THE LANCET Infectious Diseases

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: The PENPACT-1 (PENTA 9/PACTG 390) Study Team. First-line antiretroviral therapy with a protease inhibitor versus non-nucleoside reverse transcriptase inhibitor and switch at higher versus low viral load in HIV-infected children: an open-label, randomised phase 2/3 trial. *Lancet Infect Dis* 2011; published online Feb 1. DOI:10.1016/S1473-3099(10)70313-3.

Table S1: Primary and Secondary Outcomes

Primary Outcome		PI-1000		PI-30000		NNRTI-1000		NNRTI-30000	
			(n=57)		(n=61)		(n=60)		(n=56)
Mean (SE) VL change from baseline to four years[a] (log_{10}c/ml)		-3.14 (0.13)		-3.18 (0.13)		-3.38 (0.13)		-3.23 (0.14)	
Secondary Outcomes									
			(n=65)		(n=65)		(n=67)		(n=62)
VL <400c/ml at week 24 on first-line ART		44	(68%)	51	(78%)	57	(85%)	46	(74%)
			(n=54)		(n=58)		(n=60)		(n=54)
VL <400c/ml at four years[b]		45	(83%)	47	(81%)	50	(83%)	43	(80%)
			(n=66)		(n=65)		(n=68)		(n=64)
Continued VL suppression (never confirmed >400c/ml) on first-line ART		32	(48%)	42	(65%)	40	(59%)	35	(55%)
Failure of second-line ART (confirmed VL >30000c/ml or discontinuation of second-line ART)		4	(6%)	6	(9%)	7	(10%)	1	(2%)
Children experiencing grade 3/4 adverse events (non-HIV related)		15	(23%)	13	(20%)	15	(22%)	17	(27%)
Children experiencing new CDC stage C events		3	(5%)	3	(5%)	1	(1%)	2	(3%)
Regimen switch		20	(30%)	8	(12%)	17	(25%)	15	(23%)
			(n=20)		(n=8)		(n=17)		(n=15)
Median (IQR) VL at regimen switch (c/ml)		7450 (1880,30362)		35131 (2114, 66800)		6258 (1380,19170)		35712 (11800,72800)	
			(n=65)		(n=65)		(n=67)		(n=62)
Mean (SE) CD4% increase from baseline to four years[a] (cells/mm^3)		14.2	(1.2)	13.3	(1.1)	15.9	(1.1)	14.5	(1.2)
			(n=61)		(n=60)		(n=64)		(n=61)
Major NNRTI mutations[c]	none	55	(90%)	57	(95%)	49	(77%)	43	(70%)
	1-2	4	(7%)	3	(5%)	14	(22%)	13	(21%)
	3 or more	2	(3%)			1	(2%)	5	(8%)
Major PI mutations	none	52	(85%)	56	(93%)	62	(97%)	60	(98%)
	1-2	9	(15%)	4	(7%)	2	(3%)	1	(2%)
Major NRTI mutations[d]	none	49	(80%)	51	(85%)	50	(78%)	42	(69%)
	1-2	9	(15%)	6	(10%)	14	(22%)	12	(20%)
	3 or more	3	(5%)	3	(5%)			7	(11%)

[a] Four years was defined to be the mean of the measurements at weeks 192 and 204 (a single measurement was used if both were not available)
[b] Four years was defined to be the week 204 measurement.
[c] interaction p=0.02.
[d] interaction p=0.003.
VL = viral load, PI = protease inhibitor, NNRTI = non-nuceloside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor

Table S2: Adverse events

Grade 3/4 adverse events	Total (n=263)		PI (n=131)		NNRTI (n=132)		1000 (n=134)		30000 (n=129)	
Total (Episodes (children))	97	(60)	39	(28)	58	(32)	47	(30)	50	(30)
haematology/biochemistry	22	(20)	16	(14)	6	(6)	13	(12)	9	(8)
GI	21	(14)	11	(7)	10	(7)	7	(5)	14	(9)
infection/allergic reaction	26	(21)	5	(4)	21	(17)	12	(10)	14	(11)
ear/eye disorders	4	(3)	1	(1)	3	(2)	1	(1)	3	(2)
nervous system	13	(10)	2	(2)	11	(8)	9	(6)	4	(4)
airways	3	(2)			3	(2)	2	(1)	1	(1)
renal	2	(2)	2	(2)					2	(2)
trauma	5	(5)	1	(1)	4	(4)	2	(2)	3	(3)
reproductive health	1	(1)	1	(1)			1	(1)		
ART related*	17	(15)	10	(8)	7	(7)	6	(6)	11	(9)
haematology/biochemistry	7	(7)	4	(4)	3	(3)	2	(2)	5	(5)
GI	4	(4)	3	(3)	1	(1)	2	(2)	2	(2)
infection/allergic reaction	4	(4)	2	(2)	2	(2)	1	(1)	3	(3)
nervous system	2	(2)	1	(1)	1	(1)	1	(1)	1	(1)
Serious adverse events										
Total (Episodes (children))	69	(48)	29	(23)	40	(25)	24	(19)	45	(29)
haematology/biochemistry	10	(8)	6	(5)	4	(3)	3	(3)	7	(5)
GI	10	(7)	4	(3)	6	(4)	4	(3)	6	(4)
infection/allergic reaction	30	(25)	14	(12)	16	(13)	8	(8)	22	(17)
ear/eye disorders	2	(2)	1	(1)	1	(1)	1	(1)	1	(1)
nervous system	9	(7)			9	(7)	5	(4)	4	(3)
airways	3	(2)			3	(2)	2	(1)	1	(1)
renal	1	(1)	1	(1)					1	(1)
trauma	2	(2)	1	(1)	1	(1)			2	(2)
reproductive health	2	(2)	2	(2)			1	(1)	1	(1)
ART related*	17	(15)	10	(8)	7	(7)	5	(5)	12	(10)
haematology/biochemistry	6	(6)	4	(4)	2	(2)	1	(1)	5	(5)
GI	2	(2)	2	(2)			1	(1)	1	(1)
infection/allergic reaction	8	(8)	4	(4)	4	(4)	2	(2)	6	(6)
nervous system	1	(1)			1	(1)	1	(1)		

*reported as possibly, probably or definitely ART related

Events were coded using MedDRA (Version 12.0), and were grouped by primary System Organ Class as follows: **haematology/biochemistry:** Blood and lymphatic system disorders**; Investigations; Metabolism and nutrition disorders; **GI:** Gastrointestinal disorders; Hepatobiliary disorders; **infection/allergic reaction:** Immune system disorders; Infections and infestations; Skin and subcutaneous tissue disorders; Vascular disorders; General disorders and administration site conditions; **ear/eye disorders:** Ear and labyrinth disorders; Eye disorders; **nervous system:** Musculoskeletal and connective tissue disorders; Nervous system disorders; Psychiatric disorders; Progressive external ophthalmoplegia (preferred term); **airways:** Respiratory, thoracic and mediastinal disorders; **renal:** Renal and urinary disorders; **trauma:** Injury, poisoning and procedural complications; **reproductive Health:** Pregnancy, puerperium and perinatal conditions; Reproductive system and breast disorders
** all anaemia, neutropenia or thrombocyctopenia

Acknowledgements

The PENPACT-1 (PENTA 9 / PACTG 390) Study Team

Writing Committee (alphabetical)

Abdel Babiker, Hannah Castro (nee Green), Alexandra Compagnucci, Susan Fiscus, Carlo Giaquinto, Diana M Gibb, Lynda Harper, Linda Harrison, Michael Hughes, Ross McKinney, Ann Melvin, Lynne Mofenson, Yacine Saidi, M Elizabeth Smith, Gareth Tudor-Williams, A Sarah Walker.

PENPACT1 Protocol Team

PACTG/IMPAACT/NICHD: P Brouwers, D Costello, E Ferguson, S Fiscus, J Hodge, M Hughes, C Jennings, A Melvin (Co-Chair), R McKinney (Co-Chair), L Mofenson, M Warshaw, ME Smith, S Spector, E Stiehm, M Toye, R Yogev.

PENTA: JP Aboulker, A Babiker, H Castro, A Compagnucci, A De Rossi, C Giaquinto, J Darbyshire, M Debré, DM Gibb, L Harper, L Harrison, N Klein, D Pillay, Y Saidi, G Tudor-Williams (Co-Chair), AS Walker.

Data and Safety Monitoring Board: B Brody, C Hill, P Lepage, J Modlin, A Poziak, M Rein (Chair 2002- 2003), M Robb (Chair 2004 – 2009), T Fleming, S Vella, KM Kim.

Clinical Sites (L = lab, P = pharmacy)

Argentina: Hospital de Pediatria Dr JP Garrahan, Buenos Aires: R Bologna, D Mecikovsky, N Pineda, L Sen (L), A Mangano (L), S Marino (L), C Galvez (L); Laboratorio Fundai: G Deluchi (L).

Austria: Universitätsklinik für Kinder und Jugendheilkunde, Graz: B Zöhrer, W Zenz, E. Daghofer, K Pfurtscheller, B Pabst (L).

Bahamas: Princess Margaret Hospital: MP Gomez, P McNeil, M Jervis, I Whyms, D Kwolfe, S Scott (P).

Brazil: University of Sao Paulo at Ribeirao Preto: MM Mussi-Pinhata, ML Issac, MC Cervi, BVM Negrini, TC Matsubara, C BSS de Souza (L), JC Gabaldi (P); Institute of Pediatrics (IPPMG), Federal University of Rio de Janeiro: RH Oliveira, MC Sapia, T Abreu, L Evangelista , A Pala, I Fernandes, I Farias, M de F Melo (L), H Carreira (P), LM Lira (P); Instituto de Infectologia Emilio Ribas, Sao Paolo: M della Negra, W Queiroz, YC Lian; DP Pacola; Fleury Laboratories; Federal University of Minas Gerais, Belo Horizonte: J Pinto, F Ferreira, F Kakehasi, L Martins, A Diniz, V Lobato, M Diniz, C Hill (L), S Cleto (L), S Costa (P), J Romeiro (P).

France: Hôpital d'enfants Armand Trousseau, Paris: C Dollfus, MD Tabone, MF Courcoux, G Vaudre A Dehée (L), A Schnuriger (L), N Le Gueyades (P), C De Bortoli (P); CHU Hôtel Dieu, Nantes: F Méchinaud, V Reliquet, J Arias (L), A Rodallec (L), E André (L), I Falconi (P), A Le Pelletier (P); Hôpital de l'Archet II, Nice, F Monpoux, J Cottalorda (L), S Mellul (L); Hôpital Jean Verdier, Bondy: E Lachassinne; Laboratoire de virologie-Hôpital Necker Enfants Malades, Paris: J Galimand (L), C Rouzioux (L), ML Chaix (L), Z Benabadji (P), M Pourrat (P); Hôpital Cochin Port-Royal- Saint Vincent de Paul, Paris: G Firtion, D Rivaux, M Denon, N Boudjoudi, F Nganzali, A Krivine (L), JF Méritet (L), G Delommois (L), C Norgeux (L), C Guérin (P); Hôpital Louis Mourier, Colombes: C Floch, L Marty, H Hichou (L), V Tournier (P); Hôpital Robert Debré, Paris, A Faye, I Le Moal, M Sellier (P), L Dehache (P); Laboratoire de virologie-Hôpital Bichat Claude Bernard-Paris: F Damond (L), J Leleu (L), D Beniken (L), G Alexandre-Castor (L)

Germany: Universitäts - Kinderklinik Düsseldorf: J Neubert, T Niehues, HJ Laws, K Huck, S Gudowius, K Siepermann, (H Loeffler), S Bellert(L), A Ortwin (L); Universitäts - Kinderkliniken, Munich: G Notheis, U Wintergerst, F Hoffman, (A Werthmann, S Seyboldt, L Schneider, B Bucholz); Charité – Medizische Fakultät der Humboldt-Universität zu Berlin: C Feiterna-Sperling, C Peiser, R Nickel, T Schmitz, T Piening, C Müller (L); Kinder- und Jugendklinik, Universität Rostock: G Warncke, M Wigger, R Neubauer.

Ireland: Our Lady's Children's Hospital Crumlin, Dublin: K Butler, AL Chong, T Boulger, A Menon, M O'Connell, L Barrett, A Rochford, M Goode, E Hayes, S McDonagh, A Walsh, A Doyle, J Fanning (P), M O'Connor (P), M Byrne (L), N O'Sullivan (L), E Hyland (L).

Italy: Clinica Pediatrica, Ospedale L Sacco, Milan: V Giacomet, A Viganò, I Colombo, D Trabattoni (L), A Berzi (L); Clinica Pediatrica, Università di Brescia: R Badolato, F Schumacher, V Bennato, M Brusati, A Sorlini, E Spinelli, M Filisetti, C Bertulli; Clinica Pediatrica, Università di Padova: O Rampon, C Giaquinto, M Zanchetta (L); Ospedale S. Chiara, Trento: A Mazza, G Stringari, G Rossetti (L); Ospedale del Bambino Gesù, Rome: S Bernardi, A Martino, G Castelli Gattinara, P Palma, G Pontrelli, H Tchidjou, A.Furcas, C. Frillici, A. Mazzei, A Zoccano (P), C Concato (L).

Romania: Spitalul Clinic de Boli Infectioase Victor Babes, Bucharest: D Duiculescu, C Oprea, G Tardei (L), F Abaab (P),; Institutul de Boli Infectioase Matei Bals, Bucharest: M Mardarescu, R Draghicenoiu, D Otelea (L), L Alecsandru (P); Clinic Municipal, Constanta: R Matusa, S Rugina, M Ilie, Silvia Netescu (P). Clinical monitors: C Florea, E Voicu, D Poalelungi, C Belmega, L Vladau, A Chiriac

Spain: Hospital Materno-Infantil 12 de Octubre, Madrid: JT Ramos Amador, MI Gonzalez Tomé, P Rojo Conejo, M Fernandez, R Delgado Garcia (L), JM Ferrari (P); Institute de Salud Carlos III, Madrid: M Garcia Lopez, MJ Mellado Peña, P Martin Fontelos, I Jimenez Nacher (P); Biobanco Gregorio Marañon, Madrid: MA Muñoz Fernandez (L), JL Jimenez (L), A García Torre (L); clinical monitors: M Penin, R Pineiro Perez, I Garcia Mellado.

UK: Bristol Royal Children's Hospital: A Finn, M LaJeunesse, E Hutchison, J Usher (L), L Ball (P), M Dunn (P); St. George's Healthcare NHS Trust, London: M Sharland, K Doerholt, S Storey, S Donaghy, R Chakraborty, C Wells (P), K Buckberry (P), P Rice (P); University Hospital of North Staffordshire: P McMaster, P Butler, C Farmer (L), J Shenton (P), H Haley (P), J Orendi (L), University Hospital Lewisham: J Stroobant, L Navarante, P Archer, C Mazhude, D Scott, R O'Connell, J Wong (L), G Boddy (P); Sheffield Children's Hospital: F Shackley, R Lakshman, J Hobbs, G Ball (L), G Kudesia (L), J Bane (P), D Painter (P); Ealing Hospital NHS Trust: K Sloper, V Shah, A Cheng (P), A Aali (L); King's College Hospital, London: C Ball, S Hawkins, D Nayagam, A Waters, S Doshi (P); Newham University Hospital: S Liebeschuetz, B Sodiende, D Shingadia, S Wong, J Swan (P), Z Shah (P); Royal Devon and Exeter Hospital: A Collinson,

C Hayes, J King (L), K 0'Connor (L); Imperial College Healthcare NHS Trust, London: G Tudor-Williams, H Lyall, K Fidler, S Walters, C Foster, D Hamadache, C Newbould, C Monrose, S Campbell, S Yeung, J Cohen, N Martinez-Allier, D Melvin, J Dodge, S Welch, (G Tatum, A Gordon), S Kaye (L), D Muir (L), D Patel (P); Great Ormond Street Hospital: V Novelli, D Gibb, D Shingadia, K Moshal, J Lambert, N Klein, J Flynn, L Farrelly, M Clapson, L Spencer, M Depala (P); Institute of Child Health, London: M Jacobsen (L); John Radcliffe Hospital, Oxford: S Segal, A Pollard, D Kelly, S Yeadon, B Ohene-Kena Y Peng (L), T Dong (L), Y Peng (L), K Jeffries (L), M Snelling (P), Nottingham University Hospitals: A Smyth, J Smith; Chelsea and Westminster Hospital, London: B Ward; Mortimer Market Centre, London: E Jungmann; Doncaster Royal Infirmary: C Ryan, K Swaby; Health Protection Agency, London: A Buckton (L); Health Protection Agency, Birmingham: E Smit (L).

USA: Harlem Hospital Center: EJ Abrams, S Champion, AD Fernandez, D Calo, L Garrovillo, K Swaminathan, T Alford, M Frere, Columbia University laboratories, J Navarra (P, Town Total Health); NYU School of Medicine: W Borkowsky, S Deygoo, T Hastings, S Akleh, T Ilmet (L); Seattle Children's Hospital: A Melvin, K Mohan, G Bowen (Additional support by NIH Grant UL1 RR025014); University of South Florida: PJ Emmanuel, J Lujan-Zimmerman, C Rodriguez, S Johnson, A Marion, C Graisbery, D Casey, G Lewis; All Children's Hospital laboratories; Oregon Health and Science University: J Guzman-Cottrill, R Croteau; San Juan City Hospital: M Acevedo-Flores, M Gonzalez, L Angeli; L Fabregas, Lab 053, P Valentin (P); SUNY- Upstate Medical University-Syracuse: L Weiner, KA Contello, W Holz, M Butler; SUNY, Health Science Center at Stonybrook: S Nachman, MA. Kelly, DM. Ferraro, UNC Retrovirology Lab; Howard University Hospital: S Rana, C Reed, E Yeagley, A Malheiro, J Roa; LAC and USC Medical Center: M Neely, A Kovacs, L Spencer, J Homans, Y Rodriguez Lozano, Maternal Child Virology Research Laboratory, Investigational Drug Service; South Florida Childrens Diagnostic & Treatment Center: A Puga, G Talero, R Sellers; Broward General Medical Center, University of Miami (L); University College of Florida College of Medicine- Gainsville: R Lawrence; University of Rochester Pediatrics: GA. Weinberg, B Murante, S Laverty; Miller Children's Hospital Long Beach: A Deveikis, J Batra, T Chen, D Michalik, J Deville, K Elkins, S Marks, J Jackson Alvarez, J Palm, I Fineanganofo (L), M Keuth (L), L Deveikis (L), W Tomosada (P); Tulane University New Orleans: R Van Dyke, T Alchediak, M Silio, C Borne, S Bradford, S Eloby-Childress (L), K Nguyen (P); University of Florida/Jacksonville: MH. Rathore, A Alvarez; A Mirza, S Mahmoudi, M Burke; University of Puerto Rico: IL Febo, L Lugo, R Santos; Children's Hospital Los Angeles: JA Church, T Dunaway, C Rodier; St. Jude/UTHSC: P Flynn, N Patel, S DiScenza, M Donohoe; WNE Maternal Pediatric Adolescent AIDS: K Luzuriaga, D Picard; Texas Children's Hospital: M Kline, ME Paul, WT Shearer, C McMullen-Jackson; Children's Memorial Hospital, Chicago: R Yogev, E Chadwick, E Cagwin, K Kabat; New Jersey Medical School: A Dieudonne, P Palumbo, J Johnson; Robert Wood Johnson Medical School, New Brunswick : S Gaur, L Cerracchio; Columbia IMPAACT: M Foca, A Jurgrau, S Vasquez Bonilla, G Silva; Babies' Hospital, Columbia/Presbyterian Medical Center, New York (A Gershon); University of Massachusetts Medical Center, Worcester (J Sullivan); UCLA Medical Center, Los Angeles (Y Bryson); Children's Hospital, Seattle: L Frenkel; UNC-Chapel Hill Virology Lab: S Fiscus (L), J Nelson (L).

Trials Units/Support

INSERM SC10 Paris: JP Aboulker, A Compagnucci, G Hadjou, S Léonardo, Y Riault, Y Saïdi

MRC Clinical Trials Unit, UK: A Babiker, L Buck, JH Darbyshire, L Farrelly, S Forcat, DM Gibb, H Castro, L Harper, L Harrison, J Horton, D Johnson, S Moore, C Taylor, AS Walker.

Westat/NICHD: D Collins, S Buskirk, P Kamara, C Nesel, M Johnson, A Ferreira

Frontier Science: J Hodge, J Tutko, H Sprenger

IMPAACT: M. Hughes, M. Warshaw, P. Britto, C. Powell

NIAID: R DerSimonian, E Handelsman

PENTA Steering Committee: JP Aboulker, J Ananworanich, A Babiker, E Belfrage, S Bernardi, S Blanche, AB Bohlin, R Bologna, D Burger, K Butler, G Castelli-Gattinara, H Castro, P Clayden, A Compagnucci, JH Darbyshire, M Debré, R De Groot, M Della Negra, D Duiculescu, A Faye, C Giaquinto (Chair), DM Gibb, I Grosch-Wörner, M Hainault, L Harper, N Klein, M Lallemant, J Levy, H Lyall, M Marczynska, M Mardarescu, MJ Mellado Pena, D Nadal, T Niehues, C Peckham, D Pillay, JT Ramos Amador, L Rosado, R Rosso (deceased), C Rudin, Y Saïdi, H Scherpbier, M Sharland, M Stevanovic, C Thorne, PA Tovo, G Tudor-Williams, AS Walker, S Welch, U Wintergerst, N Valerius.