Long Term consequences of planned treatment interruptions in HIV infected children: results from the TICCH (Treatment Interruption in Children with Chronic HIV-Infection) / PENTA 11 trial

A. Compagnucci on behalf of the PENTA Steering Committee
- HIV-1 RNA < 50 c/ml,
- CD4% ≥ 30% (age 2-6) or CD4 ≥ 25% and CD4 ≥ 500 (age 7-15);
- HAART > 6 months (unless changed for toxicity);

**Randomise**

**Continuous HAART**

**Primary Endpoints**
- CD4% < 15% (2-6 yr)
- CD4% < 15% and CD4 < 200/mm³ (7 yr+)
- New CDC stage C diagnosis
- Death

**CD4 guided PTI**
- **STOP HAART** until CD4% < 20% (age 2-6), CD4% < 20% OR CD4 < 350 (age 7+)
  OR after 48 weeks OFF treatment
- **RESTART** same regimen and continue until CD4% ≥ 30% / CD4% ≥ 25% AND CD4 ≥ 500 and HIV-1 RNA < 50 c/ml twice;

AIDS 2010,24:231-241

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
109 children randomised: CT- 53 or PTI -56

Median follow-up 130 (range 33-180) weeks, CT group spent 4% of time off ART, PTI group spent 48%

PRIMARY ENDPOINT

- No child died or had a CDC C event
- 1 (2%) CT vs 4 (7%) PTI children had a CD4 endpoint (p=0.4)
  
  CD4% <15% (2-6yr): 0 vs 3
  CD4% <15% and CD4<200 cells/mm3 (≥7yr): 1 vs 1

AFTER 72 Weeks, CD4% change was greater in PTI group

-0.4% (SE 0.9) in CT vs -5.2 (0.9) in PTI

MORE MINOR CLINICAL EVENTS REPORTED IN PTI GROUP

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LONG TERM FOLLOW-UP (LTFU)

• Annual FU on children in PENTA 11 (5 years)
  – ROUTINE CLINICAL DATA
    • HIV-1 RNA, CD4, ART, AIDS events and death, weight and height, resistance
  – NEUROCOGNITIVE TESTS
    • 3 tests from WISC IV
  – SELF REPORTED ASSESSMENT OF QUALITY OF LIFE
    • carer and child (Pedsql)

• Immunology/virology substudy
LTFU: RESULTS: 101/109 children

- 101/109 children (79 Europe, 22 Thailand)
  - 4 US not in LTFU, 2 lost to follow-up, 2 didn’t consent
- 50 PTI, 51 CT
- 101 completed 1 year FU
- 95 completed 2 years
- Median follow-up from enrolment
  **4.6 years** (range 3.7, 5.0)
### Characteristics at baseline and end of main trial

<table>
<thead>
<tr>
<th></th>
<th>CT (N 51)</th>
<th>PTI (N 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs), median (range)</td>
<td>9.9 (2.2, 15.1)</td>
<td>8.8 (3.5, 15.9)</td>
</tr>
<tr>
<td>Time since started ART years), med (IQR)&quot;</td>
<td>6.6 (3.9, 8.9)</td>
<td>5.6 (3.2, 8.3)</td>
</tr>
<tr>
<td>CD4%, median (IQR)</td>
<td>37% (34, 40%)</td>
<td>37% (33, 42%)</td>
</tr>
<tr>
<td>CD4 count (cells/µl), median (IQR)</td>
<td>968 (739, 1225)</td>
<td>1010 (860, 1280)</td>
</tr>
<tr>
<td>HIV-1 RNA &lt;50 copies/ml</td>
<td>48 (94%)</td>
<td>43 (86%)</td>
</tr>
<tr>
<td>CDC disease stage B / C</td>
<td>13 (25%) / 19 (37%)</td>
<td>16 (32%) / 9 (18%)</td>
</tr>
<tr>
<td>Nadir CD4%, median (IQR)</td>
<td>18% (10%, 27%)</td>
<td>21% (12, 26%)</td>
</tr>
<tr>
<td>Age (yrs), median (range)</td>
<td>12.1 (4.8, 17.9)</td>
<td>11.3 (5.0, 18.7)</td>
</tr>
<tr>
<td>CD4%, median (IQR)</td>
<td>36% (31, 42%)</td>
<td>32% (28, 36%)</td>
</tr>
<tr>
<td>CD4 count (cells/µl), median (IQR)</td>
<td>927 (700, 1140)</td>
<td>792 (595, 1045)</td>
</tr>
<tr>
<td>Proportion HIV-1 RNA &lt;50 copies/ml</td>
<td>76% (39/51)</td>
<td>60% (30/50)</td>
</tr>
</tbody>
</table>

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### Treatment status at end of main trial for children in LTFU

<table>
<thead>
<tr>
<th></th>
<th><strong>PTI arm</strong></th>
<th><strong>N=50</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First PTI</strong></td>
<td></td>
<td></td>
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<tr>
<td>- on first PTI</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>- restarted ART after first PTI</td>
<td>33 (66%)</td>
<td></td>
</tr>
<tr>
<td>- non-protocol TI after first restart</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Second PTI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- on second PTI</td>
<td>5 (10%)</td>
<td></td>
</tr>
<tr>
<td>- restarted ART after second PTI</td>
<td>10 (20%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th><strong>CT arm</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- 1 child off ART</td>
<td></td>
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</tbody>
</table>
Children off treatment at end of main trial

- **PTI arm** (n=7, including 1 child with non-protocol interruption)
  - 5 restarted ART 3 within 3 months of end of main trial
    - 1 at 19 months
    - 1 at 25 months
  - 2 still off ART at last follow-up *(March and April 2010, resp)*

- **CT arm** (n=1)
  - restarted ART 13 months after end of main trial
Clinical outcomes overall follow-up

- NO Death
- NO new CDC stage C event
- Only 1 child had a new CDC stage B event (osteomyelitis, PTI during MAIN Trial)
- Weight-for-age and height-for-age z score: NO difference from baseline, at 1 and 2 years
### Proportion of time spent off ART

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>PTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to end of main trial</td>
<td>4.1%</td>
<td>45.2%</td>
</tr>
<tr>
<td>After end of main trial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- during overall follow-up</td>
<td>1.3%</td>
<td>10.4%</td>
</tr>
<tr>
<td>- excluding FU of children on a PTI at end of main trial before they restarted ART</td>
<td>1.3%</td>
<td>4.7%</td>
</tr>
</tbody>
</table>
Switching ART regimen

Switching 3 drugs for any reasons or 2 drugs for treatment failure (excluding ART used for replacement stopping strategy in PTI arm)

*1 child switched twice, first for simplification following a PTI during main trial, then later due to VL failure after end of main trial

Presented at the 3rd HIV Pediatrics Workshop, 15 - 16 July 2011, Rome, Italy
New drugs never used before prescribed after baseline, by class

NRTI

NNRTI

PI

% of children

0% 20% 40% 60% 80% 100%

CT PTI

CT PTI

CT PTI

P=0.06 comparing arms

P=0.55

P=0.92

# of drugs

≥ 2

1

0

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# Immunological and virological outcomes at 12 and 24 months after end of trial

<table>
<thead>
<tr>
<th></th>
<th>Mean (SE) or proportion</th>
<th>Difference or risk ratio (95% CI) comparing PTI vs CT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CD4%</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>12 m</td>
<td>35.8 (1.0)</td>
<td>-3.5 (-6.3, -0.7)</td>
<td>0.014</td>
</tr>
<tr>
<td>24 m</td>
<td>36.0 (1.1)</td>
<td>-1.6 (-4.5, 1.3)</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>CD4 count (cells/mm³)</strong></td>
<td>925 (45)</td>
<td>-126 (-251, -1)</td>
<td>0.048</td>
</tr>
<tr>
<td>12 m</td>
<td>808 (44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 m</td>
<td>864 (39)</td>
<td>-42 (-149, 65)</td>
<td>0.44</td>
</tr>
<tr>
<td><strong>CD8%</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 m</td>
<td>33.6 (1.3)</td>
<td>3.3 (-0.5, 7.1)</td>
<td>0.085</td>
</tr>
<tr>
<td>24 m</td>
<td>34.1 (1.5)</td>
<td>2.4 (-1.7, 6.5)</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>HIV-1 RNA</strong></td>
<td>90% (44/49)</td>
<td>0.85 (0.71, 1.02)</td>
<td>0.074</td>
</tr>
<tr>
<td>&lt;50 copies/ml</td>
<td>86% (37/43)</td>
<td>0.95 (0.79, 1.14)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

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**Mean CD4 % over time from baseline**

- **CT** 53 51 41 38 26
- **PTI** 56 51 44 38 25

**Mean CD4% over time from end of main trial**

- **CT** 46 48 45 42 47
- **PTI** 40 44 47 42 48
Proportion HIV-1 RNA <50 copies/ml from end of main trial

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Association between nadir CD4 and CD4 recovery in PTI group

Based on measurements since child restarted ART after last PTI

In adjusted analysis, estimated mean difference in CD4% comparing nadir CD4% ≥20% vs <20% = 3.7% (95% 0.7-6.7, p=0.02)

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Total cholesterol

Mean cholesterol over time from baseline

Mean cholesterol over time from end of main trial

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SUMMARY

• NO serious clinical outcomes in overall study

• CD4% continued to increase by 2 years

• Better CD4 recovery after ART re-initiation associated with higher nadir CD4 %

• VL< 50 copies by 2 years from end of trial 86%-CT , 82% PTI

• No difference in exposure to all 3 drug classes

• More switches for « simplification » in PTI arm

• Neurocognitive and immunology sub studies ongoing

• Role of Interruptions in children needs further investigation
We thank all of the children, families, and staff from the centres participating in the PENTA 11 trial

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PENTA 11 Immunology/Virology Group
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