PENPACT 1
(PENTA 9 / PACTG 390)

A phase II/III randomised, open-label trial of combination antiretroviral regimens and treatment-switching strategies in HIV-1-infected antiretroviral naïve children

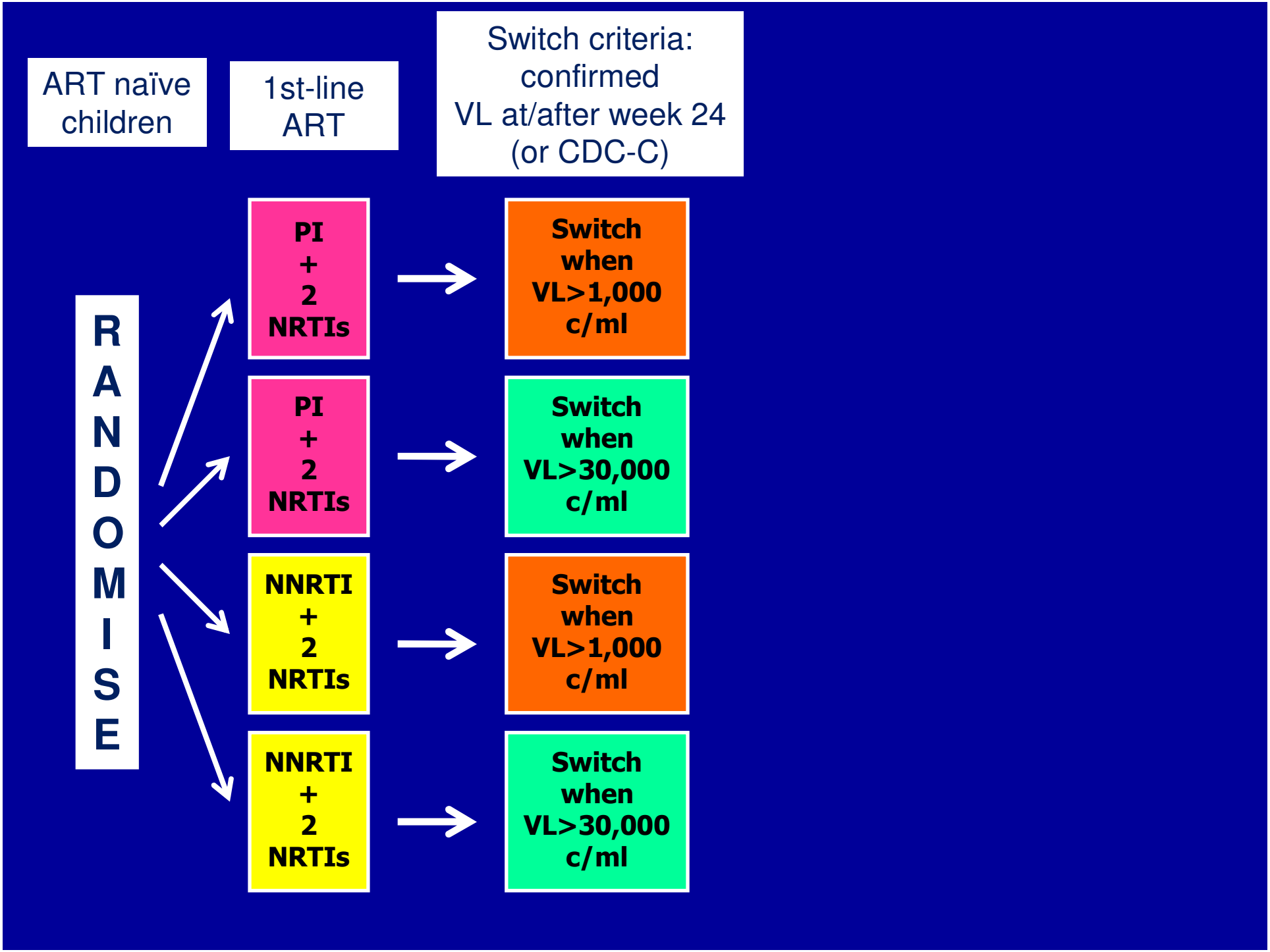
A collaboration between PENTA and PACTG / IMPAACT

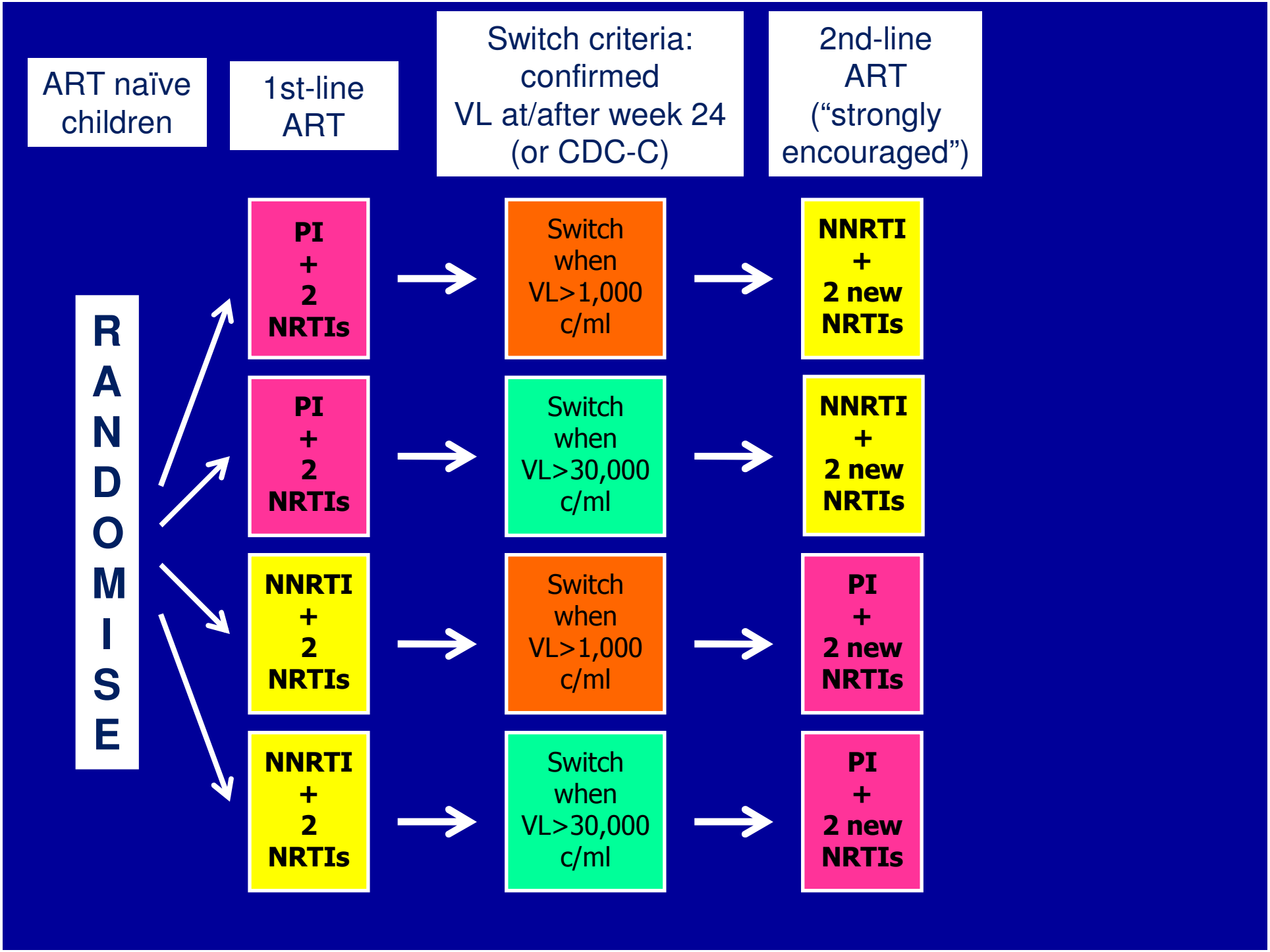
Primary Objectives

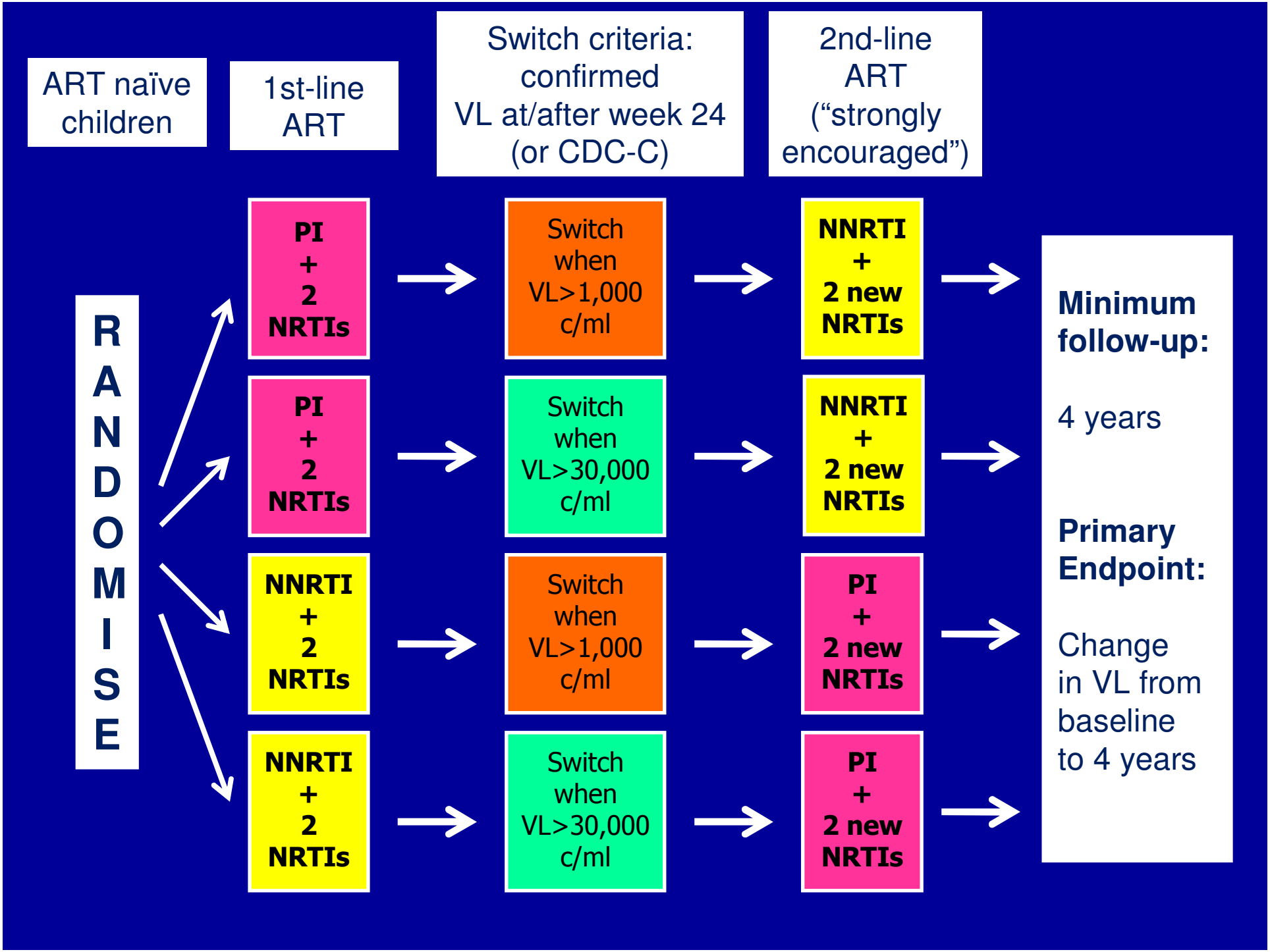
A long-term comparison in ART naïve children of:

- **PI**-based versus **NNRTI**-based initial therapy
- two different viral load criteria for switching from 1st to 2nd line therapy:

  >1,000 versus **>30,000** copies/ml


ART naïve children
1st-line ART
Switch criteria: confirmed VL at/after week 24 (or CDC-C)
RANDOMISE
PI + 2 NRTIs
PI + 2 NRTIs
NNRTI + 2 NRTIs
NNRTI + 2 NRTIs
Switch when VL>1,000 c/ml
Switch when VL>30,000 c/ml
Switch when VL>1,000 c/ml
Switch when VL>30,000 c/ml


ART naïve children
1st-line ART
Switch criteria: confirmed VL at/after week 24 (or CDC-C)
2nd-line ART ("strongly encouraged")
RANDOMISE
PI + 2 NRTIs
PI + 2 NRTIs
NNRTI + 2 NRTIs
NNRTI + 2 NRTIs
Switch when VL>1,000 c/ml
Switch when VL>30,000 c/ml
Switch when VL>1,000 c/ml
Switch when VL>30,000 c/ml
NNRTI + 2 new NRTIs
NNRTI + 2 new NRTIs
PI + 2 new NRTIs
PI + 2 new NRTIs


ART naïve children
1st-line ART
Switch criteria: confirmed VL at/after week 24 (or CDC-C)
2nd-line ART ("strongly encouraged")
RANDOMISE
PI + 2 NRTIs
PI + 2 NRTIs
NNRTI + 2 NRTIs
NNRTI + 2 NRTIs
Switch when VL>1,000 c/ml
Switch when VL>30,000 c/ml
Switch when VL>1,000 c/ml
Switch when VL>30,000 c/ml
NNRTI + 2 new NRTIs
NNRTI + 2 new NRTIs
PI + 2 new NRTIs
PI + 2 new NRTIs
Minimum follow-up:
4 years
Primary Endpoint:
Change in VL from baseline to 4 years

Accrual

266 randomised
(Sept 2002 to Sept 2005)

3 excluded from analysis:
- 2 withdrew consent & did not start ART
- 1 had 6 months of prior ART

263 analysed:

Europe:	132 (50%)
USA:	72 (27%)
Brazil/Argentina:	52 (20%)
Bahamas/Puerto Rico:	7 (3%)

218 (83%) in follow-up at end of study (August 2009)

Median follow-up **5.0 years**

IQR: 4.2 – 6.0 years, range: 5 weeks – 6.7 years

Study Population N=263

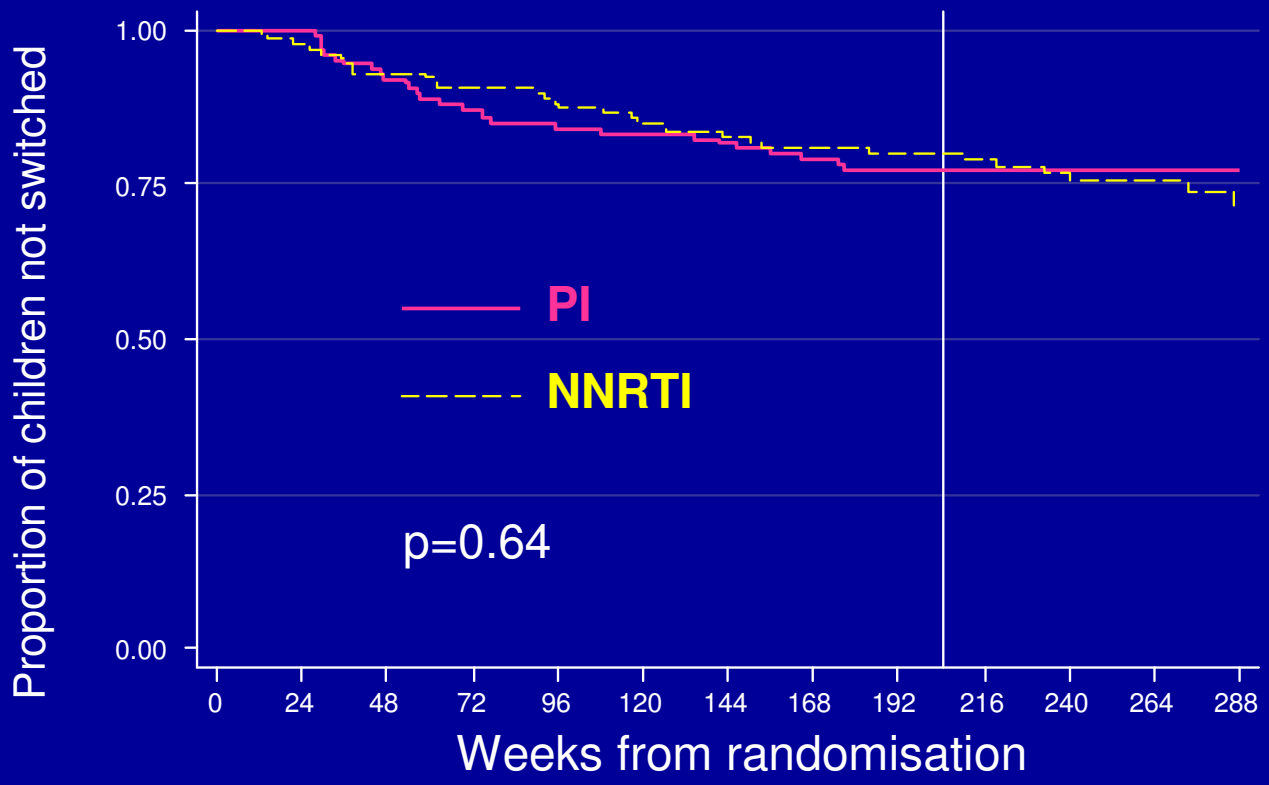
Age years, median (range)		6.5 (1 months, 17.8 years)
Gender	male	69 (53%)
Route of infection	vertical	79%
	parenteral	16%
	sexual contact	5%
Ethnicity	Black	49%
	White	26%
	Hispanic/Latino/Other	25%
ART for PMTCT		15%
CDC Stage	N/A	49%
	B/C	51%
CD4%	median	17 (IQR: 10, 25)
HIV-1 RNA	$\log_{10}$c/ml, median	5.1 (IQR: 4.5, 5.7)
≥1 major mutation		10/239 (4%)

Initial ART Started

	2 NRTIs + PI (N=131)	2 NRTIs + NNRTI (N=132)
	LPV/r 49% NFV 48% Other PI 2%	EFV 61% NVP 38%
NRTI combinations		
3TC+ZDV	40%	45%
3TC+ABC	22%	25%
3TC+d4T	24%	17%
ZDV+ddI	11%	8%
Other	3%	5%

2 children in each arm (PI / NNRTI) were started on the opposite class of drugs to which they had been randomised

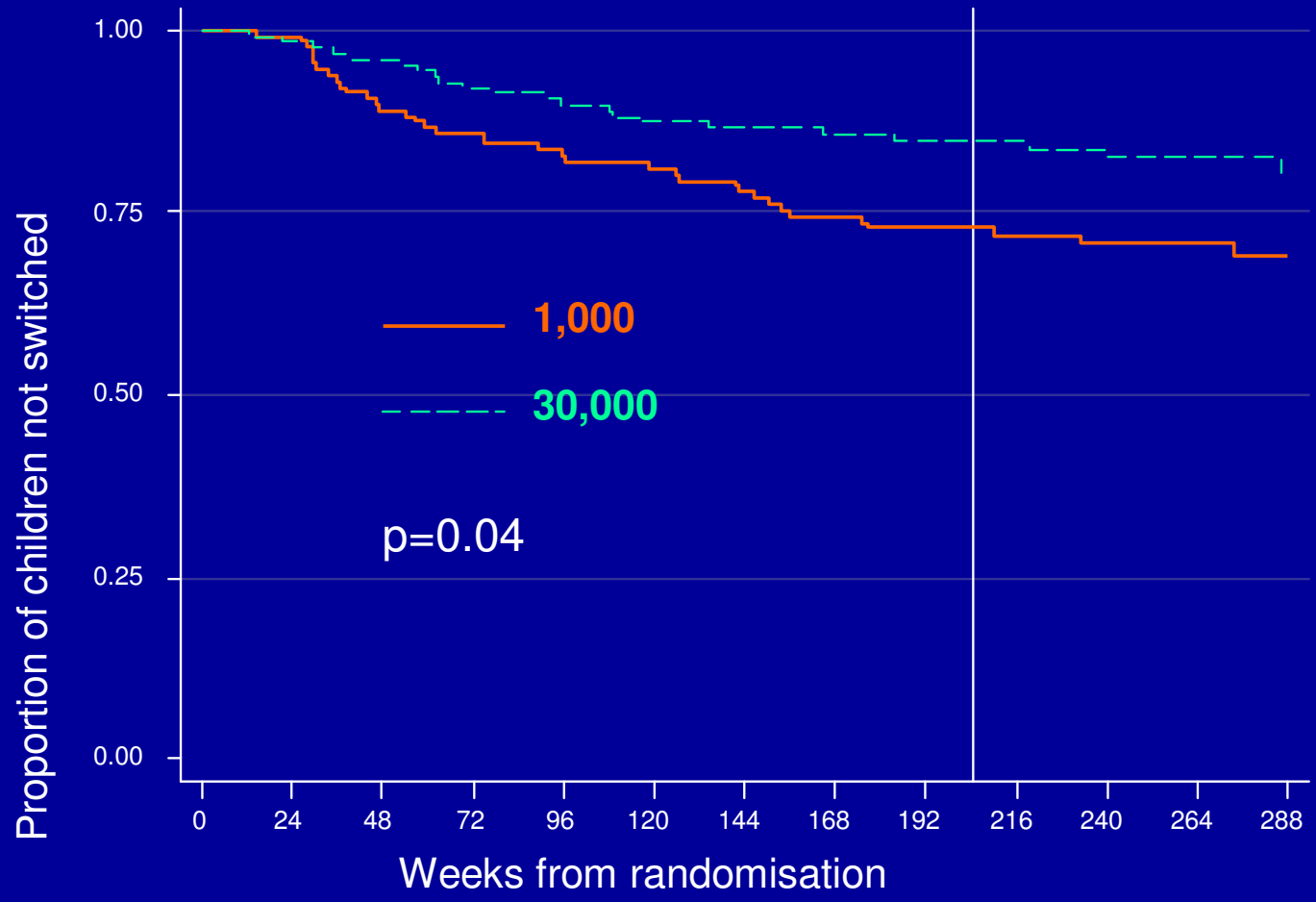
Time to Switch by Drug Class



At end of follow-up	PI	(N=131)	NNRTI	(N=132)
On 1st regimen	96	73%	92	70%
Switched to 2nd regimen	28	21%	32	24%
Off ART after 1st regimen	7	5%	8	6%

Time to Switch by Viral Load Switch-point

HIV-1 RNA at switch c/ml, median (IQR)	**1,000**	**30,000**	p-value
	6,720 (1,380; 26,100)	**35,712** (8,060; 72,800)	<0.01



Primary Endpoint

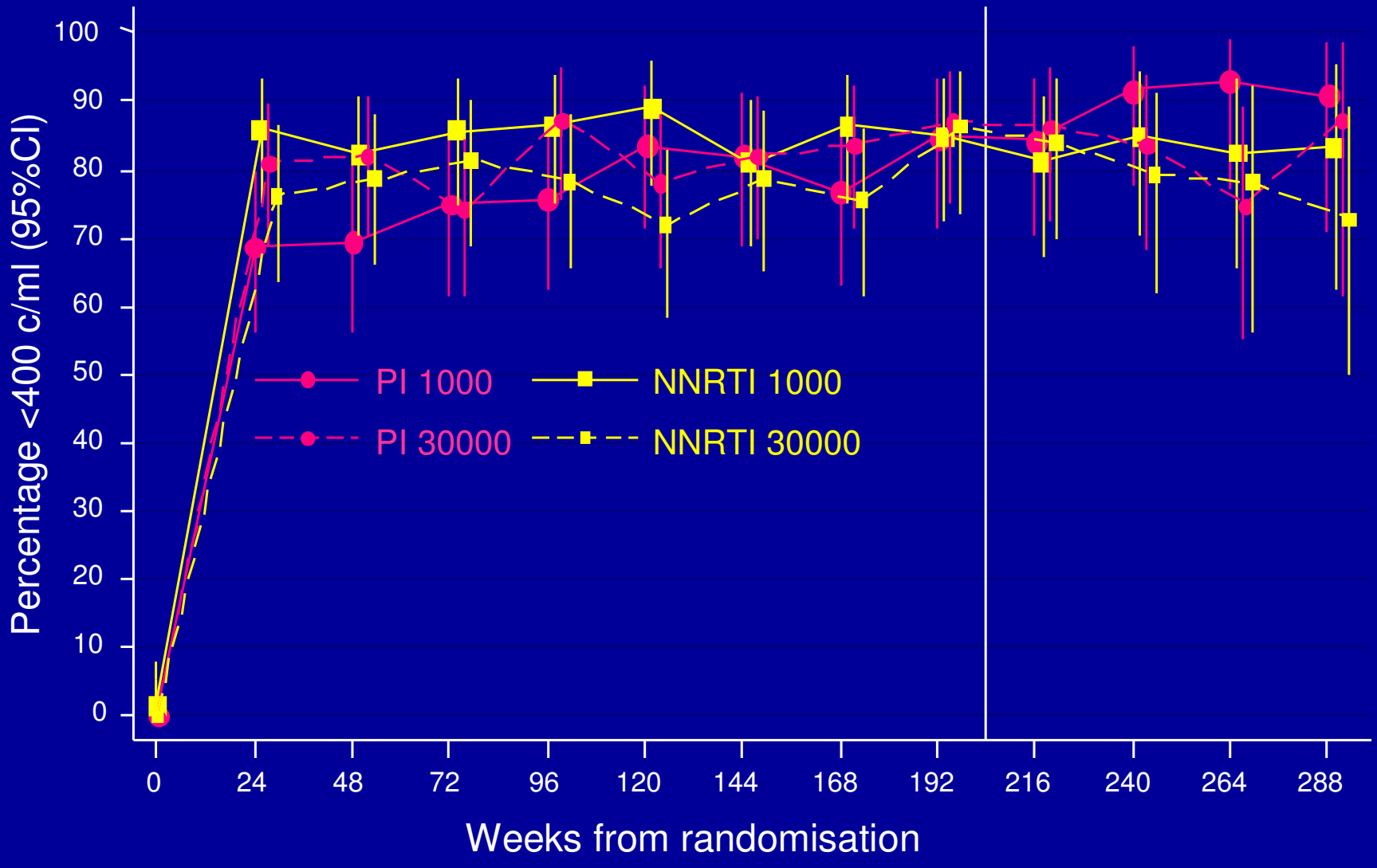
Change in HIV-1 RNA (log_{10} c/ml) between baseline and 4 years

Log_{10} c/ml VL reduction		Difference (95% CI)	P-value
PI -3.16	**NNRTI** -3.31	-0.15 (-0.41, 0.11)	0.26
1,000 -3.26	**30,000** -3.20	0.06 (-0.20, 0.32)	0.56

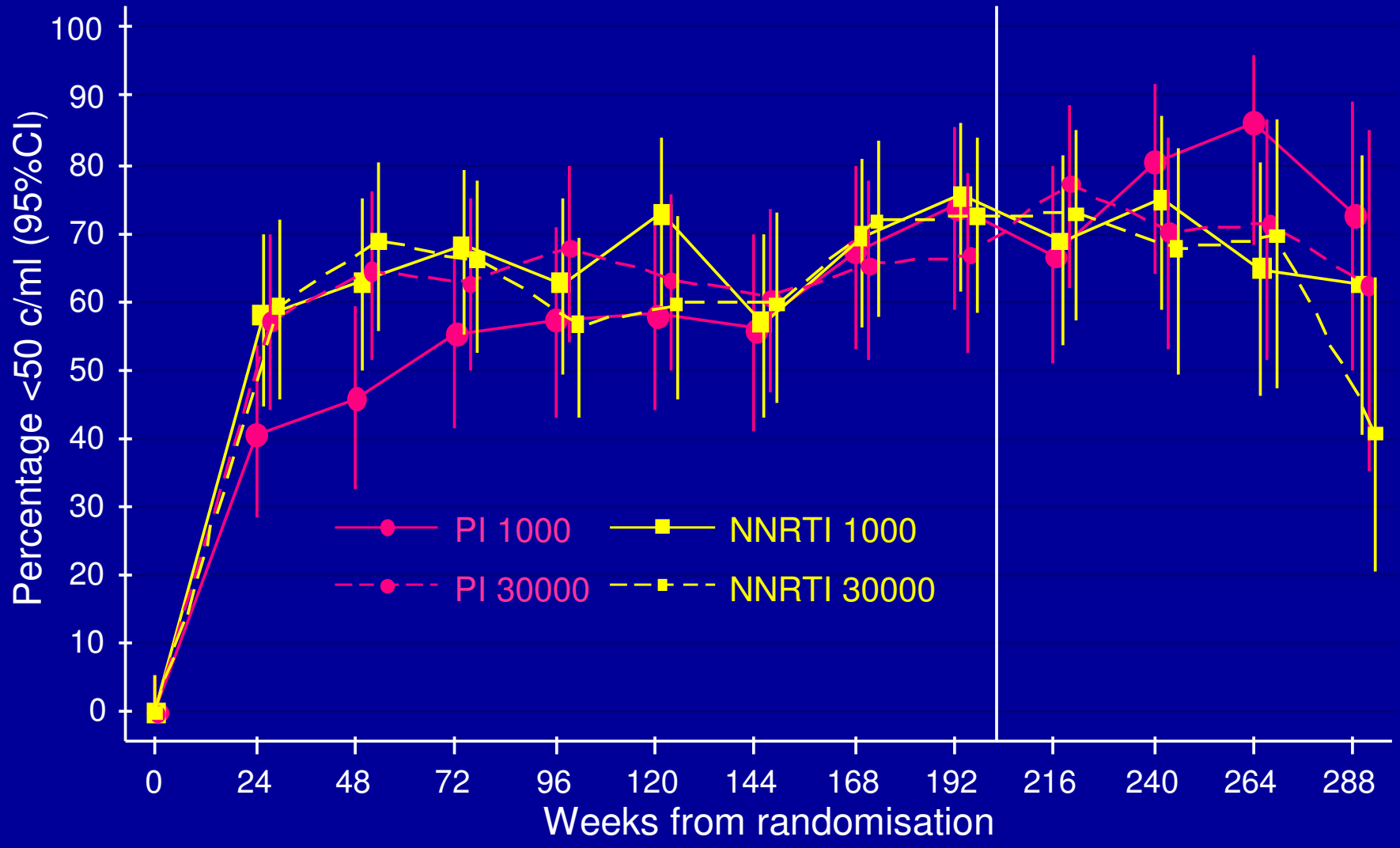
N=234 out of 263, 89%

Similar findings in sensitivity analyses to address losses to follow-up

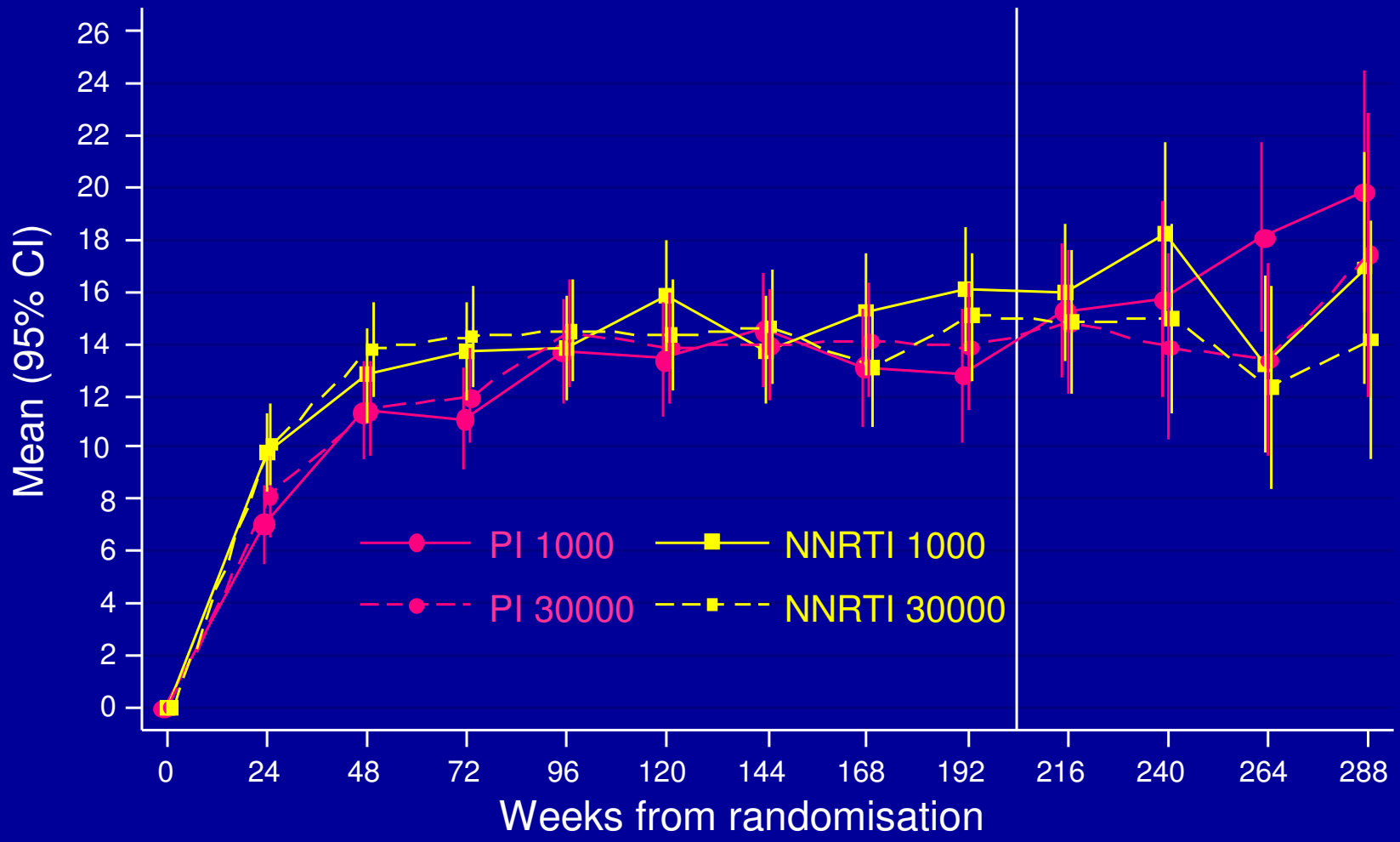
Proportion with HIV-1 RNA <400 c/ml



Proportion with HIV-1 RNA <50 c/ml



CD4% Changes


Mean (95% CI)
26
24
22
20
18
16
14
12
10
8
6
4
2
0
0
24
48
72
96
120
144
168
192
216
240
264
288
Weeks from randomisation
PI 1000
NNRTI 1000
PI 30000
NNRTI 30000

Disease Progression and Adverse Events

- **1** child died at week 277
- **14** new CDC stage C events
  - in **9** children (**3** PI 1000, **3** PI 30000, **1** NNRTI 1000, **2** NNRTI 30000)
- **60** children had grade 3 or 4 AEs
  - **PI** vs **NNRTI**: **28** vs **32** children
  - **>1,000** vs **>30,000**: **30** vs **30** children
- **17** children modified their ART due to grade 3 or 4 AE

Resistance testing

Samples tested for resistance so far:
Last sample with viral load >1000c/ml

- at switch
- at 4 years
- at end of follow-up

Preliminary Results
Cumulative Resistance at end of follow-up

	1,000	**30,000**	P-value
Total children	**134**	**129**	
Number expected to have tests	45	38	
Number with tests	38	30	
PI resistance			0.24
1 or 2 mutations	9 (7%)	4 (3%)	
NNRTI resistance			0.81
1 or 2 mutations	13 (10%)	12 (9%)	
3 or more mutations	2 (1%)	3 (2%)	
High-level **etravirine** resistance	1 (1%)	1 (1%)	

Analysis assumes those without tests were not resistant

Preliminary Results
Cumulative Resistance at end of follow-up

	PI 1,000	**PI 30,000**	**NNRTI 1,000**	**NNRTI 30,000**	P-value
Total children	**66**	**65**	**68**	**64**	
Number expected to have tests	24	17	21	21	
Number with tests	21	11	17	19	
NRTI resistance					0.01*
1 or 2 mutations	8 (12%)	5 (8%)	10 (15%)	9 (14%)	
3 or more mutations	1 (2%)	1 (2%)		**7 (11%)**	

* Driven by more children with ≥ 3 mutations in NNRTI 30,000 group

Analysis assumes those without tests were not resistant

PENPACT 1 Trial Summary

- No difference in 4-year viral load suppression:
  - **PI**- or **NNRTI**
  - switch at viral load **1,000** or **30,000** c/ml
- Children on ART had excellent clinical/CD4 outcomes:
  - >70% on first-line ART at ~5 years
  - >80% VL <400c/ml at 4 years
  - No difference in adverse events
- No difference in NNRTI or PI resistance switching at **1,000** v **30,000** c/ml
- More children accumulated NRTI resistance mutations over 5 years in **NNRTI** group switching at **30,000** c/ml

Key Messages

For HIV-infected children WORLDWIDE, the PENPACT 1 trial results send some powerful messages:

- ART has excellent clinical and immunological efficacy: avoid barriers to starting and continuing ART
- In the absence of NVP-based PMTCT either PI or NNRTI are equally good choices for first line regimens
- Although routine viral load testing may help identify children at risk of developing NRTI resistance, it is unlikely to impact the development of NNRTI resistance because this occurs very soon after viral rebound

THANK YOU to....

- ✓ the study participants and site staff for completing so well this long-term study
- ✓ numerous study team members for a very successful collaboration between PENTA and IMPAACT
- ✓ our DSMB who kept a steady nerve and enabled us to continue the trial to completion

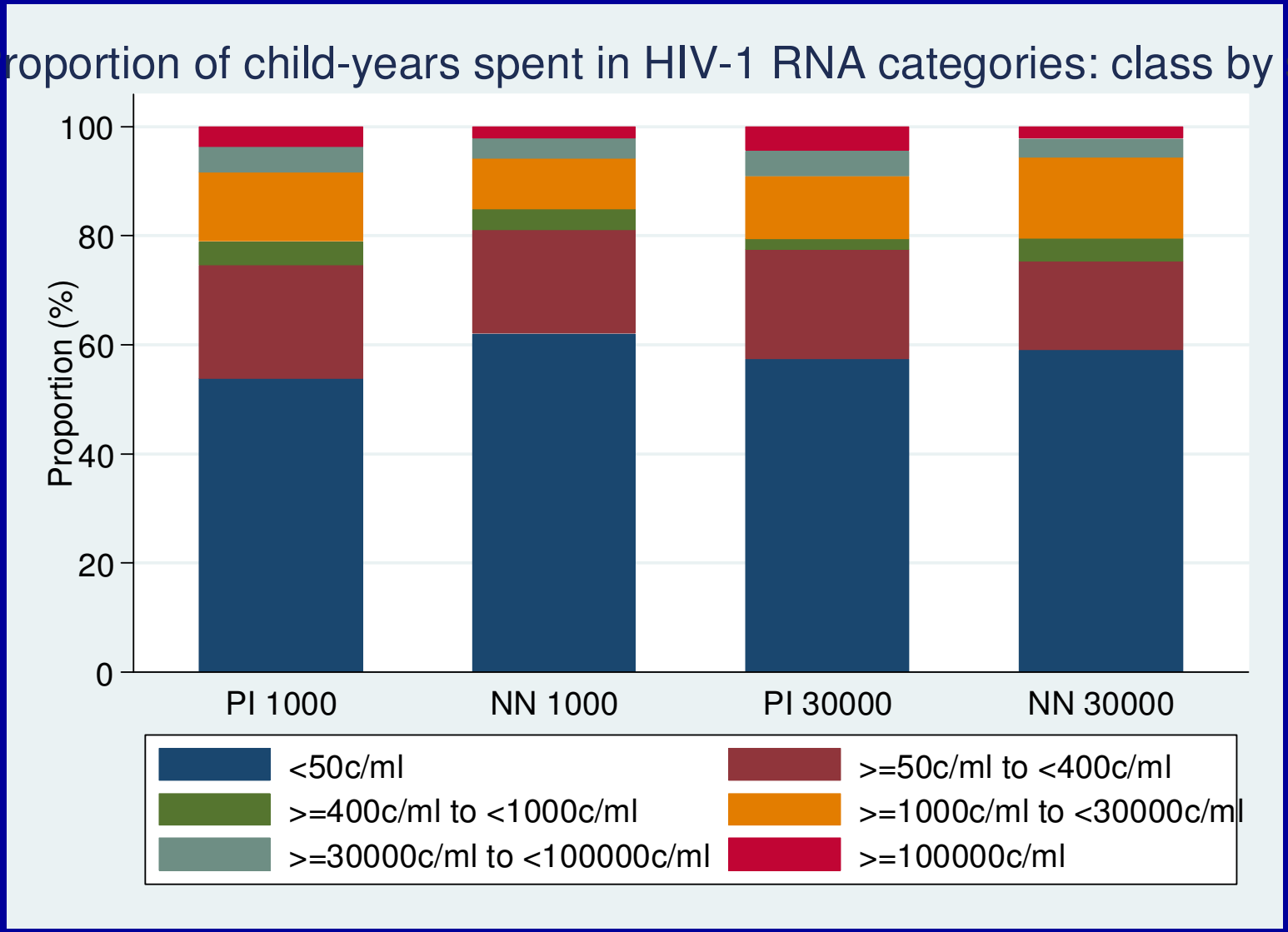
Acknowledgements

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, E Smith, S Spector, E Stiehm, M Toye, R Yogev.
PENTA: JP Aboulker, A Babiker, H Castro, A Compagnucci, C Giaquinto (Co-Chair), J Darbyshire, M Debré, DM Gibb, L Harper, L Harrison, G Tudor-Williams, Y Saidi, AS Walker. **DSMB:** 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.
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, 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, K Butler, G Castelli-Gattinara, H Castro, P Clayden, JH Darbyshire, M Debré, R De Groot, M Della Negra, D Duicelescu, A Faye, C Giaquinto (Chair), DM Gibb, I Grosch-Wörner, M Lallemant, J Levy, H Lyall, M Marczynska, M Mardarescu, MJ Mellado Pena, D Nadal, T Niehues, C Peckham, JT Ramos Amador, L Rosado, R Rosso, C Rudin, Y Saïdi, H Scherpbier, M Sharland, M Stevanovic, C Thorne, PA Tovo, AS Walker, S Welch, U Wintergerst, N Valerius.
Clinical Sites 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, M Chermont Sapia, 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, (H Loeffler), S Bellert(L), A Ortwin (L), Universitats – 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 Hospital for Sick Children, Dublin: K Butler, AL Chang, T Belger, A Menon, M O'Connell, L Barrett, A Rochford, M Goode, E Hayes, S McDonagy, 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, 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 Hadamache, C Newbould, C Monrose, S Campbell, S Yeung, J Cohen, N Martinez-Allier, (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, S Yeadon, 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; UCLH, London: E Jungmann; Doncaster Royal Infirmary: C Ryan, K Swaby; Health Protection Agency, London: A Buckton (L); Health Protection Agency, Birmingham: E Smidt (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; 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).

Back up slides

Proportion of Person-Years Spent in HIV-1 RNA Categories



Preliminary Results
Cumulative Resistance at end of follow-up

	PI 1,000	**PI 30,000**	**NNRTI 1,000**	**NNRTI 30,000**
Total children	**66**	**65**	**68**	**64**
Number expected to have tests	24	17	21	21
Number with tests	21	11	17	19
High level **NRTI** resistance				
3TC/ FTC (M184V/I)	9 (14%)	5 (8%)	8 (12%)	14 (22%)
ABC	1 (2%)		1 (1%)	3 (5%)
ddI	1 (2%)			3 (5%)
d4T				3 (5%)
ZDV				2 (3%)