Professor Georg Behrens
Hannover Medical School, Germany

COMPETING INTEREST OF FINANCIAL VALUE £1,000:

<table>
<thead>
<tr>
<th>Speaker Name</th>
<th>Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professor Georg Behrens:</td>
<td>Professor Behrens has received payment for attending Advisory Board meetings by conference sponsors. In addition, he has received speaker fees and grants used for research from conference sponsors</td>
</tr>
<tr>
<td>Date</td>
<td>April 2012</td>
</tr>
</tbody>
</table>
Spoilt for Choice?
Switching Antiretrovirals

Georg Behrens
Department for Clinical Immunology and Rheumatology
Hannover Medical School, Hannover, Germany

HIV therapy: A matter of choices?

• Our choice of tolerable, safe and effective HIV drug combinations

versus

• HIV’s choice of resistance mutation development
Spoilt for choice?  26 drugs + FixDose Combinations

NRTI
- Zidovudine
- Didanosine
- Zalcitabine
- Stavudine
- Lamivudine
- Abacavir
- Tenofovir
- Emtricitabine

PI
- Saquinavir
- Ritonavir
- Indinavir
- Nelfinavir
- Amprenavir
- Lopinavir
- Atazanavir
- Fosamprenavir
- Tipranavir
- Darunavir

Entry Inhibitor
- Maraviroc

Integrase Inhibitor
- Raltegravir

Combinations
- 6 available, combining 2 or 3 drugs

Fusion Inhibitor
- Enfuvirtide (T-20)

Spoilt for choice?  14 drugs

NRTI
- Zidovudine
- Lamivudine
- Abacavir
- Tenofovir
- Emtricitabine

PI
- Lopinavir
- Atazanavir
- Darunavir

Entry Inhibitor
- Maraviroc

Integrase Inhibitor
- Raltegravir
Don’t start with, nor switch to

- 3TC + FTC
- AZT + d4T
- ddI + d4T
- TDF + ddI
- TDF + ABC

Spoilt for choices? **NO!**

- Just enough choices to keep HIV in check
- Need for even more options in the future
- New drug classes are desirable

- HIV epidemic will spread in humans during the next decades, if not centuries!
- Think of TB and development of MDR TB!
Randomized trials: No choices

- We request for data from trials, in which we have no choice and cannot switch
  - Difficult to extrapolate
- How to best treat 100 patients versus how to best treat the patient in front of me

Randomized trials vs. "real live scenario"

- Efficiency is determined by the fact, whether or not the patient is able to take the drugs
  - Doctors decisions become more important
- Does a doctor's therapy decision for patients perform better then randomised trials?
Percent of patients with a viral load <50 copies/ml

**Antiretroviral efficacy studies**

- 20% of patients selected for randomized controlled trials does not achieve the primary virological endpoint.

**Outside antiretroviral efficacy studies**

- 30-40% of patients switch parts of their first line regime outside clinical trials within the first 24 months.
Switch of first line HIV therapy regimens

Even the “best” regimens result in some level of discontinuation

**TDF+FTC+EFV**
12/257 (5%) because of toxicity

**ABC/3TC+LPV/r**
24/444 (5%) because of adverse event

---

Even the “best” regimens result in some virological failures

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Virological Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF+FTC+EFV</td>
<td>4/255 (1.6%)</td>
</tr>
<tr>
<td>ABC/3TC+LPV/r</td>
<td>30/444 (6.7%)</td>
</tr>
</tbody>
</table>


Switch of antiretrovirals

- Why switch?
- What is possible?
- What has been looked at in clinical trials?
- What makes sense, what not?
- What needs to be considered?
Why switch antiretrovirals?

- Virological failure
- To respond to short term toxicity
- To avoid long term toxicity
- To avoid drug-drug interactions, to simplify treatment, to enhance adherence

Incomplete virological suppression

- **Incomplete viral suppression** will lead to resistance mutation accumulation
  - 68% with new mutations after median of 22 months\(^1\)
  - 33% with new TAMs, 2% K65R during 96 wks of FU\(^2\)
  - 60% with new mutations after median of 9.3 months but no shift on virtual phenotype\(^3\)

\(^{1,2,3}\) Lafouilade A, et al. IAC 2004. Abstract WeCrB1293.
Virological failure

- How resistance-sensitive is the present therapy? NNRTI, 3TC/FTC, RAL: change quickly
- The lower the VL, the greater the prospect of success after change
- Adherence?
- Resistance test
- ...

Little choices because of NRTI resistance mutations

<table>
<thead>
<tr>
<th>Failing nuke backbone</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF+3TC/FTC</td>
<td>K65R and/or <strong>M184V</strong></td>
</tr>
<tr>
<td>ABC+3TC</td>
<td>L74V, less often K65R, and /or <strong>M184V</strong></td>
</tr>
<tr>
<td>AZT/d4T+3TC</td>
<td><strong>M184V</strong> and then successive TAMs</td>
</tr>
<tr>
<td>AZT/3TC+ABC</td>
<td>TAMs, Q151M, T69ins</td>
</tr>
<tr>
<td>AZT/d4T+ddl</td>
<td>K65R</td>
</tr>
<tr>
<td>TDF+ABC/ddI</td>
<td></td>
</tr>
</tbody>
</table>

Different combinations of V118I, H208Y, and T215Y reverse transcriptase mutations produce NNRTI hypersusceptibility

Clark et al. AIDS. 2006 Apr 24;20(7):981-4
### Changing first-line therapy

<table>
<thead>
<tr>
<th>Failing initial therapy</th>
<th>Potentially successful change</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 NRTI + 1 NNRTI</td>
<td>Change NNRTI to PI/r (rapid switch) or 1-2 new NRTIs + RAL or MVC</td>
</tr>
<tr>
<td>2 NRTI + 1 PI/r</td>
<td>1-2 new NRTIs + NNRTI + new PI/r or RAL or MVC</td>
</tr>
</tbody>
</table>

TDF/FTC + EFV  →  TDF/FTC + PI/r  M184V?

### Therapeutic use of resistance mutations

- Keep 3TC/FTC because of M184V  
  - Makes the virus less fit
- Add AZT because of K65R
- Combine AZT + TDF because of divergent resistance pathways
- Add ddI (?)

Changing first-line therapy

<table>
<thead>
<tr>
<th>Failing initial therapy</th>
<th>Potentially successful change</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 NRTI + 1 NNRTI</td>
<td>PI/r + RAL (under investigation)</td>
</tr>
<tr>
<td>2 NRTI + 1 PI/r</td>
<td>1-2 new NRTIs + NNRTI + new PI/r or RAL or MVC</td>
</tr>
</tbody>
</table>

Sequencing NNRTIs? ECHO & THRIVE

Phenotypic sensitivity to NNRTIs

<table>
<thead>
<tr>
<th>Time of failure, %</th>
<th>RPV BL VL ≤ 100K c/mL</th>
<th>RPV BL VL &gt; 100K c/mL</th>
<th>EFV BL VL ≤ 100K c/mL</th>
<th>EFV BL VL &gt; 100K c/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistant to RPV**</td>
<td>N=2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Resistant to RVP</td>
<td>N=14</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Resistant to RPV**</td>
<td>N=29</td>
<td>48</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Resistant to RVP</td>
<td>N=17</td>
<td>0</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Resistant to ETR</td>
<td>50</td>
<td>48</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Resistant to ETR</td>
<td>7</td>
<td>93</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>Resistant to EFV</td>
<td>50</td>
<td>90</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Resistant to EFV</td>
<td>7</td>
<td>90</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

Cross-resistance determined by Antivirogram®

*RPV biological cut-off (BCO) = 3.7 (Antivirogram®)

Adapted from Rimsky L, et al. IWHHC 2011; Los Cabos, Mexico. Poster
Sequencing integrase inhibitors?

Virologic Response at DAY 11: Correlation with Baseline Fold Change (FC) in Susceptibility to S/GSK1349572

Mixtures:
- N=1 Q148H + G140S / Y143H
- N=1 Q148H+ E138A+G140S / Y143H
- Others: N=1 E92Q (screen: E92Q, N155H)
- N=1 none (screen: G140G/S, Q148H)

Strong correlation between baseline FC and Day 11 response (r=0.79, p value <0.001)

Patients with N155H and Y143H responded better than patients with Q148

Within class changes for virologic failure

- NRTI → NRTI
- NNRTI → NNRTI (etravirine)
- PI/r → PI/r
- RAL → nothing at this stage
- MVC → nothing
Spoilt for choice: NO!

To create the best combination regimen, often the (potentially) weakest active drug dictates the rest of the regimen composition.

Success of todays HIV therapy (start)

• Rapid and effective response to early virological failure (effective + simple switches)

• Choice to react to short term intolerability

  90% of all patients can achieve < 50 HIV-RNA copies/mL on a tolerable regimen 12 months after therapy start
Patients with TCR or TCF: some choices

<table>
<thead>
<tr>
<th>Agent tested</th>
<th>DRV</th>
<th>TPV</th>
<th>MVC</th>
<th>RAL</th>
<th>ETV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total n</td>
<td>245</td>
<td>1509</td>
<td>1049</td>
<td>701</td>
<td>612</td>
</tr>
</tbody>
</table>

**Background-Therapy**

- With de novo T-20, %
  - 29–33
  - 18–23
  - 40–44
  - 20
  - 25
  - 25

- With darunavir, %
  - 100
  - 0
  - 0
  - 25–50
  - 100

- With tipranavir, %
  - 0
  - 100
  - 14–16
  - 19–23
  - 0

**Response at 48 We**

- In total, %
  - 46 vs. 10
  - 22 vs. 10
  - 44 vs. 17
  - 64 vs. 24
  - 61 vs. 40

- With de novo T-20, %
  - 58 vs. 11
  - 28 vs. 14
  - 61 vs. 27
  - 84 vs. 62
  - 71 vs. 59

- 0-1 active drug, %
  - 37 vs. 1
  - n a
  - 37 vs. 6***
  - 48 vs. 12
  - 57 vs. 24

*Definition of an active drug varied considerably (different resistance scores were used);
**Response at 48 weeks defined as viral load <50 copies/ml; ***Data at week 24; n a—not applicable

2-3 NRTI + 1 PI/r ± (T-20) + something new (RAL, MVC, ETV)

---

Patients with **Three Class Resistance**

**Week 48**

- **TRIO trial**
  - RAL+ETV+MVC (n=103) 86% <50 copies

- **Italian study**
  - RAL+ETV+MVC (n=28) 92% <50 copies

Side effects almost always leading to discontinuation/switch

- **Severe** diarrhea, **severe** nausea (PIs)
- **Persistent** sleeping disorder (EFV)
- **Severe** allergic manifestations with involvement of mucous membranes, fever (ABC, NVP)
- **Severe** anaemia (AZT)
- Pancreatitis, polyneuropathy (d4T, ddI)
- Lactic acidosis (d4T+ddI, other NRTIs)
- Renal failure, nephrolithiasis, severe hepatotoxicity, rhabdomyolysis

React to short term toxicity

- **EFV**
  - cytochrome P450 induction!
  - viral load < 50 copies/ml?

NVP 2 x 200 mg\(^{1,2}\) (alternatively NVP XR) or lead in with 200 mg for two weeks?\(^3\)

---

React to short term toxicity

- **EFV**
  - cytochrome P450 induction!
  - viral load < 50 copies/ml?

  **Etravirine** 2 x 200 mg (plasma concentrations are only initially lower)\(^1\)

---

React to short term toxicity

- **EFV**
  - cytochrome P450 induction!
  - viral load < 50 copies/ml?

  **Rilpivirine** 1 x 25 mg (plasma concentrations are only initially lower)\(^1\)
React to short term toxicity

- **EFV**
  - cytochrome P450 induction!
  - viral load < 50 copies/ml?
  
  - **PI/r** standard dose
  - **Raltegravir** standard dose
  - **Maraviroc** 600 mg BID first week, 300 mg BID thereafter\(^1\) (unless given together with a PI/r).

1. Waters et al. EACS 2011

React to toxicity

- **PI/r** (if viral load < 50 copies/mL)
  
  - **NNRTI**
  - **Raltegravir** works well, if no prior NRTI mutation/failure
Even suppressed patients experience virologic failure when switched

**PI to EFV**¹

12/156 (8%)

**AZT/3TC to TDF/FTC**²

6% of patients with VL >400 at week 24

---


---

Simplification from suppressive PI-based therapy to NVP-based regimens

- Meta-analysis of 6 randomized clinical trials (N = 550) switching suppressive PI-based therapy to NVP-based therapy or no change¹¹

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Difference (Fixed), 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arranz</td>
<td></td>
</tr>
<tr>
<td>Barreiro</td>
<td></td>
</tr>
<tr>
<td>Calza</td>
<td></td>
</tr>
<tr>
<td>Negredo</td>
<td></td>
</tr>
<tr>
<td>Negredo</td>
<td></td>
</tr>
<tr>
<td>Ruiz</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
</tbody>
</table>

### PI → NNRTI, improves lipids

<table>
<thead>
<tr>
<th>Source</th>
<th>n</th>
<th>Wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI to NVP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barreiro 2000</td>
<td>138</td>
<td>24</td>
</tr>
<tr>
<td>Ruiz 2001</td>
<td>106</td>
<td>48</td>
</tr>
<tr>
<td>Arranz-Caso 2005</td>
<td>160</td>
<td>48</td>
</tr>
<tr>
<td>PI to EFV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Becker 2001</td>
<td>346</td>
<td>48</td>
</tr>
<tr>
<td>Molina 2005</td>
<td>355</td>
<td>48</td>
</tr>
<tr>
<td>PI to EFV vs NVP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negredo 2002</td>
<td>77</td>
<td>48</td>
</tr>
<tr>
<td>Calza 2005</td>
<td>130</td>
<td>48</td>
</tr>
</tbody>
</table>

In all studies (except Martinez 2003), randomization was against continuing PIs.

### PI → ABC or RAL

<table>
<thead>
<tr>
<th>Source</th>
<th>n</th>
<th>Wk</th>
<th>VL Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI to EFV vs NVP, ABC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martinez 2003</td>
<td>460</td>
<td>48</td>
<td>Trend against ABC</td>
</tr>
<tr>
<td>PI to ABC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clumeck 2001</td>
<td>211</td>
<td>24</td>
<td>Advantage</td>
</tr>
<tr>
<td>Oprovil 2002</td>
<td>163</td>
<td>84</td>
<td>Disadvantage (trend)</td>
</tr>
<tr>
<td>Katlama 2003</td>
<td>209*</td>
<td>48</td>
<td>n.s.</td>
</tr>
<tr>
<td>Keiser 2002</td>
<td>104</td>
<td>28</td>
<td>n.s.</td>
</tr>
<tr>
<td>PI to RAL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eron 2010</td>
<td>350</td>
<td>24</td>
<td>Disadvantage</td>
</tr>
<tr>
<td>Martinez 2010</td>
<td>139</td>
<td>48</td>
<td>n.s.</td>
</tr>
</tbody>
</table>
**SPIRAL: Switch to RAL noninferior to maintaining PI/RTV regimens**

**Free of Treatment Failure at Wk 48**

(ITT, S = F)

<table>
<thead>
<tr>
<th>Switch to RAL</th>
<th>Continue PI/RTV</th>
</tr>
</thead>
<tbody>
<tr>
<td>89.2</td>
<td>86.6</td>
</tr>
</tbody>
</table>

**Avoid long term toxicity**

- Take out/replace thymidine analogues
  - AZT/d4T → TDF/ABC
  - AZT/d4T → PI/r + NNRTI

**Table: Main effects of the switch**

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Switch to</th>
<th>Wks</th>
<th>Main effects of the switch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negro 2009 (MULTINEKA)</td>
<td>16*</td>
<td>LPV/r + NVP</td>
<td>48</td>
<td>Virologically effective, lipids and mitochondrial DNA better</td>
</tr>
<tr>
<td>Tebas 2009 (ACTG 5110)</td>
<td>101</td>
<td>LPV/r + NVP</td>
<td>48</td>
<td>Virologically effective, lipodystrophy better</td>
</tr>
<tr>
<td>Tebas 2007 (ACTG 5125)</td>
<td>62</td>
<td>LPV/r + EFV</td>
<td>48</td>
<td>Many metabolic disturbances and LA better</td>
</tr>
<tr>
<td>Fischl 2007 (ACTG 5116)</td>
<td>118*</td>
<td>LPV/r + EFV</td>
<td>110</td>
<td>Trend towards more virologic failure, more side effects</td>
</tr>
</tbody>
</table>
Avoid long term toxicity

• Take out/replace thymidine analogues
  - AZT/d4T out, TDF/ABC in
  - PI/r + NNRTI

Don’ts
- EFV/NVP + ATV unboosted
- EFV/NVP + LPV/r
- ETR + TPV/r

AZT/d4T out, TDF/ABC in
- PI/r + NNRTI

SPARTAN TRIAL:
ATV (300mg BID) + RAL (400 mg BID)

Hyperbilirubinemia
RAL resistance mutations
ARIES: Switch From a RTV-Boosted PI to Unboosted ATV


Nuke-sparing: Switch to double PI

<table>
<thead>
<tr>
<th>Combination</th>
<th>Daily Dose/comment</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>More favorable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopinavir/r + saquinavir</td>
<td>800/200/2000</td>
<td>Staszewski 2006</td>
</tr>
<tr>
<td>Saquinavir/r + fosamprenavir</td>
<td>2000/200/1400</td>
<td>Roffito 2004</td>
</tr>
<tr>
<td>Indinavir/r + indinavir</td>
<td>800/200/1600</td>
<td>Staszewski 2003</td>
</tr>
<tr>
<td>Less favorable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopinavir/r + fosamprenavir</td>
<td>Poor PK data</td>
<td>Kashuba 2005</td>
</tr>
<tr>
<td>Lopinavir/r + atazanavir</td>
<td>Poor activity</td>
<td>Ulbricht 2008</td>
</tr>
<tr>
<td>Lopinavir/r + nefinavir</td>
<td>Poor PK data, diarrhea</td>
<td>Klein 2003</td>
</tr>
<tr>
<td>Atazanavir + indinavir</td>
<td>Elevated lippinrin</td>
<td>Chien-Lin-Rums 2007</td>
</tr>
<tr>
<td>Atazanavir + fosamprenavir</td>
<td>Poor activity</td>
<td>Landman 2009</td>
</tr>
<tr>
<td>Atazanavir + saquinavir without /r</td>
<td>Poor activity</td>
<td>Johnson 2005</td>
</tr>
<tr>
<td>Tipranavir + LPV/APV/SQV</td>
<td>Poor PK data</td>
<td>Wallmsley 2004</td>
</tr>
<tr>
<td>Indinavir + nefinavir</td>
<td>Relatively poor activity</td>
<td>Riddler 2002</td>
</tr>
</tbody>
</table>
Nuke-sparing: **Switch** to double PI

**Combination** | **Daily Dose/Comment** | **Source**
--- | --- | ---
**More favorable**
Lopinavir/r + saquinavir | 800/200/200 | Staszewska 2006
Stavudine/r + lamivudine | 300/200/200 | New Horizon 2007
Stavudine/r + idoxuridine | 300/200 |
**Less favorable**
Lopinavir/r |
Lopinavir/r + atazanavir |
Lopinavir/r + ritonavir |
Atazanavir |
Stavudine/r + lamivudine | Postact vity | Landman 2009
Stavudine/r + lamivudine without/r | Postact vity | Johnson 2005
Lopinavir/r + FPV/VPV/SQV | Poor PK Data | Watersley 2004
Indinavir + delavirdine | Relatively poor activity | Guidotti 2007

**Don’ts**
- TPV + PI (FPV, LPV, SQV, ATV)
- LPV/r + FPV
- IDV + ATV

**Systematic review of LPV/r monotherapy**

**Therapy Failure, Intent to Treat**

<table>
<thead>
<tr>
<th>Studies</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OK04 2005</td>
<td>4.71 (0.48-46.2)</td>
</tr>
<tr>
<td>Singh et al. 2007</td>
<td>1.70 (0.46-6.21)</td>
</tr>
<tr>
<td>KALMO</td>
<td>2.17 (0.49-9.64)</td>
</tr>
<tr>
<td>OK04 2008</td>
<td>1.03 (0.53-2.01)</td>
</tr>
<tr>
<td>MO3-613</td>
<td>1.67 (0.85-3.31)</td>
</tr>
<tr>
<td>MONARK</td>
<td>1.48 (0.68-3.22)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>1.48 (1.02-2.13)</td>
</tr>
</tbody>
</table>

Systematic review of PI monotherapy

Risk ratios for maintaining viral suppression, intention to treat analysis, 48 week follow-up, viral suppression, <50 copies/ml.

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Arribas (2005)</td>
<td>0.85 (0.68,1.07)</td>
<td>6.00</td>
</tr>
<tr>
<td>Pulido (2007)</td>
<td>0.95 (0.85,1.05)</td>
<td>17.93</td>
</tr>
<tr>
<td>Echeverna (2008)</td>
<td>0.78 (0.58,1.05)</td>
<td>3.91</td>
</tr>
<tr>
<td>Waters (2008)</td>
<td>0.93 (0.69,1.26)</td>
<td>3.65</td>
</tr>
<tr>
<td>Cahn (2009)</td>
<td>1.17 (0.96,1.43)</td>
<td>7.53</td>
</tr>
<tr>
<td>Gutmann (2010)</td>
<td>0.75 (0.59,0.95)</td>
<td>5.77</td>
</tr>
<tr>
<td>Meynard (2010)</td>
<td>0.95 (0.85,1.07)</td>
<td>15.93</td>
</tr>
<tr>
<td>Arribas (2010)</td>
<td>0.99 (0.89,1.10)</td>
<td>18.31</td>
</tr>
<tr>
<td>Katlama (2010)</td>
<td>0.94 (0.86,1.03)</td>
<td>20.97</td>
</tr>
<tr>
<td>Overall (I-squared= 30.7%, p=0.173)</td>
<td>0.94 (0.89,1.00)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from the random effects analysis

Modified from Mathis et al PlosONE 2011

PI monotherapy: A simple therapy?

<table>
<thead>
<tr>
<th>Source</th>
<th>n</th>
<th>Maintenance</th>
<th>Wks</th>
<th>Less than 50 copies/ml?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nunes 2009 (KalMo)</td>
<td>60</td>
<td>LPV/r versus 2 NRTIs+LPV/r</td>
<td>96</td>
<td>80% vs 87% (ITT, VL &lt; 80)</td>
</tr>
<tr>
<td>Carigu 2009 (M03 613)</td>
<td>155</td>
<td>LPV/r versus CBV+EFV</td>
<td>96</td>
<td>60% vs 63% (ITT), but low-level viremia more frequently</td>
</tr>
<tr>
<td>Pulido 2008 (OKO4 Study)</td>
<td>205</td>
<td>LPV/r versus 2 NRTIs+LPV/r</td>
<td>48</td>
<td>85% vs 90% (ITT), Non-Inferiority shown, but more frequent low level viremia</td>
</tr>
<tr>
<td>Meynard 2010 (KALESLO)</td>
<td>186</td>
<td>LPV/r vs ARI continuation</td>
<td>48</td>
<td>84 vs 88% (ITT), Non-inferiority not shown, more frequent low viremia</td>
</tr>
<tr>
<td>Gutman 2010</td>
<td>60</td>
<td>LPV/r vs ART-continuation</td>
<td>24</td>
<td>21% VF on Mono. Especially those with low CD4 nadir, study discontinued.</td>
</tr>
<tr>
<td>Arribas 2010 (MONEI)</td>
<td>256</td>
<td>DRV/r versus 2 NRTIs+DRV/r</td>
<td>96</td>
<td>75% vs. 81% (ITT), Non-inferiority not shown</td>
</tr>
<tr>
<td>Katlama 2010 (MONOII)</td>
<td>225</td>
<td>DRV/r versus 2 NRTIs+DRV/r</td>
<td>48</td>
<td>94% vs. 99%, Non-inferiority not clearly shown (low viremia more frequently)</td>
</tr>
</tbody>
</table>
MONET Trial (switch to DRV/r only)

Switch failure analysis (TLOVR)
Difference = -5.8% (-16.0%, +4.4%)*

Switch included analysis
Difference = +1.4% (-5.5%, +8.3%)*

* 95% confidence intervals from univariate analysis

PI monotherapy (LPV/r or DRV/r):
Is the absence of harm a benefit?

- Data from selected patients for selected patients
- Safe (NRTI reintroduction) + cheap
- Clinical benefits not fully known
Switch to nothing: half-lives of antiretrovirals


<table>
<thead>
<tr>
<th>Drug</th>
<th>Serum/Plasma Half-life (hours)</th>
<th>Intracellular Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV</td>
<td>40-55</td>
<td>39</td>
</tr>
<tr>
<td>FTC</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>TDF</td>
<td>&gt;60</td>
<td></td>
</tr>
</tbody>
</table>

Switch to nothing

- NNRTI and NRTI resistance mutations
- Strategies to avoid mutation development:
  - simultaneously stop all drugs, if drugs have similar half lives
  - discontinue the drug with the longest half life first in a regimen containing drugs with short and long half lives
  - replace all drugs with i.e. a protease inhibitor
- HBV/HIV coinfection: no stop of TDF, FTC, 3TC!

Switch to simplify the regimen

• Current regimens are either twice or once daily
  - Little evidence suggests that clinical outcomes actually improve from twice to once daily
  - Concomittant treatments may have twice-daily dosing

Switch to simplify the regimen

• Current regimens are low pill burden
  - NRTI FDC + EFV: 1-3 pills
  - NRTI FDC + ATV: 2-4 pills
  - NRTI FDC + boosted PI: 4-6 pills

• Will patients who cannot take 2 or 4 per day really adhere better on 1 pill per day?
Durability of initial ART before and after availability of QD FDC NRTI backbones

Spoilt for choices? NO!

• Just enough choices to keep HIV in check
  - 1-2 switches lead to long-lasting efficiency in most, but not all patients
  - Choices/switch ratio goes down from ~5/1 to almost 1 (salvage no choice)

• Need for even more options in the future
  - More resistance mutations (resource-limited settings)
  - Patient’s histories become more complex, patients move
  - Comorbidity, co-medication

• New drug classes are desirable

Why Do We Need New Antiretroviral Agents?

• Resistance
  - Primary drug resistance occurs in 5% to 15% of patients\(^1\)\(^-\)\(^3\)
  - Multiclass resistance in a substantial proportion of highly treatment–experienced patients\(^4\)\(^,\)\(^5\)

• Toxicity/tolerability issues with current classes
  - Metabolic: lipodystrophy, lipoatrophy, dyslipidemia, insulin resistance
  - Other: bone, hematologic, renal, CNS, reproductive, gastrointestinal

• Need for lifelong therapy

**GS 111 Secondary Endpoint:**

**RPV PK after Switching from EFV**

<table>
<thead>
<tr>
<th>Weeks Post-Switch (EFV/FTC/TDF to RPV/FTC/TDF)</th>
<th>EFV Concentration</th>
<th>RPV C\text{trough}</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2500</td>
<td>52 (47)</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>120</td>
</tr>
<tr>
<td>4-12</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- EFV mean C\text{trough} above IC\text{90} (~10 ng/ml\textsuperscript{*}) up to ~4 weeks
- No subject had RPV below quantifiable levels at any visit
- RPV mean C\text{trough} within historic range by 2 weeks

<table>
<thead>
<tr>
<th>Week</th>
<th>RPV C\text{trough} Mean (%CV), ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>52 (47)</td>
</tr>
<tr>
<td>4-12</td>
<td>66 (51) - 84 (76)</td>
</tr>
</tbody>
</table>


---

**Fig. 3** Rate of virological failure after baseline by time since last rebound after combination antiretroviral therapy (cART) initiation prior to baseline. PYFU, person-years of follow-up.

Reekie, Mocroft et al. HIV Med. 2010;11:469-478
Incidence of Second Virologic Failure Declining Over Time

*Adjusted for time from HAART initiation, sex, age, AIDS, CD4+ cell count, HIV-1 RNA level at HAART initiation and switch, and type of HAART.