Pharmacokinetic and virological evaluations after stopping NNRTIs in children: a substudy of the PENTA 11 (TI1CH) trial


Background/ Objectives
HAART regimens typically contain drugs with different half-lives. In particular, non-nucleoside reverse transcriptase inhibitors (NNRTIs) and Lamivudine (3TC) have half lives in excess of 26 hours (for 3TC, this relates to its active intracellular diphosphate metabolite), compared to less than 12 hours for some nucleoside reverse transcriptase inhibitors and most nucleoside reverse transcriptase inhibitors (NRTIs).

Currently, there is limited paediatric pharmacokinetic data on how to best stop High Intensity AntiRetroviral Therapy (HAART) for various reasons, whether planned or unplanned.

If all drugs in a HAART regimen are stopped simultaneously, plasma drug concentrations will decay at different rates and there may be reasons, whether planned or unplanned. Whether children will tolerate a regimen that includes a “problematic” agent (NNRTI or 3TC) that has been stopped for a period of time when only one or two drugs persist in the plasma, resulting in an increased risk of selecting drug resistant viruses.

The objective of this study was to assess the pharmacokinetics of agents with long half-lives, such as NNRTIs and lamivudine (3TC) and their association with the development of resistance in the context of planned treatment interruptions.

Methods
Trial design and participants
All children were enrolled in the PedaNet European Network for Treatment of AIDS (PENTA 11 trial). Treatment intervention in children with Chronic HIV-infection: the TI1CH trial.

PENTA 11 is a multicentre, open labelled, randomised, parallel group phase II/exploratory trial evaluating the role of planned treatment interruptions in the management of HIV-infected children who have responded well to antiretroviral therapy.

Children randomised to the planned treatment interruption strategy and taking a regimen that includes a “problematic” agent (NNRTI or 3TC) stop therapy using one of two strategies:

1. Staggered Stop: NNRTI stopped at randomisation and two drugs continued for a further week.
2. Replacement Stop: NNRTI switched to a single or ritonavir-boosted protease inhibitor and three drugs continued for 3-14 days.

Note: In either strategy, “Problematic” 3TC could be either retained or switched at the discretion of the treating physician

Baseline characteristics

- 70 Children have been randomised between 12 Nov 04 and 17 Jan 06
- 13 children had stopped a nevirapine based HAART regimen
- Children had responded well to antiretroviral therapy.
- Children were enrolled from 6 countries: Germany (4 children), Italy (8), Spain (14), Thailand (11), UK (18) and France (7).

Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>(5-14)</td>
</tr>
<tr>
<td>Sex</td>
<td>7 Male, 3 Female</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>White/Black/Asian/Other: 4 / 4 / 3</td>
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<tr>
<td>Dose/kg</td>
<td>11.5 (7.3-14.1)</td>
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<tr>
<td>HIV-1 RNA (copies/ml)</td>
<td>&lt; 50 (&lt;100-700)</td>
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Results reported

- All children tolerated the regimen.
- Children have stopped either a different NNRTI based HAART regimen
- Children were enrolled from 6 countries: Germany (4 children), Italy (8), Spain (14), Thailand (11), UK (18) and France (7).

Viral rebound & Drug Resistance

Virological rebound

- Viral rebound following treatment interruption was similar between stopping strategies. The majority of patients had detectable viremia 4 weeks after treatment interruption.

Conclusion

- These preliminary data suggest that to avoid the development of resistance for virologically suppressed children interrupting a NNRTI based HAART regimen, the adoption of a staggered stop or replacement strategy of:
  - 7 days for children interrupting nevirapine and
  - at least 2 weeks for children interrupting efavirenz may be sufficient to prevent the selection of resistant mutations.

- Additional children are being recruited into the substudy.
- The subsequent response to ARV treatment and possible selection of resistance mutations under drug pressures following a PT is currently under investigation in these children.

The NRTIs in 22 children interrupting lamivudine are currently being evaluated.

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PENTA Immunology/Virology Group:

- C Blanchet, M Clerici, A de Rossi, N Klein, M Muñoz Fernandez, N Ngo, D Pillay, R Sakk, M Clerici, M Zanchetta; Università di Genova, (R Rosso); Ospedale Bambino Gesù, Rome (G Peongjakta, S Chailert).
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HIV-1 Drug Resistance

- NVP: 2 out of 13 children tested had NNRTI resistance (K103N) detected at 4 weeks, however, this child had detectable viral load at interruption (VL=700 c/ml) and the K103N NNRTI resistance mutation was also detect at this time.
- EFV: no NNRTI drug resistance was detected in the 8 children evaluated so far.

Next steps

- Additional children are being recruited into the substudy.
- The subsequent response to ARV treatment and possible selection of resistance mutations under drug pressures following a PT is currently under investigation in these children.

- The NRTIs in 22 children interrupting lamivudine are currently being evaluated.