ISRCTN36694210

MOPE0206

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

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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 20 hours (for 3TC, this relates to its active intracellular drug triphosphate moiety), compared to less than 12 hours for protease inhibitors (PIs) and most nucleoside reverse transcriptase inhibitors (NRTIs).

Currently, there is limited paediatric pharmacokinetic data on how to best stop Highly Active 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 a period of time when only one or two drugs persist in the plasma, resulting in an increased risk of selecting drug resistant viruses [Arnedo-Valero, CID 2005; 2005] and subsequent treatment failure

The objective of this study was to assess the pharmacokinetics of agents with long half-lives, such as NNRTIs inhibitors 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 Paediatric European Network for Treatment of AIDS (PENTA) 11 trial: Treatment Interruption in Children with Chronic HIV-Infection: the TICCH trial.

PENTA 11 is a multicentre, open, randomised, concurrent, parallel group phase II exploratory trial evaluating the role of planned treatment interruptions (PTIs) 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 7-14 days.

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

NNRTI plasma drug levels were tested at weeks 0, 1, 2 and 4 after stopping treatment and HIV-1 resistance mutations assessed at week 4.

Drug Level assay

Nevirapine and efavirenz plasma drug concentrations were measured by validated High Performance Liquid Chromatography (HPLC); with a limit of detection ranging between 0.05-0.15 mg/L for nevirapine and 0.05-0.2 mg/L for efavirenz. For this analysis, values ≥0.15 for nevirapine and ≥0.2 for efavirenz were considered detectable.

Resistance assay

HIV resistance mutations were identified in local laboratories by sequencing of plasma virus and interpreted by use of the Stanford University HIV database.

Baseline characteristics

- ★ 70 children have been randomised between 12 Nov 04 and 17 Jan 06
  - 13 children have stopped a nevirapine based HAART regimen
  - 9 children have stopped a efavirenz based HAART regimen
- ★ Children were enrolled from 6 countries: Germany (4 children), Italy (18), Spain (14), Thailand (11), UK (16) and France (7).

Table 1: Baseline characteristics

	NVP (N=13)		**EFV** (N=9)	
Sex				
Male	7		3	
Female	6		6	
Ethnicity				
White/ Black/Asian/Other	4 / 4 / 3 / 2		3 /2 / 2/ 2	
Age at Wk 0 (yrs)	8	(5-15)	9	(5-14)
Dose / kg	11.5	(7.3-14.1)	13.0	(8.1-17.9)
HIV-1 RNA (copies/ml)	< 50	(<50-700)	< 50	(<50-67)
No. drugs received				
All	4	(3-7)	4	(3-7)
NRTI	3	(2-4)	3	(2-5)
NNRTI	1	(1-1)	1	(1-2)
PI	0	(0-2)	0	(0-2)
Cum. ART Exposure (yrs)				
All	5.4	(1.7-15.3)	6.1	(2.7-10.8)
NRTI	5.4	(1.7-9.5)	6.1	(2.7-10.8)
NNRTI	5.1	(1.7-7.7)	3.2	(1.9-5.5)
PI	0	(0-6.7)	0	(0-6.3)
Exp. Drug clases				
All 3 classes	4 (31%)		3 (33.3%)	
NRTI+NNRTI	9 (69%)		6 (66.6%)	

median (range)

Stopping Strategies

★ Choice of stopping strategy was at the discretion of the treating paediatrician

Figure 1: Chosen Stopping Strategies

Regimen	Staggered Stop (SS)	Replacement (R)
2NRTI+NVP	3	0
NRTI+3TC+NVP		
Retained 3TC	4	1#
Switched 3TC with ddI	2	3*
2NRTI+EFV	1	2 *
NRTI+3TC+EFV		
Retained 3TC	3	1 *
Switched 3TC with ddI	1	1*

For NNRTI replacement:
* Replaced NNRTI with LPV/r
\# Replaced NNRTI with NFV

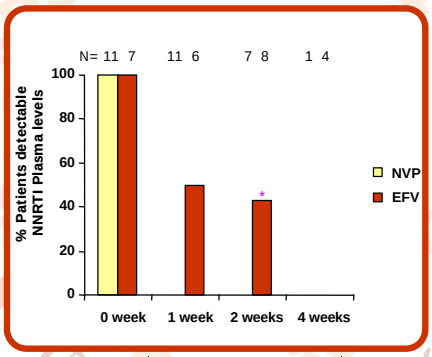
Other ARV drugs used at part of the NNRTI HAART regimen:

- ★ NVP based Regimens:
  d4T/3TC (6), ZDV/3TC (2), ddI/3TC (1), ABC/3TC (1) and ZDV/ABC (1), d4T/ddI (1), d4T/NFV (1)
- ★ EFV based Regimens:
  ZDV/3TC (2), ddI/3TC (2), ABC/D4T (1), ABC/3TC (1), d4T/LPVr (1), ABC/ddI (1) and d4T/3TC (1)

NNRTI Plasma drug Levels

Pre-interruption NNRTI Levels

★ Median NVP Levels: 4.8 (2.2-15.1) mg/L (n=11)
Median EFV levels: 3.2 (0.9-3.5) mg/L (n=7)



* After results for the first 6 children stopping EFV became available, the stagger stop/replace recommendation for EFV was increased to 2 weeks.

Detectable NNRTI Levels

★ At Week 1:
No patients had detectable NVP levels.
(Out of the 5 samples tested with a more sensitive assay (lower limit of detection 0.05 mg/L) 2 were detectable)
3 patients with detectable EFV levels: 0.614, 0.54 and 0.20 mg/L

★ At Week 2:
No patients had detectable NVP levels
3 patients had detectable EFV levels: 0.258, 0.32 and 0.29 mg/L

★ At Week 4:
No patients had detectable NVP or EFV plasma levels

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.

Figure 3: Viral Load Rebound after stopping NVP

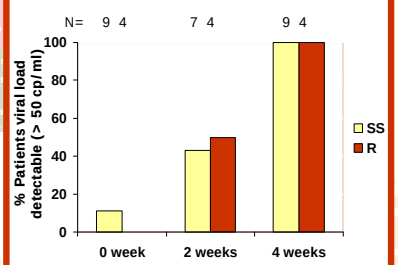
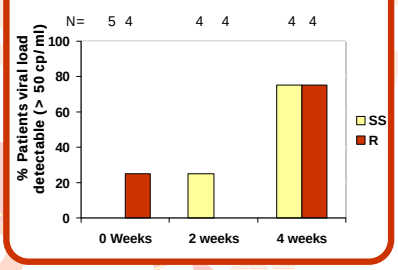


Figure 4: Viral Load Rebound after stopping EFV



HIV-1 Drug Resistance

★ NVP: 1 out of 11 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.

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:
  - 7-10 days for children interrupting nevirapine; and
  - at least 2 weeks for children interrupting efavirenz may be sufficient to prevent the selection of resistant mutations.

  However the threshold of drug levels below which resistance never occurs with low or undetectable HIV viral load is unknown and more sensitive assays may be required to detect low level resistance.
- Choice of stopping strategy did not influence HIV viral rebound.

Next steps

- Additional children are being recruited into the substudy.
- The subsequent response to ARV treatment and possible selection of resistance mutations under drug pressure following a PTI is currently under investigation in these children.
- The NRTI mutations in 22 children interrupting lamivudine are currently being evaluated.

Acknowledgements

We thank all the children, families and staff from the centres participating in the PENTA 11 - TICCH Trial.

PENTA Steering Committee: J-P Aboulker, A Babiker, S Blanche, AB Bohlin, P Clayden, K Butler, G Castelli-Gattinara, J Darbyshire, M Debré, Della Negra, D Duiculescu, R de Groot, A Faye, C Giaquinto (chairperson), DM Gibb, I Grosch-Wörner, M Lallemant, J Levy, H Lyall, M Marczynska, M Mellado Pena, D Nadal, C Peckham, JT Ramos Amador, L Rosado, C Rudin, H Scherpbier, M Sharland, M Stevanovic, PA Tovo, G Tudor-Williams, N Valerius, AS Walker, U Wintergerst. **Executive Committee for PENTA 11:** J-P Aboulker, A Babiker, D Burger, A Compagnucci, JH Darbyshire, M Debré, C Giaquinto, DM Gibb, H Green, N Klein, M Lallemant, H Lyall, D Nadal, Y Saidi. **PENTA Pharmacology Group:** D Burger, T Cressey, G Gatti, E Jacqz-Aigrain, S Khoo, JM Tréluyer. **PENTA Immunology/Virology Group:** C Boucher, M Clerici, A de Rossi, N Klein, M Muñoz Fernandez, N Ngo, D Pillay, G Sterckers, C Rouzioux. **INSERM SC10, France:** JP Aboulker, A Compagnucci, V Eliette, C Pitrou, Y Saidi. **MRC Clinical Trials Unit, UK:** A Babiker, L Buck, J Darbyshire, D Dunn, L Farrelly, DM Gibb, H Green, L Harper, D Johnson, AS Walker. **PHPT, Thailand:** F Fregonese, G Jourdain, M Lallemant, T Cressey. **Clinical sites: France:** Hôpital Edouard Herriot, Lyon (D Floret); Hôpital de l'Archet, Nice (F Monpoux); Hôpital Cochin Port-Royal, Paris (G Firtion); Hôpital Robert Debré, Paris (A Faye); Hôpital Purpan, Toulouse (J Tricoire). **Germany:** Universitäts Kinderklinik, München (U Wintergerst, G Notheis). **Italy:** Università di Padova (C Giaquinto, O Rampon, M Zanchetta); Università di Genova (R Rosso); Ospedale Bambino Gesù, Rome (G Castelli-Gattinara, A Martino, S Bernardi); Ospedale S. Chiara, Trento (A Mazza); Dip di Farmacologia, IRCCS Policlinico San Matteo, Pavia (M Regazzi, S Villani). **Netherlands:** Dept of Clinical Pharmacology, UMC Nijmegen (D Burger). **Spain:** Hospital Carlos III, Madrid (MJ Mellado Pena, P Martin Fontelos); Hospital Gregorio Maranon, Madrid (ML Navarro Gomez, D Gurbindo, JL Jimenez); Hospital 12 de Octobre, Madrid (JT Ramos Amador, J Contreras); Hospital La Paz, Madrid (I Jose Gomez); Hospital Materno-Infantil, Malaga (D Moreno, F Garcia Martin); Unidad de farmacocinética, Hospital Carlos III (S Rodriguez Novoa); monitors F Baquero, P Rojo Conejo, A Alimenti, M Penin. **Thailand:** HIV-NAT, Bangkok (T Bunupuradah, J Ananworanich, P Phanuphak, J Intasan, S Ubolyam); Nakornping Hospital (S Kanjanavanit, T Namwong); PHPT trial centre (S. Chalermpantmetagul, R. Peongjakta, S. Chailert). **UK:** St Mary's Hospital, London (H Lyall, G Tudor-Williams, C Foster, S Campbell, C Hanley, C Walsh); Chelsea and Westminster Hospital, London (H Lyall, P Seery); Great Ormond Street Hospital for Children (V Novelli, D Gibb, N Klein, J Flynn, M Clapson, L Farrelly, M Jacobsen); University Hospital of North Stafford, Stoke on Trent (P McMaster, E Hawkes); Pharmacology Research Laboratories, University of Liverpool (S Khoo, S Gibbons, M Stainsby-Tron)