• Stay on current ART
  [Could, but most would switch]

• Switch to:
  – Dolutegravir/Abacavir/3TC
    [OK, if HLA-B*5701 neg]
  – Elvitegravir/Cobicistat/TAF/FTC
    [OK]
  – Rilpivirine/TAF/FTC
    [OK, if no acid blockers, takes w food]
  – Dolutegravir + TAF/FTC
    [OK, but 2 pill regimen]
  – Something else
Switching in Success - III

• 41 yo woman on diagnosed with HIV in 2013
• Started Elvitegravir \textsuperscript{INSTI} /Cobicistat/ Tenofovir DF/FTC \textsuperscript{NRTI}. No baseline resistance.
• Baseline HIV RNA = 11,000 copies/mL $\rightarrow$ Undetectable
• CD4 cell count was 540 $\rightarrow$ 900
• Feels well
• Comorbidities:
  – Lower back pain: just received two intra-articular injections with corticosteroid, which helped tremendously
• eGFR > 60
• At visit complains of bruising, weight gain and polyuria
• Fasting blood glucose = 300, UA with 2+ glucose
41 yo woman on Elvitegravir \textsuperscript{INSTI}/Cobicistat/ Tenofovir DF/FTC \textsuperscript{NRTI} \rightarrow Undetectable, CD4 900, s/p corticosteroid injections

After checking cortisol level, the patient should be advised to:
1. Stay on current ART and wait it out
2. Switch to Dolutegravir/Abacavir/3TC
3. Switch to Elvitegravir/Cobicistat/TAF/FTC
4. Switch to Rilpivirine/TAF/FTC
5. Switch to Dolutegravir + TAF/FTC
6. Switch to something else
Iatrogenic Cushing syndrome after intra-articular triamcinolone in a patient receiving ritonavir-boosted darunavir

Jill J Hall¹, Christine A Hughes¹, Michelle M Foisy¹, Stan Houston² and Stephen Shafran²

Abstract

Drug interactions involving human immunodeficiency virus protease inhibitors and cytochrome P450 3A4 isoenzyme. We describe the case of a patient receiving ritonavir-boosted darunavir who developed cushingoid features following a single injection of intra-articular triamcinolone, review the probable mechanism for this interaction and discuss the potential implications.

There are, however, important differences in the action of ritonavir and coformulated ritonavir and coadministered with cytochrome P450 3A4 substrates is assumed to be similar to that of ritonavir. It is clinically important to provide clinical evidence which confirms or refutes these assumptions.

The interaction between the inhaled and internal corticosteroids and ritonavir is well recognized. Most corticosteroid medications are substrates of CYP3A4 and coformulated with ritonavir can result in extremely high systemic levels of exogenous corticosteroids. Adrenal suppression and Cushing’s syndrome have been described in case reports [4]. Data for evidence of an interaction between coformulated ritonavir and corticosteroids are sparse, and the manufacturer advises caution in their use [3].

In June 2014, a 39-year-old man attended a routine HIV clinic appointment and complained of reduced libido and erectile dysfunction. He was diagnosed with HIV in 2009 after being treated for latent syphilis. He had a past history of hiatus hernia, gastro-oesophageal reflux, polycystic ovary syndrome secondary to cigarette smoking, migraine, depression, and intermittent cocaine use. He also had mild chronic obstructive pulmonary disease (COPD) and nasal congestion for which he was under the care of the ENT department.

He was started on antiretrovirals in September 2011 and had a fully suppressed HIV viral load since October 2012. His antiretrovirals were changed from co-formulated ritonavir, tenofovir and emtricitabine (Efavirenz) to co-formulated elvitegravir, cobicistat, emtricitabine and tenofovir (Strida), in March 2014, because of concerns about reduced absorption of ritonavir with the use of prion pump inhibitors. His most recent CD4⁺ cell count in February 2014 was 796 cells/µl.
Switching in Success - III

41 yo woman on Elvitegravir\textsuperscript{INSTI}/Cobicistat/ Tenofovir DF/FTC \textsuperscript{NRTI} → Undetectable, CD4 900, s/p corticosteroid injections

After checking cortisol level, options:

• Stay on current ART and wait it out  [Not OK]
• Switch to:
  – Dolutegravir/Abacavir/3TC  [OK, if HLA-B*5701 neg]
  – Elvitegravir/Cobicistat/TAF/FTC  [Not OK]
  – Rilpivirine/TAF/FTC  [OK, if no acid blockers, takes w food]
  – Dolutegravir + TAF/FTC  [OK]
  – Something else
2 drug maintenance RX: SWORD 1 & 2: Switch From Suppressive ART to DTG + RPV

• Randomized, open-label, multicenter phase III trials

Adult pts on stable ART* ≥ 6 mos with HIV-1 RNA < 50 copies/mL at BL; no previous virologic failure or current HBV infection (N = 1024)

Baseline ART (n = 511)

DTG 50 mg QD + RPV 25 mg QD (n = 513)

Wk 52
Primary Endpoint

Wk 48

Pts continued or switched to DTG + RPV through Wk 148

*Comprising an INSTI, NNRTI, or PI plus 2 NRTIs.

• 70% to 73% of pts receiving TDF at baseline

Llibre JM, et al. CROI 2017. Abstract 44LB.
SWORD 1 & 2: Key Efficacy Results

- 1 pt receiving DTG + RPV with confirmed criteria for virologic withdrawal at Wk 36 had K101K/E
  - Documented nonadherence at virologic failure
  - Resuppressed with continued DTG + RPV
  - No INSTI resistance

Llibre JM, et al. CROI 2017. Abstract 44LB.
Switching in Failure

- 35 yo man on diagnosed with HIV in 2006
- Started on Efavirenz\textsuperscript{NNRTI} / Tenofovir DF/FTC \textsuperscript{NRTI}. Took for 3 months then was lost to follow-up (no genotype available).
- Re-presented for care in 2008 and started on Lopinavir/Ritonavir \textsuperscript{PI} + Tenofovir DF/FTC \textsuperscript{NRTI} \rightarrow Undetectable
- In 2014, enters prison off ART for “few months” with HIV RNA = 43,000 and CD4 = 279. Genotype without resistance.
  - Started on Elvitegravir\textsuperscript{INSTI}/Cobicistat/ Tenofovir DF/FTC \textsuperscript{NRTI}
- Released in 2015 and now re-incarcerated and on this regimen has HIV RNA = 28,000; CD4 = 51
- Genotype: T69N [NRTI], M184V [3-FTC], INI N155H [RAL, EVG], L63I [Minor PI]
- eGFR > 60
- No opportunistic infections
- No comorbid conditions or chronic medications
- Will be in prison for several years
Switching in Failure

35 yo man on Elvitegravir\textsuperscript{INSTI}/Cobicistat/ Tenofovir DF/FTC\textsuperscript{NRTI} → Failing with resistance mutations to NRTI and INSTI, CD4 51.

In addition to starting opportunistic infection prophylaxis and adherence interventions, what ART would you recommend:

1. Darunavir/Cobicistat + TAF/FTC
2. Darunavir/Cobicistat + TAF/FTC + Dolutegravir
3. Darunavir/Cobicistat + TAF/FTC/Rilpivirine
4. Darunavir/Cobicistat + Dolutegravir
5. Dolutegravir + TAF/FTC
6. Something else
“All happy families are alike; each unhappy family is unhappy in its own way.”

- Leo Tolstoy, *Anna Karenina*
Switching after Failure

“All suppressed patients are alike; each unsuppressed patient is unhappy in its own way.”

- Me, Now
DHHS Guidelines for Virologic Failure

- Assess adherence, drug–drug or drug–food interactions, tolerability, HIV-1 RNA and CD4+ count trends, treatment history, and prior and current resistance data
- Perform resistance test while the pt is on failing ART or within 4 wks of discontinuation; testing after this point may still provide useful information
- Goal of Rx for ART-experienced pts with drug resistance and virologic failure is to suppress HIV-1 RNA
- New regimen should include ≥ 2, and preferably 3, fully active agents, ie, agents with uncompromised activity based on treatment and resistance, and/or novel action
DHHS Guidelines: Management of ARV Failure

First-line therapy

**Failing regimen (+ NRTI)**
- **Boosted PI**
  - Enforce adherence
  - Modify for convenience or toxicity
- **NNRTI**
  - Boosted PI + NRTIs
  - Boosted PI + INSTI
- **INSTI**
  - Boosted PI + NRTIs
  - Boosted PI + active INSTI †

Second line and beyond

- **PI Susceptible**
  - Yes
  - Boosted PI + NRTIs
  - Boosted PI + active INSTI

- **No** *
  - 2 and preferably 3 fully active drugs
### Major Recent Switch Studies: Failing Pts

<table>
<thead>
<tr>
<th>Trial</th>
<th>Experimental Arm</th>
<th>Standard Control</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td><strong>SAILING</strong></td>
<td>DTG + best RX</td>
<td>RAL + BR</td>
<td>✔️</td>
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<tr>
<td><strong>SECOND LINE</strong></td>
<td>LPV/RTV + RAL</td>
<td>LPV/RTV + 2 NRTI</td>
<td>✔️</td>
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<tr>
<td><strong>EARNEST</strong></td>
<td>LPV/RTV + RAL&lt;br&gt;LPV/RTV + RAL -&gt; LPV/RTV</td>
<td>LPV/RTV + 2 NRTI</td>
<td>✔️</td>
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<tr>
<td><strong>OPTIONS</strong></td>
<td>NRTI(s) + Background RX</td>
<td>No NRTI(s) + BR</td>
<td>✔️</td>
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</table>
GARDEL (Naive):
Dual ART of LPV/RTV + 3TC vs Triple ART of LPV/RTV + 2 NRTIs

- Randomized, open-label phase III noninferiority trial

**Stratified by HIV-1 RNA**
(≤ vs > 100,000 copies/mL)

**Wk 24 interim analysis**

**Wk 48 primary analysis**

**Lopinavir/Ritonavir 400/100 mg BID + Lamivudine 150 mg BID**
(n = 217)

**Lopinavir/Ritonavir 400/100 mg BID + Lamivudine or Emtricitabine + Investigator-selected NRTIs in FDC**
(n = 209)

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

- Primary endpoint: HIV-1 RNA < 50 copies/mL (ITT-e, FDA snapshot analysis)

GARDEL: Dual ART Noninferior to Triple ART at Wk 48

- CD4+ cell count increase
  - +227 with dual ART vs +217 with triple ART
- Grade 2-3 adverse events more frequent in triple-ART arm (88 vs 65 events)
- Hyperlipidemia more common in dual-ART arm (23 vs 16 pts)
- Lab abnormalities similar
- VF in 22 pts, of whom 2 had resistance (M184V)
  - Both on dual ART

*HIV-1 RNA < 50 c/mL as defined by FDA Snapshot algorithm.

SECOND-LINE:
LPV/RTV + NRTIs vs LPV/RTV + RAL

- Primary Endpoint:
  - Proportion of pts with HIV-1 RNA < 200 copies/mL at Wk 48 in the modified intention-to-treat population, with a noninferiority margin of 12%.

SECOND-LINE: Noninferiority of LPV/RTV + RAL vs LPV/RTV + NRTIs

At Wk 48, 219 (81%) pts in the LPV/RTV + 2-3 NRTIs group vs 223 (83%) in the LPV/RTV + RAL group met the primary endpoint, fulfilling the criterion for noninferiority.

**EARNEST:**
**LPV/RTV+NRTIs vs LPV/RTV+RAL**

- Randomized, controlled, open-label, phase III trial

HIV-infected adults and adolescents received first-line NNRTI-based ART > 12 mos, > 90% adherence in previous mo, treatment failure by WHO (2010) criteria* (N = 1277)

- Baseline demographics (medians): HIV-1 RNA 69,782 copies/mL; CD4+ 71 cells/mm³; time on ART 4 yrs

**EARNEST: Clinical Outcomes at Wk 96**

- LPV/RTV + NRTIs had excellent clinical outcome (90% WHO4 event-free survival) and VL suppression (86% < 400 c/mL)
- LPV/RTV + RAL was not superior to LPV/RTV + NRTIs
- LPV/RTV monotherapy was inferior to LPV/RTV + NRTIs with lower VL suppression and resistance

"Good disease control" at Wk 96 defined as pt alive, no new WHO 4 events from Wks 0-96, and CD4+ cell count > 250 cells/mm³, and HIV-1 RNA < 10,000 copies/mL or > 10,000 copies/mL without PI resistance mutations

SAILING: DTG versus RAL in RX-Experienced

- HIV ART-experienced, INI-naive
  - HIV-1 RNA >400 c/mL
- Randomization
  - 1:1 Randomization stratified by HIV-1 RNA (≤ or >50,000), DRV/r use and # of fully active drugs

Randomization

- Week 24 planned interim
- Week 48 primary primary analysis

- DTG 50 mg QD +
  - RAL PBO + BR
- RAL 400 mg BID +
  - DTG PBO + BR

\[\text{a At Screening and a second consecutive test } >400 \text{ c/mL within 4 months prior to Screening (if Screening HIV-1 RNA } >1000 \text{ c/mL, no additional HIV-1 RNA assessment was needed).}\]

PBO, placebo;

BR, background regimen comprising at least 1 and no more than 2 active agents.

Cahn P, et al. IAS 2013
SAILING: HIV-1 RNA <50 c/mL at Week 48

Virologic success

Virologic non-response

No W48 data

Percentage of subjects (%)

• Lower incidence of INSTI resistance at VF with DTG
  – R263K at VF in 2 DTG pts; first report of treatment-emergent resistance on DTG
    • < 2-fold change in IC50 for both DTG and RAL
  – Y143, Q148, and/or N155 at VF in 9 RAL pts; consistent with previous studies
    • High-level resistance to RAL
• Both regimens well tolerated with similar AE profiles

95% CI for difference

Favors RAL

0.7 7.4 14.2

Favors DTG

-20% -12% 0 20%

Study 119: Switch to EVG/COBI/TAF/FTC + DRV in Treatment-Experienced Pts

- Multicenter, open-label randomized trial
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Week 24

- Treatment-experienced pts, HIV-1 RNA < 50 c/mL for ≥ 4 mos on DRV-containing ART, with history of drug resistance* and eGFR > 50 mL/min (N = 135)
  - 37% pts receiving ≥ 6 pills/day at baseline

*Resistance to ≥ 2 ARV classes, including ≤ 3 thymidine analogue mutations and K65R, but not integrase inhibitors, unless currently receiving raltegravir, and no DRV resistance.

Study 119: Virologic Suppression After Switch to EVG/COBI/TAF/FTC + DRV

- Similar rates of maintained virologic suppression at Wk 24, but significantly higher rates with switch vs baseline ART at Wk 48

ACTG OPTIONS: Are NRTIs necessary in treatment-experienced patients?

- 360 pts failing ART w/ NRTI, NNRTI, and PI resistance or experience
- Regimen chosen based on review of ART history, resistance, and tropism
  - PSS >2 required
- Randomized to omit or include NRTIs

<table>
<thead>
<tr>
<th></th>
<th>Omit NRTIs</th>
<th>Include NRTIs</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N=179</td>
<td>N=181</td>
</tr>
<tr>
<td>Regimen failure through wk 48</td>
<td>53 (30%)</td>
<td>48 (26%)</td>
</tr>
<tr>
<td>VL &lt;50 at wk 48</td>
<td>64%</td>
<td>68%</td>
</tr>
<tr>
<td>Severe signs/Sx or lab abnormality</td>
<td>67 (38%)</td>
<td>65 (35%)</td>
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- NRTIs not necessary if >2 active drugs included in regimen

Switching in Failure

35 yo man on Elvitegravir_{INSTI}/Cobicistat/ Tenofovir DF/FTC_{NRTI} →
Failing with resistance mutations to NRTI and INSTI, CD4 51.

In addition to starting opportunistic infection prophylaxis and adherence interventions, ART options:

- Darunavir/Cobicistat + TAF/FTC  [Probably OK]
- Darunavir/Cobicistat + TAF/FTC + Dolutegravir  [OK]
- Darunavir/Cobicistat + TAF/FTC/Rilpivirine  [OK, if eats and no acid blocker]
- Darunavir/Cobicistat + Dolutegravir  [Probably not OK]
- Dolutegravir + TAF/FTC  [Probably not OK]
- Something else
Summary

• There are reasons to consider ART switch in patients with viral suppression, and attractive switch options.

• Maintaining suppression may require fewer or less potent agents than that needed to achieve an undetectable viral load; however:
  – Switch regimen must be tolerated, adhered to, and active

• Switching therapy in the patient with unsuppressed viremia, requires careful consideration of detected and likely drug resistance.

• Failure of initial regimen increasingly easier to manage given availability of agents in new classes.

• Adherence continues to be the main driver of ART failure and advances in therapeutics and in behavioral interventions must remain important goals.

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