UK-CAB

lunch.... Bella Restaurant

MRC

Bella

Euston

Euston Road
Mexico feedback:
17th Intl AIDS Conference, Aug08

24 October 2008
Simon Collins
www.i-Base.info
Conference stats

- ~ 4500 studies
- 25,000 delegates
- Good web coverage:
  - abstracts, powerpoint slides, webcasts, transcriptions, summary reports etc
- www.aids2008.org
Main issues

- all ‘community-related’
- new drugs
- abacavir, heart disease
- abacavir & high viral load
- prevention: ARVs and viral load
- nelfinavir contamination
- other studies
ʻcommunity-relatedʻ

- Emphasis on track C, D, E
- Epidemiology, prevention, policy
- Community involvement ‘village’
- HIV-positive speakers
- Issues for marginalised people (women, children, gender-based violence, IDUs, MSM etc)
New drugs

- raltegravir ‘naïve’
- rilpivirpine ‘naïve’
- apricitabine
- other NNRTIs: IDX899, RDEA806
- paediatric formulations
- non-refrigerated ritonavir
## Rilpivirine side effects

Incidences of rash, nervous system- and psychiatric-related AEs were lower with TMC278 than with EFV

<table>
<thead>
<tr>
<th></th>
<th>TMC278</th>
<th>EFV</th>
</tr>
</thead>
<tbody>
<tr>
<td>rash</td>
<td>9%</td>
<td>21%</td>
</tr>
<tr>
<td>nervous system</td>
<td>31%</td>
<td>48%</td>
</tr>
<tr>
<td>psychiatric-related</td>
<td>16%</td>
<td>21%</td>
</tr>
</tbody>
</table>

Prolonged QT interval with AZT/3TC, lowest in 25mg dose

Lipids slightly better with TMC278
RDEA806 Activity In Vitro Against Common Resistant NNRTI-Resistant Viruses

Moyle et al. Mexico THAB0403
Median Change in Viral Load*

* Viral load reduction censored in 4 patients who reached 50 copies/ml LOQ of assay
**Some patients started on triple therapy prior to follow-up visit

Moyle et al. Mexico THAB0403
## Summary Viral Load Results

<table>
<thead>
<tr>
<th>Median (IQR) Change (log10 copies/mL)</th>
<th>Day 8</th>
<th>Day 8 minus Placebo</th>
<th>Nadir*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.2 (-0.02; 0.03)</td>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td>400 mg BID</td>
<td>-1.8 (-2.1; -1.7)</td>
<td>-1.9</td>
<td>-2.0</td>
</tr>
<tr>
<td>600 mg QD</td>
<td>-1.3 (-1.9; -1.0)</td>
<td>-1.5</td>
<td>-1.8</td>
</tr>
<tr>
<td>800 mg QD</td>
<td>-1.8 (-1.9; -1.2)</td>
<td>-2.0</td>
<td>-1.9</td>
</tr>
<tr>
<td>1000 mg QD</td>
<td>-1.8 (-1.8; -1.4)</td>
<td>-1.9</td>
<td>-1.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percent Patients</th>
<th>≥ 1 log Decrease</th>
<th>&lt; 400 copies/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>400 mg BID</td>
<td>100%</td>
<td>56%</td>
</tr>
<tr>
<td>600 mg QD</td>
<td>78%</td>
<td>33%</td>
</tr>
<tr>
<td>800 mg QD</td>
<td>100%</td>
<td>67%</td>
</tr>
<tr>
<td>1000 mg QD</td>
<td>100%</td>
<td>44%</td>
</tr>
</tbody>
</table>

*Lowest value reached for each patient

Moyle et al. Mexico THAB0403
Abacavir & heart disease

- Background: D:A:D – 3rd cohort
- SMART study
- Summary results
- GSK study
- Underlying risk in high risk patients
- Framingham and CVD risk factors
- Relative vs absolute risk
Hazard ratios for four types of CVD while receiving "ABC (no ddl)" versus using "Other NRTIs"

- CVD, major (n=70)
- Myocardial infarction (n=19)
- CVD, expanded def. (n=112)
- CVD, minor (n=58)

Hazard ratio (95% CI) of CVD

- CVD, major: 1.8
- Myocardial infarction: 12.6
- CVD, expanded def.: 4.3
- CVD, minor: 1.9

Unadjusted vs. Adjusted for CV risk factors

Lundgren et al. Mexico THAB0305
Hazards ratios* for using "ABC (no ddl)" versus using "Other NRTIs" according to CV risk status at study entry

At study entry:

- **> 5 cardiovascular risk factors**
  - Yes
  - No

- **Ischemic abnormalities on ECG**
  - Yes
  - No

Hazard ratio* (95% CI) of CVD (expanded definition)

- Favors ABC
- Favors “Other”

P-value for interaction:
* = 0.1; ** > 0.4

*: Adjusted for CV risk factors
Adjusted mean differences in biomarker levels at study entry for using "ABC (no ddi)" or "ddI (w/wo ABC)" versus using "Other NRTIs"

- **hs-CRP**
  - ABC (no ddi): 25%
  - ddI (w/wo ABC): 0%
  - *: p=0.07
- **IL-6**
  - ABC (no ddi): 15%
  - ddI (w/wo ABC): 5%
  - *: p=0.02
- **Amyloid A**
  - ABC (no ddi): 10%
  - ddI (w/wo ABC): 5%
  - **: p=0.02
- **Amyloid P**
  - ABC (no ddi): 5%
  - ddI (w/wo ABC): 2%
  - For all others: p>0.1
- **D-dimer**
  - ABC (no ddi): 25%
  - ddI (w/wo ABC): 0%
- **F1.2**
  - ABC (no ddi): 10%
  - ddI (w/wo ABC): 5%

Median (IQR) levels in "Others NRTIs"

- hs-CRP: 2.3 (1.0-5.3) µg/mL
- IL-6: 2.2 (1.4-3.7) pg/mL
- Amyloid A: 3.6 (1.9-6.8) mg/mL
- Amyloid P: 65 (51-86) µg/L
- D-dimer: 0.3 (0.2-0.5) µg/mL
- F1.2: 0.4 (0.3-0.5) nmol/L

Lundgren et al. Mexico THAB0305
Abacavir & high VL

- ACTG A5205 (n=1800)
  Kivexa vs Truvada (& ATZ/r vs EFV)
- DSMB summary: higher virological failure with viral load over 100,000c/mL
- HEAT study
- GSK meta analysis
- Guidelines
GSK Conclusions from HEAT and meta-analysis

• Recent A5202 findings:
  – are unexpected
  – different from clinical experience
• A5202 primary efficacy & safety endpoints are unique
• Using A5202 endpoints, analysis of 6 other clinical studies utilizing an ABC/3TC regimen demonstrates robust results irrespective of baseline viral loads
Conclusions (cont.)

- 96 week HEAT data:
  - confirms non-inferiority of ABC/3TC & TDF/FTC
  - both regimens are:
    - well-tolerated
    - comparable safety
    - few study discontinuations due to AEs
  - no increase in hs-CRP and IL-6 from baseline to weeks 48/96 with ABC/3TC or TDF/FTC. No significant differences between the treatment groups

\(^1\)Smith K, et al. 17\(^{th}\) IAC 2008: Poster LBPE1138.
GSK’s A5202 Questions

• Study is still ongoing
• What is the impact of:
  – Baseline resistance
  – Treatment interruptions
  – Adherence data
  – Lipid changes using NCEP guidelines
  – Stratifying by screening VL using local labs
  – Differences in endpoints
Prevention: ARVs!

- **Background:** Swiss statement
  - stable, undetectable > 6 months
  - adherent, no STIs, monogomous
  - condom break, pregnancy, PEP
- **Basis:** viral load drives transmission risk
- **Questions:** anal sex? Risk as continuous vs lower cut-off etc
Nelfinavir contamination

Toxicity risk

Maximum possible EMS exposure

Concentration for EMS toxicity

370 x difference

Exposure concentration
Other studies

- twice-daily PI/r switch to ATZ/r
- T-20 switch to raltegravir
- raltegravir+darunavir+etravirine
- race and gender studies
- the cure: Tony Fauci talk
Thank you…

www.i-Base.info

simon.collins@i-Base.org.uk
TMC278: high response rate and sustained virologic response over 96 weeks similar to EFV

HIV-1 RNA <50 copies/mL to Week 96 (ITT-TLOVR algorithm)

- TMC278 25mg qd (n=93)
- TMC278 75mg qd (n=95)
- TMC278 150mg qd (n=91)
- EFV 600mg qd (n=89)

CI = confidence interval
Time to Virologic Failure
Primary Endpoint, intention-to-treat

ABC/3TC (57 events) vs TDF/FTC (26 events)

Log rank test p-value: 0.0003
HR (95% CI) 2.33 (1.46, 3.72)

Number at Risk
- ABC/3TC: 398, 363, 313, 267, 222, 188, 137, 87, 49
- TDF/FTC: 399, 361, 321, 284, 236, 204, 160, 104, 65

Weeks from Randomization
### Timing and Type of Virologic Failure

<table>
<thead>
<tr>
<th></th>
<th>ABC/3TC (n=398)</th>
<th>TDF/FTC (n=399)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total with Virologic Failure</strong></td>
<td>57 (14%)</td>
<td>26 (7%)</td>
</tr>
<tr>
<td>≥1000 c/mL, &lt;24 weeks, no prior &lt;200 c/mL</td>
<td>19</td>
<td>9</td>
</tr>
<tr>
<td>≥200 c/mL, ≥24 weeks, no prior &lt;200 c/mL</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>≥200 c/mL, ≥24 weeks, prior &lt;200 c/mL</td>
<td>29</td>
<td>15</td>
</tr>
</tbody>
</table>

*Post hoc* analysis: for subjects achieving two <50 c/mL on therapy, no significant difference in risk of virologic rebound (p=0.247)
Time to First Safety Event
As-Treated: While on Initial NRTI

Sax et al. Mexico THAB0303

ABC/3TC (130 events) log rank test p-value: <0.0001
TDF/FTC (78 events) HR (95%CI) 1.89 (1.43,2.50)

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>ABC/3TC</th>
<th>TDF/FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>397</td>
<td>311</td>
<td>258</td>
</tr>
<tr>
<td>299</td>
<td>272</td>
<td>219</td>
</tr>
<tr>
<td>177</td>
<td>148</td>
<td>118</td>
</tr>
<tr>
<td>118</td>
<td>82</td>
<td>49</td>
</tr>
<tr>
<td>49</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

Weeks from Treatment Dispensation
### Grade 3 or 4 Safety Events

#### Selected Events Among Those Reported in ≥5%

<table>
<thead>
<tr>
<th>Safety Events</th>
<th>ABC/3TC</th>
<th>TDF/FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (all events)</td>
<td>130 (33%)</td>
<td>78 (19%)</td>
</tr>
<tr>
<td>Metabolic (lipids)</td>
<td>41 (10%)</td>
<td>11 (3%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>AST</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea/loose stool</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>General body</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aches/pains</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>Itchy/pruritis</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Asthenia</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Headache</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>