Antiretroviral Switch Studies

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Presentation prepared by:
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1. To raltegravir (Isentress): SWITCHMRK, SPIRAL
2. To tenofovir/emtricitabine (Truvada): SWIFT
3. To tenofovir/emtricitabine/rilpivirine (Complera): SPIRIT
4. To atazanavir (Reyataz): ATAZIP, SWAN, SLOAT
5. From tenofovir/emtricitabine/efavirenz (Atripla)
Why Switch?

• To reduce side effects (acute or chronic)
• To decrease pill burden, simplify regimen
• Key = must maintain virological control
• Are switch studies ethical?

The Ethics of Switch/Simplify in Antiretroviral Trials: Non-Inferior or Just Inferior?

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Switch to Raltegravir: SWITCHMRK, SPIRAL
SWITCHMRK 1 & 2: Boosted PI to Raltegravir

**Study Design**

- **N = 707 HIV-infected adults**
- Virologically suppressed on lopinavir/ritonavir (Kaletra) + >2 NRTI’s for ≥3 months
- Multicenter, double-blind, double-dummy, phase 3 RCT’s
- Goal: improve lipids and other side effects
- Endpoints: change in lipids at week 12, VL <50 at week 24

350: Switch to raltegravir (Isentress)

352: Continue lopinavir/ritonavir (Kaletra)

24 Weeks

SWITCHMRK 1& 2 Combined Results

<table>
<thead>
<tr>
<th></th>
<th>Total cholesterol</th>
<th>LDL</th>
<th>Triglycerides</th>
<th>HIV RNA &lt;50 copies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lopinavir/ritonavir (Kaletra)</td>
<td>+1.0%</td>
<td>+2.6%</td>
<td>+6.2%</td>
<td>90.6%</td>
</tr>
<tr>
<td>Raltegravir (Isentress)</td>
<td>-12.6%</td>
<td>-15.0%</td>
<td>-42.2%</td>
<td>84.4%</td>
</tr>
</tbody>
</table>

- **What did we learn?** Raltegravir is not for everyone! Increased risk of virological failure when switching from a PI, particularly if prior ART failure or NRTI resistance.

SPIRAL: Another PI to Raltegravir Switch With Remarkably Different Results

• Conclusion:
  - Switch to raltegravir non-inferior, also improves lipids\(^1\) and bone mineral density\(^2\)

• What accounts for the difference?
  - Smaller study (273 participants), 48 weeks, open label
  - Participants VL suppressed for $\geq 6$ months (median 6 years)
  - Other boosted PI’s included (lopinavir 44%, atazanavir 35%)
  - NRTI backbones not equivalent?
  - Prior virological failure: SPIRAL 38%, SWITCHMRK 34%

Sources:
Switching Boosted PI to Raltegravir

**Summary:**
- Requires caution and likely should be avoided if history of multiple prior regimens, poor adherence, or prior virological failure
- If suppressed on boosted PI for a long time without that history, more likely the switch will be ok
- Switch leads to improvement in metabolic parameters
Switch to Complera: SPIRIT
SPIRIT: Switch to Tenofovir-Emtricitabine-Rilpivirine (Complera)

Study Design
- N = 476 HIV+ adults
- HIV RNA <50 on 2 NRTI’s + boosted PI x >6 months
- On 1st or 2nd regimen with no h/o NNRTI use or resistance to study drugs
- 1o endpoint: HIV RNA <50 at 24 weeks
- 2o endpoints: tolerability, lipids at 24 & 48 wks

## SPIRIT Results

<table>
<thead>
<tr>
<th></th>
<th>Total cholesterol</th>
<th>LDL</th>
<th>Triglycerides</th>
<th>HIV RNA &lt;50 copies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boosted PI</td>
<td>-1</td>
<td>0</td>
<td>+3</td>
<td>89.9%</td>
</tr>
<tr>
<td>Complera</td>
<td>-25</td>
<td>-16</td>
<td>-53</td>
<td>93.7%</td>
</tr>
</tbody>
</table>

- PI: 30% lopinavir, 30% atazanavir, 20% darunavir
- *What did we learn?* For select patients, a switch to Complera may be safe and may improve lipid parameters

To Tenofovir/Emtricitabine (Truvada): SWIFT
To Tenofovir/Emtricitabine (Truvada): SWIFT

**Study Design**
- N = 311 HIV-infected adults
- On abacavir/lamivudine (Epzicom) + boosted PI with HIV RNA <50
- Prospective, randomized, double-blind, multicenter trial
- 1° endpoint: Proportion with HIV RNA <200 at 48 weeks
- 2° endpoints: virological failure, safety and tolerability, lipid changes, renal changes

**Endpoints**
- Abacavir/lamivudine (Epzicom) + boosted PI (n = 156)
- Tenofovir/emtricitabine (Truvada) + boosted PI (n = 155)

48 Weeks

## SWIFT Results

<table>
<thead>
<tr>
<th></th>
<th>HIV RNA &lt;200</th>
<th>Virological failure</th>
<th>Discontinued due to AE</th>
<th>Renal AE</th>
<th>Lipid Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir-emtricitabine (Truvada)</td>
<td>86.4%</td>
<td>1.9%</td>
<td>4.5%</td>
<td>4.5%</td>
<td>TC -21, LDL -7, HDL -18</td>
</tr>
<tr>
<td>Abacavir-lamivudine (Epzicom)</td>
<td>83.3%</td>
<td>7.9%</td>
<td>1.9%</td>
<td>5.1%</td>
<td>TC -3, LDL -1, HDL -9</td>
</tr>
</tbody>
</table>

- **What did we learn?** Confirms results of A5202 and ASSERT: less virological failure with Truvada
- Biggest limitation: few participants taking boosted darunavir

To Atazanavir (Reyataz): ATAZIP, SWAN, SLOAT
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**ATAZIP & SLOAT:**
- Lopinavir/ritonavir (Kaletra) to atazanavir (Reyataz) + ritonavir (Norvir) maintains VL <50 and improves lipids through 48 weeks

**SWAN:**
- Boosted PI (70% lopinavir/ritonavir) to atazanavir + ritonavir in maintains VL <50 and improves lipids through 48 weeks

Sources:
Switching From Efavirenz

• Efavirenz to rilpivirine:
  - 50 participants (46 men), suppressed on tenofovir-emtricitabine-efavirenz (Atripla) for ≥8 weeks
  - All remained suppressed at 12 weeks despite lower rilpivirine levels

• Efavirenz to raltegavir:
  - 40 participants (38 men), suppressed on tenofovir-emtricitabine-efavirenz (Atripla)
  - All remained suppressed, plus improved CNS symptoms and sleep (by 4 weeks) and lipids (by 12 weeks)

Sources:
Ongoing and Future Studies

- Switch studies to tenofovir/emtricitabine/cobicistat/elvitegravir (Stribild)
- MARCH: switch to maraviroc (Selzentry)
- Switch studies to dolutegravir