EFFECTS OF METFORMIN AND ROSIGLITAZONE ON BODY COMPOSITION IN HIV-INFECTED PATIENTS WITH HYPERINSULINEMIA AND ELEVATED WAIST/HIP RATIO: A RANDOMIZED, PLACEBO-CONTROLLED TRIAL (ACTG 5082)

K Mulligan, Y Yang, S Koletar, D Wininger, R Parker, B Alston-Smith, M Basar, S Grinspoon for the A5082 Team
Insulin resistance is a central feature of metabolic complications in HIV and a significant independent risk factor for cardiovascular disease.

Excess visceral fat can contribute to insulin resistance and CVD risk.
ORAL INSULIN SENSITIZING AGENTS

Thiazolidinediones

♦ Troglitazone in HIV-negative: ↑↓ visceral fat (VAT) and ↑ subcutaneous fat (SAT) in 4 studies in subjects with lipodystrophy and/or diabetes

♦ Rosiglitazone, pioglitazone in HIV+ subjects with lipoatrophy:
  • 2 studies: No effect of rosi on VAT or SAT
  • ↑ SAT in 3 studies of rosi and 1 of pio

Metformin in HIV

♦ ↓ VAT, SAT, total fat, waist circumference, weight

Metformin + thiazolidinedione in HIV:

♦ Not studied; potential for interaction

ACTG 5082

Weeks 0-16

- Metformin 1000 mg BID* + Rosiglitazone Placebo (Met/P; N=26)
- Rosiglitazone 4 mg/d + Metformin Placebo (Rosi/P; N=27)
- Metformin 1000 mg BID* + Rosiglitazone 4 mg/d (Met/Rosi; N=25)
- Metformin Placebo + Rosiglitazone Placebo (P/P; N=27)

*Metformin dose for first 2 weeks was 500 mg BID, then escalated to 1000 BID for the remainder of the study period
KEY ELIGIBILITY CRITERIA

- Self-report of increased central fat plus:
  - Waist:hip ratio >0.95 (men) or >0.85 (women) OR
  - Abdominal circumference > 100 cm
- Evidence of insulin resistance or impaired glucose tolerance:
  - Fasting insulin $\geq 15$ µIU/ml OR
  - 2-hour insulin $\geq 75$ µIU/ml after 75 g glucose load OR
  - Fasting insulin $\geq 10$ µIU/ml & 2-h glucose $>140$ mg/dL
- Stable ART and no plans to change ART
- Lactate, LFTs, kidney function within acceptable limits
- Patients with diabetes were excluded
Primary endpoints: change from baseline to week 16:
- Insulin sensitivity:
  - 120 minute insulin AUC (75 g OGTT)
  - Fasting insulin
- Abdominal visceral and subcutaneous fat (CT)
- Safety

Key secondary endpoints (changes):
- Central and peripheral fat (DEXA)
- Lipids
- Glucose
- Adiponectin

ITT analyses; data are medians unless otherwise indicated
# BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Met/P</th>
<th>Rosi/P</th>
<th>Met/Rosi</th>
<th>P/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>105</td>
<td>26</td>
<td>27</td>
<td>25</td>
<td>27</td>
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<tr>
<td>% Male</td>
<td>66</td>
<td>65</td>
<td>67</td>
<td>68</td>
<td>63</td>
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<tr>
<td>% Female</td>
<td>34</td>
<td>35</td>
<td>33</td>
<td>32</td>
<td>37</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% White</td>
<td>64</td>
<td>61</td>
<td>56</td>
<td>68</td>
<td>70</td>
</tr>
<tr>
<td>% Black</td>
<td>27</td>
<td>31</td>
<td>30</td>
<td>24</td>
<td>22</td>
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<tr>
<td>% Hispanic</td>
<td>9</td>
<td>8</td>
<td>15</td>
<td>8</td>
<td>7</td>
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<tr>
<td>Age (years)</td>
<td>45</td>
<td>44</td>
<td>45</td>
<td>48</td>
<td>44</td>
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<tr>
<td>CD4 (/µL)</td>
<td>567</td>
<td>551</td>
<td>573</td>
<td>494</td>
<td>665</td>
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<tr>
<td>HIV RNA &lt;400 (%)</td>
<td>67</td>
<td>54</td>
<td>63</td>
<td>72</td>
<td>78</td>
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</table>

*No statistically significant differences among groups (Kruskal-Wallis test)*
## BASELINE ANTIRETROVIRALS

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Met/P</th>
<th>Rosi/P</th>
<th>Met/Rosi</th>
<th>P/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI (%)</td>
<td>96</td>
<td>100</td>
<td>96</td>
<td>100</td>
<td>89</td>
</tr>
<tr>
<td>PI (%)</td>
<td>65</td>
<td>65</td>
<td>77</td>
<td>64</td>
<td>56</td>
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<tr>
<td>NNRTI (%)</td>
<td>43</td>
<td>35</td>
<td>42</td>
<td>40</td>
<td>56</td>
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*No statistically significant differences among groups (Fisher’s exact test)*
<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Met/P</th>
<th>Rosi/P</th>
<th>Met/Rosi</th>
<th>P/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>27.6</td>
<td>27.3</td>
<td>28.6</td>
<td>28.2</td>
<td>27.2</td>
</tr>
<tr>
<td>Waist/hip (M)</td>
<td>1.01</td>
<td>1.04</td>
<td>1.04</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>Waist/hip (F)</td>
<td>0.99</td>
<td>1.00</td>
<td>0.99</td>
<td>0.92</td>
<td>1.01</td>
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<tr>
<td>Waist circ (cm)</td>
<td>99</td>
<td>99</td>
<td>101</td>
<td>103</td>
<td>98</td>
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<tr>
<td>Trunk fat (kg)</td>
<td>12.5</td>
<td>12.6</td>
<td>13.8</td>
<td>11.8</td>
<td>12.4</td>
</tr>
<tr>
<td>Leg fat (kg)</td>
<td>3.8</td>
<td>4.4</td>
<td>4.6</td>
<td>3.4</td>
<td>3.4</td>
</tr>
<tr>
<td>VAT (cm²)</td>
<td>173</td>
<td>177</td>
<td>172</td>
<td>173</td>
<td>173</td>
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<tr>
<td>SAT (cm²)</td>
<td>218</td>
<td>254</td>
<td>208</td>
<td>245</td>
<td>213</td>
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<tr>
<td>Insulin (µIU/mL)</td>
<td>16</td>
<td>16</td>
<td>17</td>
<td>16</td>
<td>16</td>
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<tr>
<td>Insulin AUC</td>
<td>88</td>
<td>86</td>
<td>92</td>
<td>82</td>
<td>91</td>
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<tr>
<td>Fasting glucose (mg/dL)</td>
<td>96</td>
<td>96</td>
<td>93</td>
<td>93</td>
<td>99</td>
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</table>

No statistically significant differences among groups (Kruskal-Wallis test)
SAFETY (I)
Adverse Events on Study

- Hyperlactatemia: no significant differences among groups; most elevations 1.5-2.0 X ULN
- Diarrhea: more frequent in both metformin groups (P<0.001 and =0.007 for Met/P and Met/Rosi vs. placebo)
- Vomiting: more frequent with combined therapy (P=0.023 vs. placebo)
- No significant differences in any LFT, creatinine, Hgb, nausea, HIV RNA
**SAFETY (II)**

Premature discontinuation of study medication

<table>
<thead>
<tr>
<th>Condition</th>
<th>Met/P</th>
<th>Rosi/P</th>
<th>Met/Rosi</th>
<th>P/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total discontinued</td>
<td>12/26</td>
<td>3/27</td>
<td>4/25</td>
<td>8/27</td>
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<tr>
<td>↑ lactate</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>diarrhea</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>subject request</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>&gt;1 toxicity</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>clinician request</td>
<td>1</td>
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<tr>
<td>weight change</td>
<td>1</td>
<td>0</td>
<td>0</td>
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</table>
CHANGES IN INSULIN AUC AND FASTING INSULIN

Insulin AUC

<table>
<thead>
<tr>
<th>Condition</th>
<th>Change (µIU/mL)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met/P</td>
<td>-6</td>
<td></td>
</tr>
<tr>
<td>Rosi/P</td>
<td>-4</td>
<td></td>
</tr>
<tr>
<td>Met/Rosi</td>
<td>-2</td>
<td></td>
</tr>
<tr>
<td>P/P</td>
<td>0</td>
<td></td>
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</tbody>
</table>

Fasting Insulin

<table>
<thead>
<tr>
<th>Condition</th>
<th>Change (µIU/mL)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met/P</td>
<td>-15</td>
<td></td>
</tr>
<tr>
<td>Rosi/P</td>
<td>-10</td>
<td></td>
</tr>
<tr>
<td>Met/Rosi</td>
<td>-5</td>
<td></td>
</tr>
<tr>
<td>P/P</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

P-values in boxes denote significance of within-group changes (Wilcoxon signed rank test). Between-group differences evaluated by Wilcoxon rank sum test.
CHANGES IN VISCERAL AND SUBCUTANEOUS ABDOMINAL FAT

No statistically significant differences within or between groups (Wilcoxon signed rank and rank sum tests)
DEXA: Leg fat changed significantly in Rosi/P, compared with placebo. No significant within or between group changes in arm or combined limb fat.

Weight decreased in both metformin groups compared to placebo (P=.029 and .056 for Met/P and Met/Rosi, respectively).

Wilcoxon signed rank test (within-group changes); Wilcoxon rank sum test (between-group differences)
CHANGES IN LIPIDS

Triglycerides
No statistically significant changes

Total cholesterol
No statistically significant changes

LDL cholesterol (direct)

HDL cholesterol

P-values in boxes denote significance of within-group changes (Wilcoxon signed rank test). Between-group differences evaluated by Wilcoxon rank sum test.
**OTHER BIOCHEMICAL RESULTS**

- Adiponectin increased significantly in both rosiglitazone groups
- No significant changes in fasting or 2-h glucose or glucose AUC

*P-values in boxes denote significance of within-group changes (Wilcoxon signed rank test). Between-group differences evaluated by Wilcoxon rank sum test*
SUMMARY (I)

- Both metformin and rosiglitazone, alone and in combination, decreased insulin AUC compared with baseline; the improvement in the combination arm was significant vs. placebo.

- Neither metformin nor rosiglitazone, alone or in combination, significantly decreased visceral fat.

- Leg fat increased and subcutaneous fat tended to increase with rosiglitazone, providing additional evidence that rosiglitazone may increase subcutaneous fat in some individuals.
Rosiglitazone alone adversely affected lipids, but no such effect was seen when rosiglitazone was given in combination with metformin.

Rosiglitazone alone and combined with metformin increased adiponectin.

The power to detect significant changes in the metformin/placebo group may have been limited by a relatively high dropout rate.
A5082 STUDY TEAM AND AACTG SUPPORT

- **A5082 team**
  - Steven Grinspoon
  - Kathleen Mulligan
  - Susan Koletar
  - David Wininger
  - Beverly Alston-Smith
  - Rebecca Clark
  - Lynette Purdue
  - Joan Dragavon
  - Jeffrey Murray
  - Susie McCarthy
  - Carol Greisberger
  - Holly Boyd

- **SDAC**
  - Yang Yang
  - Robert Parker
  - Doug Kitch
  - Robert Zackin

- **Data Management Center**
  - Michael Basar
  - Heather Sprenger

- **Ops Center**
  - Laura Mahon
  - Marilyn Foutes
  - Jessica Hass

- **CCG Reps**
  - James Weihe
  - Harry Wingfield
  - George Bishopric

- **Tufts Image Reading Center**
  - Abby Shevitz
  - Jodi Weiner
  - Roger Fielding

- **Quest Diagnostics**
  - William A. Meyer III

- **Complications RAC**

- **NIAID**

- **Pharmaceutical Support:**
  - Bristol-Myers Squibb
  - GlaxoSmithKline

**All the subjects and sites**

*In memoriam: Robert Zackin, Laura Mahon, Abby Shevitz*
• Abstract categories
  – Adipocyte biology
  – Cardiovascular disease
  – Mitochondrial disorders
  – Clinical management of ADRs
  – Other toxicities
  – Body composition
  – Hepatotoxicity
  – Lipid metabolism
  – Insulin resistance

For further details, please visit:
www.intmedpress.com/lipodystrophy