Antiretroviral Switch Studies: An Update

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Last Updated: July 3, 2014
Case and Question

• 45-year-old HIV-infected man presents for follow-up
• Diagnosed 12 months ago, at which time HIV RNA was 175,000 copies and baseline K103N detected
• Started tenofovir-emtricitabine (Truvada), darunavir (Prezista), and ritonavir (Norvir) 9 months ago
• HIV RNA now undetectable
• He complains of stomach cramps and loose stools and feels he is taking too many pills
45 yom, baseline VL 175K, K103N, on TDF-FTC + DRV+RTV, VL UD

Would you offer a switch to the following?

A. Tenofovir-emtricitabine-rilpivirine (*Complera*)
B. Tenofovir-emtricitabine-elvitegravir-cobicistat (*Stribild*)
C. Either
D. Neither
Reasons to consider ART regimen switch if VL suppressed:
- Side effects
- Pill burden/dosing frequency
- Drug interactions
- Food requirement
- Cost

Background

• Lessons from prior switch studies:
  - See ECHO talk 7/18/13
  - Some switches risky, especially if prior virological failure/resistance
  - Switch from regimen with higher barrier to resistance to regimen with lower barrier may be successful in select patients

• Essential to review before switch:
  - ARV history and past virological responses
  - Prior resistance history
  - Prior intolerances
  - Concurrent medications
Outline

1) SPIRIT (Boosted PI to Complera)
2) STRATEGY-PI (Boosted PI to Stribild)
3) STRATEGY-NNRTI (NNRTI to Stribild)
4) Other New and Upcoming Switch Studies
Simplification to rilpivirine/emtricitabine/tenofovir disoproxil fumarate from ritonavir-boosted protease inhibitor antiretroviral therapy in a randomized trial of HIV-1 RNA-suppressed participants

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SPIRIT Study

**Study Design**

- Prospective, randomized, open-label, ongoing phase 3 trial (industry-sponsored)
- Inclusion criteria:
  - VL suppressed on boosted PI + 2 NRTI’s for ≥6 months
  - No h/o virological failure
  - On 1st or 2nd regimen
  - No resistance to study drugs or NRTI’s
- Primary endpoint: proportion with VL<50 copies/mL at 24 weeks

**Immediate Switch**

317: Switch to TDF-FTC-RPV (*Complera*)

**Continue**

TDF-FTC-RPV (*Complera*)

**Switch to**

TDF-FTC-RPV (*Complera*)

24 weeks

**Delayed Switch**

159: Continue Boosted PI + 2 NRTI’s

Switch to TDF-FTC-RPV (*Complera*)

48 weeks

Baseline Characteristics

- 88% male, 87% white, median CD4 588 cells/mm$^3$
- Median time on ART: 2.75 years
- Boosted PI: 36% atazanavir, 33% lopinavir, 20% darunavir
- NRTI’s: 81% tenofovir-emtricitabine
- Baseline characteristics similar between groups

### Key Results at 24 and 48 weeks

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HIV RNA &lt;50 at 24 weeks</th>
<th>HIV RNA &lt;50 at 24 weeks if baseline RNA &gt;100K</th>
<th>HIV RNA &lt;50 at 48 weeks if baseline K103N</th>
<th>Change in lipids at 24 weeks</th>
<th>Change in eGFR (mL/min) at 24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF-FTC-RPV (Complera)</td>
<td>93.7%</td>
<td>95.4% (125/131)</td>
<td>91.7% (22/24)</td>
<td>TC -25, LDL -16, TG -53</td>
<td>-4.4</td>
</tr>
<tr>
<td>Boosted PI + 2 NRTI’s</td>
<td>89.9%</td>
<td>92.3% (48/52)</td>
<td></td>
<td>TC -1, LDL 0, TG +3</td>
<td>+0.1</td>
</tr>
</tbody>
</table>

- Two participants with baseline K103N who failed at 48 weeks:
  - One also had baseline V179I/V; developed M184V, E138K, V108I/V
  - Other counted as failure due to missing data at 48 weeks

SPIRIT Study: Lessons Learned

• Switch to TDF-FTC-RPV (*Complera*) from boosted PI + 2 NRTI’s may be safe and tolerable for *very select* patients
  - Pre-ART VL >100K not a contraindication if VL now suppressed
  - Baseline K103N mutation likely not a contraindication
  - Lipids expected to improve
Simplification to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of ritonavir-boosted protease inhibitor with emtricitabine and tenofovir in adults with virologically suppressed HIV (STRATEGY-PI): 48 week results of a randomised, open-label, phase 3b, non-inferiority trial

Jose R Arribas, Gilles Pialoux, Joseph Gathe, Giovanni Di Perri, Jacques Reynes, Pablo Tebas, Thai Nguyen, Ramin Ebrahimi, Kirsten White, David Piontkowsky

STRATEGY-PI

Study Design

- Prospective, randomized, open-label, ongoing phase 3 trial (industry-sponsored)
- Inclusion criteria:
  • VL suppressed on boosted PI + TDF-FTC for ≥6 months
  • CrCl ≥70 mL/min
  • No FTC or TDF resistance
  • On 1st or 2nd regimen
  • No h/o virological failure
- Primary endpoint: proportion with VL <50 copies/mL at 48 weeks

Baseline Characteristics

- 86% male, 18% non-white, 19% over age 50
- 40% on boosted atazanavir, 40% on boosted darunavir
- Median time since first ARV use: 3 years
- 19% on their second regimen
- Baseline characteristics similar between groups

48-Week Results

<table>
<thead>
<tr>
<th></th>
<th>HIV RNA &lt;50 copies</th>
<th>Virologic Failure</th>
<th>Grade 2-4 AE’s</th>
<th>Change in CrCl (mL/min)</th>
<th>Change in TG’s (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E-C-F-TDF</td>
<td>93.8%</td>
<td>0.7%</td>
<td>3.8%</td>
<td>-7.5</td>
<td>-16</td>
</tr>
<tr>
<td>Boosted PI + TDF-FTC</td>
<td>87.1%</td>
<td>1.4%</td>
<td>2.9%</td>
<td>0.4</td>
<td>+3</td>
</tr>
</tbody>
</table>

- Primary outcome: 6.7% difference, 95% CI 0.4-13.7%, p = 0.025
  *Difference driven by more treatment discontinuations for non-virological reasons in the no-switch group
- No emergent resistance in either group
- AE’s causing treatment discontinuations equivalent
- Most common reason for enrolling in study: wanting to simplify (86%)

Switching to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of non-nucleoside reverse transcriptase inhibitor with emtricitabine and tenofovir in virologically suppressed adults with HIV (STRATEGY-NNRTI): 48 week results of a randomised, open-label, phase 3b non-inferiority trial

Anton Pozniak, Martin Markowitz, Anthony Mills, Hans-Juergen Stellbrink, Antonio Antela, Pere Domingo, Pierre-Marie Girard, Keith Henry, Thai Nguyen, David Piontkowsky, Will Garner, Kirsten White, Bill Guyer

STRATEGY-NNRTI

Study Design

- Prospective, randomized, open-label, ongoing phase 3 trial (industry-sponsored)
- Inclusion criteria:
  - VL suppressed on NNRTI + TDF-FTC for ≥6 months
  - CrCl ≥70 mL/min
  - No FTC or TDF resistance
  - On 1st or 2nd regimen
  - No h/o virological failure
- Primary endpoint: proportion with VL<50 copies/mL at 48 weeks

Baseline Characteristics

- 93% male, 22% non-white, 22% over age 50
- 78% on efavirenz, 17% on nevirapine
- Median time since first ARV use: 3 years
- 31% enrolled because of current or long term side effects
- Baseline characteristics similar between groups

### 48-Week Results

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<tr>
<td>E-C-F-TDF</td>
<td>93%</td>
<td>1.0%</td>
<td>5.5%</td>
<td>-11.6</td>
<td>-16</td>
</tr>
<tr>
<td>NNRTI + TDF-FTC</td>
<td>88%</td>
<td>1.0%</td>
<td>1.4%</td>
<td>-0.2</td>
<td>+3</td>
</tr>
</tbody>
</table>

- Primary outcome: difference 5.3%, 95% CI -0.5%-12.0%
- No emergent resistance in either group
- Similar treatment discontinuations (2.1% vs. 0.7%)
- No proximal tubulopathy

Additional Results

- Small decreases from baseline in TC, LDL, and HDL in those switching from efavirenz-based regimens
- Also decreases in neuropsychiatric symptoms
  - Vivid dreams (-15%, p <0.001)
  - Dizziness (-11%, p <0.001)
  - Anxiety (-9%, p =0.008)
  - Insomnia (-10%, p =0.004)

STRATEGY Studies: Lessons Learned

- Switch to E-C-F-TDF (*Stribild*) from boosted PI or NNRTI-based regimen likely safe and tolerable for select patients
  - May see slight improvement in lipids
  - Switch from efavirenz (*Sustiva*) improves neuropsychiatric symptoms
Other New and Upcoming Switch Studies

- **STUDY 123**: Raltegravir (*Isentress*) switch to *Stribild*- data presented at IAS 2013 and available online

- **DORISS**: Switch from 3-drug ART to dolutegravir (*Tivicay*) + rilpivirine (*Edurant*) vs. continuation of 3-drug ART

- **MARCH**: Switch from boosted PI + 2 NRTI’s to maraviroc (*Selzentry*) + boosted PI vs. maraviroc + 2 NRTI’s vs. continuation of boosted PI + 2 NRTI’s

- **CV risk in patients switching from boosted PI to dolutegravir**

Sources:
2) http://clinicaltrials.gov/show/NCT02069834
3) http://clinicaltrials.gov/show/NCT01384682
4) http://clinicaltrials.gov/show/NCT02098837