NECT FIELD PHASE III B TRIAL: FINAL EFFECTIVENESS RESULTS.
Dr Olaf Valverde Mordt.
Medical Manager

32 ISCTRC conference, Khartoum, 8-12 September 2013
Outline

- Background
- Objectives
- Methods
- Results
- Conclusions
Outline

- Background
- Objectives
- Methods
- Results
- Conclusions
Improved treatment for T.b. gambiense

- Human African trypanosomiasis is lethal without treatment.
- In 2012, over 7000 cases of HAT have been diagnosed in Sub-Saharan Africa, more than 85% in Democratic Republic of Congo.
- Until 2009, only toxic (Melarsoprol) or complex treatments (Eflornithine) were available for neurological infection, 2nd stage T.b.gambiense.
- This led to research and develop a combination treatment, easier to use: Nifurtimox + Eflornithine.
- NECT was introduced in the WHO Essential Medicines List for Adults in 2009 and for Children in 2013.
NECT
Nifurtimox-Eflornithine Combined Therapy

- Clinical trial showed non inferiority to eflornithine treatment (Priotto, Lancet 2009)
- Clear improvement in treatment schedule by adding 10 days oral nifurtimox
  - 14 vs 56 IV infusions
  - 10 vs 14 days
- Ease of logistics
  - 4 treatments in 110 dm³ vs 2 in 170 dm³
- Cost cut by half (554 to 288 Euros per treatment including transport)
NECT FIELD
Implemented by DRC PNLTHA

Kwamouth (n = 98)
Bandundu (n = 98)
Yasa Bonga (n = 62)
Dipumba (n = 146)
Katanda (n = 132)
N’gandajika (n = 94)
NECT Field: Trial objectives

- **Primary objective**
  - Assess the *clinical response* of NECT under field conditions (discharged alive from the hospital*)

- **Secondary objectives:**
  - Assess the incidence and type of *adverse events* (AE), and the capacity of the treatment centers to deal with these
  - Assess the *feasibility* of the implementation of NECT by the health center
  - Assess the *effectiveness* of NECT at 24 months after treatment
Outline

- Background
- Objectives
- Methods
- Results
- Conclusions
NECT Field: Study design

- Multicentre, open-labeled, non-controlled
  - All stage 2 HAT patients (diagnosed according local rules)
    - Pregnant/breastfeeding women, children
    - Other underlying disease, poor health, old age
    - At the decision of investigator or national rules
  - Target sample size: 620 patients
  - DSMB and stopping rule
  - Study duration 12 months (enrolment May 2009 - June 2010)
    - Follow up: for each patient 24 months (6, 12, 18, 24 months)
  - Ethical Clearance by Basel and Kinshasa Ethics Committees
Final Effectiveness analysis

- Main population analysis (Follow-Up)
  - Modified ITT population
    - ITT patients who were not completely lost to follow-up. (i.e. main effectiveness criterion available)

- Main effectiveness criterion
  - The clinical cure rate
    - Survival without clinical and/or parasitological signs of HAT under real-life conditions were assessed at 24 months (22-26 months).

- Safety criteria
  - Serious adverse events and deaths
## Results

<table>
<thead>
<tr>
<th>Patients Characteristics</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients treated (ITT)</strong></td>
<td>629</td>
<td>100</td>
</tr>
<tr>
<td>Completely lost to follow up</td>
<td>16</td>
<td>2.5</td>
</tr>
<tr>
<td><strong>Modified ITT population</strong>*</td>
<td>613</td>
<td>97.5</td>
</tr>
<tr>
<td>Children 0 to 4 years</td>
<td>35</td>
<td>5</td>
</tr>
<tr>
<td>Children 5 to &gt;12 years</td>
<td>65</td>
<td>11</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Breastfeeding women</td>
<td>33</td>
<td>5</td>
</tr>
</tbody>
</table>

* mITT population excludes those without an endpoint (death or relapse) and who missed all follow up visits
Flow Chart of follow up analysis population

Analysis populations

Patients treated* (n=629)

ITT population (n=629)
Intention to treat
(Main population for safety analysis)

PP2 population (n=561)
Per protocol
Endpoint (death / relapse) or
24m FU visit

MITT population (n=613)
Modified ITT (not lost to FU
Main population for effectiveness analysis)

No FU visit at 24m (n=68)

No FU visit at all (n=16)

(N cured=577/613) CLTFU** excluded

*patients having received at least one dose of study medication;

**Complete lost to follow up; FU (Follow up)
Effectiveness Results

- Cure rate at 24 months - mITT population
  - Whole population: 94.13% (577/613), 95% CI = [91.96; 95.85]
  - Sub-populations:
    - Adults: 93.8% (438/467), 95% CI = [91.2; 95.8]
    - Children: 93.9% (93/99), 95% CI = [87.3; 97.7]
    - Breastfeeding and pregnant women: 97.9% (46/47), 95% CI = [88.71; 99.95]

- Similar for adults and children below 12 years
- No variation shown after sensitivity analysis
## Relapses: Age and Time after treatment

<table>
<thead>
<tr>
<th>Type of Relapse</th>
<th>Patients age at NECT treatment</th>
<th>Time of detection after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed</td>
<td>3</td>
<td>1y 6m 12d</td>
</tr>
<tr>
<td>Confirmed</td>
<td>8</td>
<td>2y 0m 11d</td>
</tr>
<tr>
<td>Confirmed</td>
<td>9</td>
<td>6m 14d</td>
</tr>
<tr>
<td>Probable</td>
<td>12</td>
<td>8m 18d</td>
</tr>
<tr>
<td>Confirmed</td>
<td>36</td>
<td>2y 4m 18d</td>
</tr>
<tr>
<td>Probable</td>
<td>41</td>
<td>1y 0m 7d</td>
</tr>
<tr>
<td>Confirmed</td>
<td>56</td>
<td>6m 22d</td>
</tr>
</tbody>
</table>

Confirmed: parasite found.
Probable: WBC raised in CSF, no parasite found.
# Safety Comparison with RCT

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>NECT FIELD</th>
<th>NECT (Priotto 2009)</th>
<th>DFMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>629</td>
<td>143</td>
<td>143</td>
</tr>
<tr>
<td>Average events per patient</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Patients with at least one event</td>
<td>597 (95%)</td>
<td>95%</td>
<td>96%</td>
</tr>
<tr>
<td>Severe adverse events*</td>
<td>77 (12%)</td>
<td>14%</td>
<td>29%</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>61 (10%)</td>
<td>0.7%</td>
<td>4%</td>
</tr>
<tr>
<td>Fatalities**</td>
<td>28 (3.5%)</td>
<td>0.6%</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

### Notes:

* Severity was not monitored during follow up, just passive reports.

**Fatalities include all deaths even unrelated to the treatment or disease.
Prediction of Final Outcome at 6 & 12 months

- Mumba algorithm in two steps at 6 and 12 months [5-50-20]
  - At 6 months
    - Patients with <=5 WBC count in CSF: cured
    - Patients with >=50 WBC count in CSF: relapsed
  - All remaining patients at 12 months
    - (patients with 5 < WBC in CSF < 50)
    - discriminated with a cut-off at 20 WBC count in CSF.
Prediction in NECT Field

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>N</th>
<th>Sensitivity (%)</th>
<th>95% CI</th>
<th>Specificity (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-50-20 A</td>
<td>213</td>
<td>94.4</td>
<td>86-98</td>
<td>97.8</td>
<td>94-100</td>
</tr>
<tr>
<td>5-50-20 B</td>
<td>2190</td>
<td>87.4</td>
<td>85-90</td>
<td>97.7</td>
<td>97-98</td>
</tr>
<tr>
<td>5-50-20 C</td>
<td>437</td>
<td>66.7</td>
<td>22-96</td>
<td>100</td>
<td>99-100</td>
</tr>
</tbody>
</table>

A: reported by Mumba (2010) JID. Algorithm C”: includes deaths as treatment failures and patients with incomplete follow-up. 
B: reported by Priotto et al. (2012) PLoS NTD
C: same algorithm tested in NECT-FIELD cohort
Conclusions

- NECT for treatment of second stage HAT
  - Safe, effective and easy to use in field referral hospital settings
  - Special subgroups (children…) did not show marked differences for both safety and effectiveness
  - Similar results with NECT Randomised Control Trial (2009)
  - This trial supported inclusion in EML for Children 2013
Thanks to

Swiss TPH

Donors:
Department for International Development (DFID) / UNITED KINGDOM
Ministry of Foreign and European Affairs (MAEE) / FRANCE
Republic and Canton of Geneva, Department International Solidarity / SWITZERLAND
Spanish Agency for International Development Cooperation (AECID)/ SPAIN
Swiss Agency for Development and Cooperation (SDC) / SWITZERLAND
Médecins Sans Frontières (Doctors without Borders) / INTERNATIONAL
Medicor Foundation / LIECHTENSTEIN
and others who would like to remain anonymous.