Simplification of Successful Antiretroviral Therapy with Nucleoside Analogues: Studies and Clinical Practice

Milos Opravil
Division of Infectious Diseases
University Hospital
Zurich, Switzerland
Rationale for simplification of PI-HAART with NRTI or NNRTI

Supporting adherence
- less pill burden
- no dietary restriction
- reduction in adverse events (GIT)

Preventing or reversing metabolic complications
- hyperlipidemia
- fat accumulation

Avoiding CYP interactions (NRTI)

Equal efficacy and durability as PI continuation?
- virological, also in lymphoid tissue
- immunological

Other/new toxicity?
- mitochondrial toxicity, lipoatrophy (NRTI)
- rash (ABC, NNRTI)
- CNS (EFV)
- liver (NNRTI)
ACTG5095: randomized, double-blind study of 3 regimens for the initial treatment of HIV: zidovudine–lamivudine–abacavir, lamivudine–abacavir, and zidovudine–lamivudine–abacavir plus efavirenz

Gulick et al., NEJM 2004;350:1850
ACTG5095: Virologic failure in pts with at least once HIV RNA <200 c./ml – Less durable effect of triple NRTI

Gulick et al., NEJM 2004;350:1850
Meta-analysis of 9 randomized controlled trials of simplified versus continued PI-based HAART: virologic failure

Bucher et al., AIDS 2003;17:2451-2459
Meta-analysis of 3 randomized controlled trials of simplification to ABC / Trizivir: virologic failure

<table>
<thead>
<tr>
<th>Trials with abacavir</th>
<th>Risk ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clumeck et al 2001</td>
<td>1.98 (0.37–10.58)</td>
<td>22.2</td>
</tr>
<tr>
<td>Katlama et al 2001</td>
<td>4.86 (0.58–40.88)</td>
<td>13.7</td>
</tr>
<tr>
<td>Opravil et al 2002</td>
<td>2.45 (0.91–6.55)</td>
<td>64.1</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>2.56 (1.17–5.64)</td>
<td></td>
</tr>
</tbody>
</table>

Bucher et al., AIDS 2003;17:2451-2459
Discontinuation of therapy (secondary endpoint)

<table>
<thead>
<tr>
<th>All trials</th>
<th>Risk ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clumeck et al 2001</td>
<td>0.50 (0.25–0.97)</td>
<td>13.8</td>
</tr>
<tr>
<td>Katlama et al 2001</td>
<td>0.76 (0.44–1.32)</td>
<td>14.6</td>
</tr>
<tr>
<td>Opravil et al 2002</td>
<td>0.40 (0.24–0.68)</td>
<td>22.5</td>
</tr>
<tr>
<td>Becker et al 2002</td>
<td>0.61 (0.39–0.97)</td>
<td>21.9</td>
</tr>
<tr>
<td>Katlama et al 2001</td>
<td>0.08 (0.01–0.59)</td>
<td>7.7</td>
</tr>
<tr>
<td>Martinez et al 2002</td>
<td>1.70 (0.43–6.72)</td>
<td>1.9</td>
</tr>
<tr>
<td>Barreiro et al 2000</td>
<td>0.46 (0.16–1.35)</td>
<td>4.7</td>
</tr>
<tr>
<td>Ruiz et al 2001</td>
<td>1.12 (0.58–2.15)</td>
<td>8.0</td>
</tr>
<tr>
<td>Negredo et al 2002</td>
<td>0.59 (0.22–1.59)</td>
<td>5.0</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>0.61 (0.48–0.77)</td>
<td></td>
</tr>
</tbody>
</table>
Studies in which some patients received sub-optimal regimens prior to HAART
<table>
<thead>
<tr>
<th>N patients</th>
<th>NEV (N = 155)</th>
<th>EFA (N = 156)</th>
<th>ABA (N = 149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suboptimal Rx+HAART (n=237)</td>
<td>5</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Only HAART (n=223)</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total VF</td>
<td>8</td>
<td>5</td>
<td>16</td>
</tr>
</tbody>
</table>

Martinez et al., NEJM 2003;349:1036-46
SMT Study Design

Initial mono/dual NRTI (46%)

PI-containing HAART

HIV-1 RNA undetectable ≥ 6 months induced by PI-containing HAART

Randomize

At screening:
- negative for 215 ZDV resistance mutation (PBMC DNA)
- <50 HIV-1 RNA copies/ml

Switch to ABC + COM (Trizivir > Mar 2000)

Continue

Opravil et al., JID 2002;185:1251-60
SMT: Time to virologic failure (ITT analysis)

Proportion not failing vs Weeks

N (cont.): 79 79 77 73 68 45 34 25 22 10 3
N (simpl.): 84 80 75 74 71 53 38 24 16 8 3

P = 0.061
logrank test

Opravil et al., JID 2002;185:1251-60
Treatment failure vs. virologic failure

Change of treatment due to AE or preference

• Today many options
• May even be desirable if it improves adherence

Virologic failure

• More severe because resistance possible: decreases future treatment options
SMT: Time to virologic failure (ITT analysis)
Pre-treatment with ZDV before HAART predicts virologic failure

Opravil et al., JID 2002;185:1251-60
**SMT: original study + extended follow-up**

- **Initial mono/dual NRTI (46%)**
  - **PI-containing HAART**
    - HIV-1 RNA undetectable ≥ 6 months induced by PI-containing HAART
    - Randomize
      - At screening:
        - negative for 215 ZDV resistance mutation (PBMC DNA)
        - <50 HIV-1 RNA copies/ml
      - Switch to ABC + COM (Trizivir > Mar 2000)
    - Continue
  - End of randomized comparison
    - **Trizivir Extended Follow-up**
SMT study: long-term efficacy

Propotion of patients without virologic failure

Time after switch (years)

# at risk: 51 25 44 14 44 14 24 10 24 10

Incidence of virologic failure:
- 3.4/100 PY (N = 53)
- 13.5/100 PY (N = 31)

(P = 0.008)

Opravil et al., AIDS 2004 in print
Virologic failure among all 81 patients without prior ZDV mono/dual therapy who switched from PI-regimens to Trizivir: 2.45/100 PY (95% Poisson CI: 0.90 – 5.33/100 PY)
Subjects with a history of mainly HAART from initiation of therapy
TRIZAL: Proportion of Subjects with Plasma HIV-1 RNA < 50c/ml at Week 48

Percentage of Subjects

Study Week

Trizivir (AT)
Continued HAART (AT)
Trizivir (ITT)
Continued HAART (ITT)

Katlama C et al. HIV Medicine 2003;4:79-86
Switch Maintenance Therapy (Maggiolo)  
Virological Failures over 104 Weeks  

No significant differences across the 3 study arms

Maggiolo F et al. CID 2003;37:41-49
Switch studies (PI → ABC), compared to continued PI

<table>
<thead>
<tr>
<th>Study</th>
<th>PI arm</th>
<th>ABC arm</th>
<th>Virologic failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&quot;Optimal&quot; patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clumeck (CNA30017)</td>
<td>1.9% of 103</td>
<td>3.8% of 104</td>
<td>2.9%</td>
</tr>
<tr>
<td>direct start of HAART</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Katlama (Trizal)</td>
<td>1.0% of 103</td>
<td>4.7% of 106</td>
<td>1.9%</td>
</tr>
<tr>
<td>direct start of HAART</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maggiolo</td>
<td>5.7% of 70</td>
<td>10.1% of 69</td>
<td>0%</td>
</tr>
<tr>
<td>direct start of HAART</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pre-treated patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opravil (SMT)</td>
<td>6.4% of 79</td>
<td>15.5% of 84</td>
<td>8.2%</td>
</tr>
<tr>
<td>direct start of HAART</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martinez</td>
<td>n.a.</td>
<td>10.7% of 149</td>
<td>2.5%</td>
</tr>
<tr>
<td>direct start of HAART</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial</td>
<td>Switch to</td>
<td>Chol.</td>
<td>Triglyc.</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------</td>
<td>-------</td>
<td>----------</td>
</tr>
<tr>
<td>Opravil JID 02</td>
<td>Trizivir</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Clumeck AIDS 01</td>
<td>ABC</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Katlama: Trizal</td>
<td>Trizivir</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Maggiolo CID 03</td>
<td>ABC</td>
<td>↓</td>
<td>⇒</td>
</tr>
<tr>
<td></td>
<td>EFV</td>
<td>↑</td>
<td>⇒</td>
</tr>
<tr>
<td>Ruiz JAIDS 01</td>
<td>NVP</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Barreiro AIDS 00</td>
<td>NVP</td>
<td>⇒</td>
<td>⇒</td>
</tr>
<tr>
<td>Negredo CID 02</td>
<td>NVP</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>EFV</td>
<td>⇒</td>
<td>⇒</td>
</tr>
<tr>
<td>DMP266-049</td>
<td>EFV</td>
<td>⇒</td>
<td>⇒</td>
</tr>
<tr>
<td>DMP266-027</td>
<td>EFV</td>
<td>⇒</td>
<td>⇒</td>
</tr>
<tr>
<td>Martinez CROI 01</td>
<td>EFV</td>
<td>⇒</td>
<td>⇒</td>
</tr>
<tr>
<td>Martinez NEJM 03</td>
<td>ABC</td>
<td>↓</td>
<td>⇒</td>
</tr>
<tr>
<td></td>
<td>NVP</td>
<td>⇒</td>
<td>⇒</td>
</tr>
<tr>
<td></td>
<td>EFV</td>
<td>⇒</td>
<td>⇒</td>
</tr>
</tbody>
</table>
A baseline, une grande proportion de patients affirme prendre toutes les doses des molécules de l’étude ou oublie moins de 1 dose par semaine.

ABC: 90/101 (89%) ; PI: 77/93 (83%)

A la semaine 48, cette proportion a augmenté dans le bras ABC et diminué dans le bras IP

ABC: 86/94 (91%) ; PI: 72/95 (76%)
Conclusions for simplified therapy with ABC or NNRTI

Treatment efficacy against HIV infection:

- documented for patients with $\geq 6$ months of suppressed VL on PI-based HAART
- if treatment started as HAART and no virologic failure: switch to Trizivir (ABC) and NNRTI equally effective
- if NRTI mono/dual therapy prior to HAART: switch to NNRTI usually works
- switch to Trizivir (ABC) has high virological failure rate
- no $\Delta$ in immunology between PI continuation and simplification
- no $\Delta$ in VL in lymphoid tissue shown for both abacavir and efavirenz
- if virologic failure: salvage therapy with PI still works
Conclusions for simplified therapy with ABC or NNRTI

**Patients’ benefit:**

- less treatment changes due to AE / intolerance shown for most switch strategies in comparison to PI continuation
- improved adherence and patient satisfaction shown for all switch strategies
- effect on cholesterol and triglycerides:
  - consistently ↓ only after switch to abacavir
  - variable after switch to nevirapine
  - not significantly lower after switch to efavirenz
- effect on lipodystrophy not finally resolved: both fat accumulation and lipoatrophy may reverse, but effects variable between patients and studies
Who may simplify their HAART to Trizivir?

Simplification to Trizivir:

- Well documented regimen, but not for everybody
- Effective in absence of archived NRTI resistance mutations (in pts. who started directly with HAART)
- Spares all other classes for the future
- Best of all simplification strategies for blood lipids
- No CYP interactions

Data not applicable to other triple NRTI regimens

→ individualized assessment in treatment simplification:
  consider treatment history, cardiovascular risk, and CYP !
→ good adherence always important !
Triple NRTI regimens that don't work

**Simplification**
Retrospective analysis of 8 pts
- RNA <50 c./ml during median 8 months (7.5 - 18)
- all had started with mainly PI-containing HAART
after switch to ABC + 3TC + TDF:
63% (5/8) failed virologically,
emergence of 184V and 65R mutations

Hoogewerf et al., Lancet 2003;362:1979

⇒ if simplification to ABC:
inclusion of ZDV or d4T seems important
Triple NRTI regimens that don't work

**Start of therapy in naive patients**

- d4T + ddI + ABC [Gerstoft AIDS 03]
- d4T + ddI + 3TC [CLASS, ATLANTIC]
- TDF + 3TC + ABC [Gallant ICAAC 03, COL40263, TONUS Landman CROI 04]
- TDF + 3TC + ddI [Jemsek CROI 04]

- in all of them, higher rates of virological failure than in Trizivir studies
  - ⇒ caution if used for simplification
- emergence of 184V and/or 65R mutations

Trizivir [ACTG5095] – differentiate between treatment start and simplification