A Randomised, Open-Label Comparative Trial of Abacavir or Tenofovir DF as Replacement for a Thymidine Analogue in Persons with Lipoatrophy and Suppressed HIV RNA on HAART

The RAVE Study

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12th Conference on Retroviruses and Opportunistic Infections, Boston USA
23rd February 2005
RAVE
Rationale

- Thymidine analogue therapy is associated with peripheral fat loss and lipoatrophy
- Treatment modification of thymidine analogue to abacavir is associated with gradual recovery of peripheral fat
- Neither Abacavir nor Tenofovir DF have been convincingly associated with peripheral fat loss in prospective studies in treatment naïve persons
ACTG 384
Median Percent Change in Limb Fat From Baseline by NRTI Assignment

Dubé MP, et al. 4th IWADRLH;2002; San Diego, Calif. Abstract 27.
Thymidine analogue therapy is associated with peripheral fat loss and lipoatrophy.

Treatment modification of thymidine analogue to abacavir is associated with gradual recovery of peripheral fat.

Neither Abacavir nor Tenofovir DF have been convincingly associated with peripheral fat loss in prospective studies in treatment naïve persons.
MITOX
Limb Fat Over 18 Months

(mean change; kg)

1.5
1.0
0.5
0.0

12
24
36
48
60
72
weeks

N
ABC 47 42 35 33
ABC Week 24 23 19 15 13
d4T/AZT 29 25 22 19

1.29 kg (36%)
0.55 kg (15%)
0.16 kg (4%)

Martin AIDS 2004
RAVE
Rationale

- Thymidine analogue therapy is associated with peripheral fat loss and lipoatrophy
- Treatment modification of thymidine analogue to abacavir is associated with gradual recovery of peripheral fat
- Neither Abacavir nor Tenofovir DF have been convincingly associated with peripheral fat loss in prospective studies in treatment naïve persons
FIRST
Rates of Change of Skinfold Fat Area

Mid-arm (cm^2)

<table>
<thead>
<tr>
<th>Change (cm^2/month)</th>
<th>SE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ddl+d4T</td>
<td>-0.22</td>
<td>0.04</td>
</tr>
<tr>
<td>ABC+3TC</td>
<td>0.03</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Mid-thigh (cm^2)

<table>
<thead>
<tr>
<th>Change (cm^2/month)</th>
<th>SE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ddl+d4T</td>
<td>-0.35</td>
<td>0.08</td>
</tr>
<tr>
<td>ABC+3TC</td>
<td>-0.02</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Shlay JAIDS 2005
Study 903
Mean (95% CI) Total Limb Fat at Weeks 96 and 144

Gallant JE. XV Int AIDS Conf, July 2004, Bangkok, #4538
RAVE Design

Thymidine analogue recipients
(n = 105)
randomised 1:1

<table>
<thead>
<tr>
<th>TDF</th>
<th>QD</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ NRTI</td>
<td></td>
</tr>
<tr>
<td>+ PI, PI/r or NNRTI</td>
<td></td>
</tr>
</tbody>
</table>

48 wks

Moderate-Severe Lipoatrophy
Any CD4 cell count
HIV RNA <50 c/mL
Stable ARV Therapy for >24 weeks

<table>
<thead>
<tr>
<th>ABC</th>
<th>BD</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ NRTI</td>
<td></td>
</tr>
<tr>
<td>+ PI, PI/r or NNRTI</td>
<td></td>
</tr>
</tbody>
</table>

48 wks

No history of TDF or ABC use or resistance
Adequate Renal and Hepatic Function at baseline
RAVE
Statistical considerations

- Primary endpoint: Change in total limb fat mass (by DEXA) over 48 weeks
- 80% power to detect (5% significance level) a 0.5kg difference in primary endpoint
- Secondary endpoints: Changes in lipid measurements, VAT (from CT), CD4 count, HIV RNA, BMD and body fat over 48 weeks; incidence of clinical events
- Analyses performed using intention-to-treat approach; missing values imputed using LOCF
### RAVE

#### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>TDF (n=52)</th>
<th>ABC (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>White race:</strong></td>
<td>94%</td>
<td>87%</td>
</tr>
<tr>
<td><strong>Median age (years):</strong></td>
<td>42</td>
<td>43</td>
</tr>
<tr>
<td><strong>Nadir CD4 (median, IQR):</strong></td>
<td>114 (0, 818)</td>
<td>154 (2, 783)</td>
</tr>
<tr>
<td><strong>Current CD4 (median, IQR):</strong></td>
<td>522 (314, 724)</td>
<td>478 (340, 653)</td>
</tr>
<tr>
<td><strong>Years on ART (median, IQR):</strong></td>
<td>5.7 (0.8, 11.5)</td>
<td>4.9 (0.8, 8.1)</td>
</tr>
<tr>
<td><strong>Current PI-sparing regimen</strong></td>
<td>63%</td>
<td>74%</td>
</tr>
<tr>
<td><strong>Current thymidine analogue:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d4T</td>
<td>77%</td>
<td>59%</td>
</tr>
<tr>
<td>AZT</td>
<td>23%</td>
<td>41%</td>
</tr>
</tbody>
</table>
## RAVE Baseline Median Body Composition

<table>
<thead>
<tr>
<th></th>
<th>TDF (n=52)</th>
<th>ABC (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Body Fat (kg)</td>
<td>11.1</td>
<td>10.6</td>
</tr>
<tr>
<td>Total Limb Fat (kg)</td>
<td>3.0</td>
<td>2.9</td>
</tr>
<tr>
<td>Trunk Fat (kg)</td>
<td>7.1</td>
<td>6.8</td>
</tr>
<tr>
<td>VAT (cm³)</td>
<td>150</td>
<td>148</td>
</tr>
<tr>
<td>SAT (cm³)</td>
<td>87</td>
<td>81</td>
</tr>
<tr>
<td>TAT (cm³)</td>
<td>237</td>
<td>241</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74</td>
<td>72</td>
</tr>
</tbody>
</table>
# RAVE Baseline Median Metabolics

<table>
<thead>
<tr>
<th></th>
<th>TDF (n=52)</th>
<th>ABC (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol (mmol/l)</td>
<td>5.6</td>
<td>5.3</td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>LDL-C (mmol/l)</td>
<td>3.3</td>
<td>3.0</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>2.0</td>
<td>1.7</td>
</tr>
<tr>
<td>Insulin (IU/l)</td>
<td>8.8</td>
<td>7.2</td>
</tr>
<tr>
<td>Fasting Glucose (mmol/l)</td>
<td>5.1</td>
<td>5.2</td>
</tr>
<tr>
<td>Lactate (mmol/l)</td>
<td>1.5</td>
<td>1.3</td>
</tr>
</tbody>
</table>
### RAVE

**Patient Disposition through Week 48**

<table>
<thead>
<tr>
<th>N (%) discontinued study</th>
<th>TDF (n=52)</th>
<th>ABC (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3 (6%)</td>
<td>8 (15%)</td>
</tr>
<tr>
<td>- Lost to follow-up</td>
<td>-</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>- Patient withdrew consent</td>
<td>1 (2%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>- Protocol violation</td>
<td>-</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>- Adverse event</td>
<td>1 (2%)</td>
<td>3 (6%)*</td>
</tr>
<tr>
<td>- Other</td>
<td>1 (2%)</td>
<td>-</td>
</tr>
</tbody>
</table>

| Median time to discontinuation (weeks, range) | 36 (4, 39) | 19 (1.6, 40) |

* All discontinuations due to adverse events in ABC group were due to hypersensitivity reaction, TDF related discontinuation was secondary to diarrhoea.
RAVE

Median Change in Limb Fat
DEXA arm fat + total leg fat in grams (ITT m=f analysis)

Median Baseline Limb Fat  
TDF 3.0kg, ABC 2.9kg

Baseline  Week 24  Week 48

Limb fat (grams)

TDF (n=52)  ABC (n=52)

199  198  393
p=0.97

316

Moyle 12th CROI 2005: 44LB
Within group change in Limb Fat from baseline TDF $p=0.01$, ABC $p=0.001$
RAVE
Median changes at week 48 in Limb Fat by DEXA by baseline characteristics

Median Baseline Limb Fat

<table>
<thead>
<tr>
<th></th>
<th>TDF</th>
<th>ABC</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0kg</td>
<td>393</td>
<td>316</td>
</tr>
<tr>
<td>5.12kg</td>
<td>66</td>
<td>210</td>
</tr>
<tr>
<td>2.91kg</td>
<td>529</td>
<td>357</td>
</tr>
<tr>
<td>2.74kg</td>
<td>374</td>
<td>363</td>
</tr>
<tr>
<td>3.91kg</td>
<td>432</td>
<td>247</td>
</tr>
</tbody>
</table>

p=0.97

Moyle 12th CROI 2005: 44LB
RAVE
Median Changes in abdominal fat by CT

![Bar chart showing median changes in abdominal fat by CT for VAT, SAT, and TAT compared to ABC and TDF conditions.](Moyle 12th CROI 2005: 44LB)
RAVE
Median Change in Metabolic Outcomes to Week 48

*P values by Mann-Whitney U test

Lactate
-0.3

Total Cholesterol
-0.2

HDL Cholesterol
-0.01

LDL Cholesterol
-0.1

Triglycerides

P=0.27

P=0.016

P=0.043

P=0.043

P=0.031

All data LOCF

All individuals included. Lipid lowering therapy commenced during study for TDF n=1, at 273 days, ABC n=8, at median 91.5 days.

Includes fasting and non-fasting samples. Observations are similar when only fasting samples are included.
RAVE
Median Fasting Cholesterol (mmol/l)

Fasting Cholesterol (mmol/l)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 36</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDF</td>
<td>5.5</td>
<td>5.3</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
<td>5.4</td>
</tr>
<tr>
<td>ABC</td>
<td>5.7</td>
<td>5.7</td>
<td>5.7</td>
<td>5.7</td>
<td>5.7</td>
<td>5.7</td>
</tr>
</tbody>
</table>

Change from baseline
TDF: +0.22 mmol/l
ABC: -0.49 mmol/l

P=0.39

All data LOCF
All individuals included. Lipid lowering therapy commenced during study for TDF n=1, at 273 days, ABC n=8, at median 91.5 days
Includes fasting and non-fasting samples. Observations are similar when only fasting samples are included.

Moyle 12th CROI 2005: 44LB
RAVE
Median Change in Haemoglobin and Absolute Creatinine to Week 48

*P values by Mann-Whitney U test

Moyle 12th CROI 2005: 44LB
RAVE
Changes in Bone Mineral Density and proportion with osteopenia by T-score by DEXA to Week 48

*P values by Mann-Whitney U test all greater than 0.05

*P values by Mann-Whitney U test all greater than 0.05

Moyle 12th CROI 2005: 44LB
RAVE
% Patients <50 Copies/mL

Number with 2 consecutive value >200 copies/ml: TDF 0, ABC 1

Moyle 12th CROI 2005: 44LB
RAVE
Median CD4 counts to week 48

TDF (n=52)  
ABC (n=53)

Baseline Week 4 Week 12 Week 24 Week 36 Week 48

Change from baseline (LOCF)

CD4 Cell count (cells/mm³)

0 100 200 300 400 500 600

Baseline  Week 4  Week 12  Week 24  Week 36  Week 48

521  529  590

465  529  590

P=0.51

Moyle 12th CROI 2005: 44LB
RAVE

Summary

- TDF and ABC similarly allow restoration of limb and SAT over 48 weeks when switching from thymidine analogues in persons with lipoatrophy
- CD4 and control of HIV RNA were similar across arms
- Lipid changes favoured the TDF arm. Fewer TDF patients initiated lipid lowering therapy
- Rates of discontinuation were higher in the ABC group, in part due to HSR
- No effects on BMD were observed
Acknowledgements

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♦ Maurice Murphy
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♦ Clifford Leen
♦ Geraldine Reilly
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