

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

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PENTA 11 DESIGN

- HIV-1 RNA < 50 c/ml,
- CD4% \geq 30% (age 2-6) or CD4 \geq 25% and CD4 \geq 500 (age 7-15);
- HAART > 6 months (unless changed for toxicity);

RANDOMISE

Continuous HAART

Primary Endpoints

CD4% < 15% (2-6yr)
CD4% < 15% and CD4 < 200/mm³ (\geq 7yr)
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% \geq 30% / CD4% \geq 25% AND CD4 \geq 500 and HIV-1 RNA < 50 c/ml twice;

Repeat

MAIN TRIAL : MAIN FINDINGS

- 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**



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 (PedsqI)
- **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

	CT (N 51)	PTI (N 50)
Age (yrs), median (range)	9.9 (2.2, 15.1)	8.8 (3.5, 15.9)
Time since started ART years), med (IQR)"	6.6 (3.9, 8.9)	5.6 (3.2, 8.3)
CD4%, median (IQR)	37% (34, 40%)	37% (33, 42%)
CD4 count (cells/μl), median (IQR)	968 (739, 1225)	1010 (860, 1280)
HIV-1 RNA <50 copies/ml	48 (94%)	43 (86%)
CDC disease stage B / C	13 (25%) / 19 (37%)	16 (32%) / 9 (18%)
Nadir CD4%, median (IQR)	18% (10%, 27%)	21% (12, 26%)

Age (yrs), median (range)	12.1 (4.8, 17.9)	11.3 (5.0, 18.7)
CD4%, median (IQR)	36% (31, 42%)	32% (28, 36%)
CD4 count (cells/μl), median (IQR)	927 (700, 1140)	792 (595, 1045)
Proportion HIV-1 RNA <50 copies/ml	76% (39/51)	60% (30/50)



Treatment status at end of main trial for children in LTFU

■ PTI arm

N=50

First PTI

- on first PTI 1 (2%)
- restarted ART after first PTI 33 (66%)
- non-protocol TI after first restart 1 (2%)

Second PTI

- on second PTI 5 (10%)
 - restarted ART after second PTI 10 (20%)
-

■ CT arm

- 1 child off ART



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

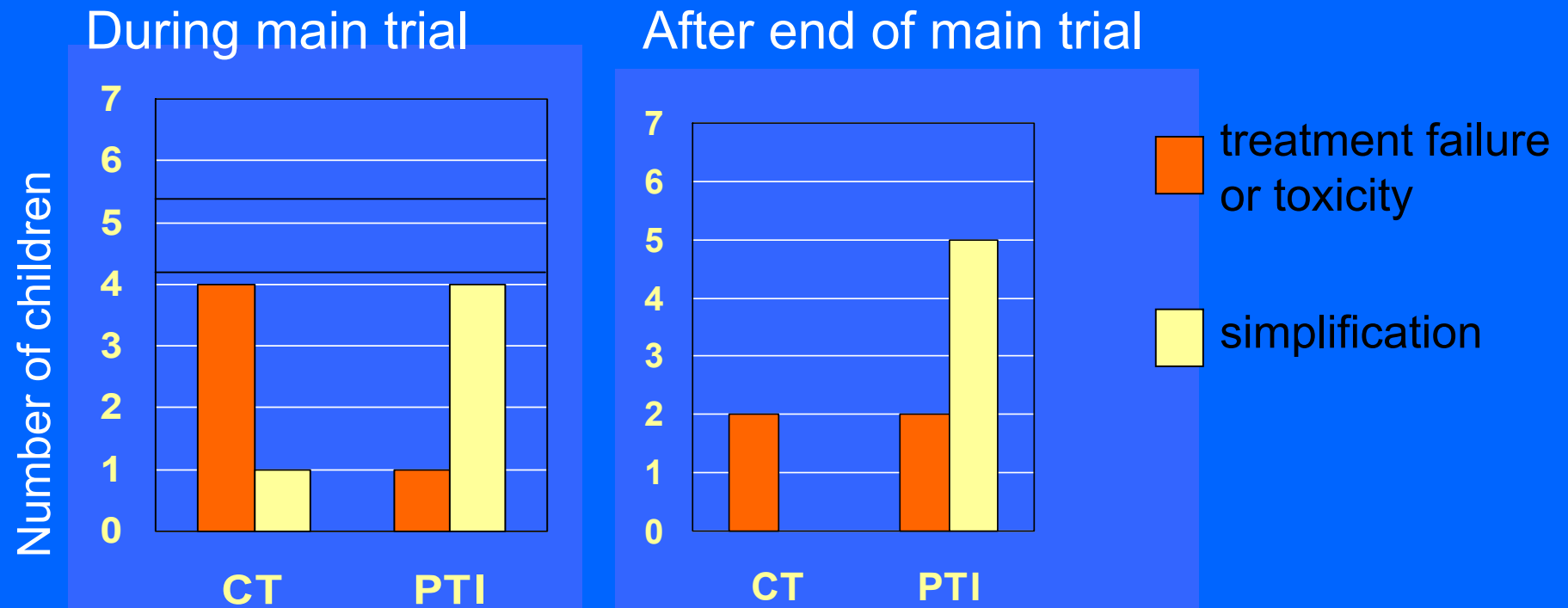


Proportion of time spent off ART

	CT	PTI
Up to end of main trial	4.1%	45.2%
After end of main trial		
- during overall follow-up	1.3%	10.4%
- excluding FU of children on a PTI at end of main trial before they restarted ART	1.3%	4.7%

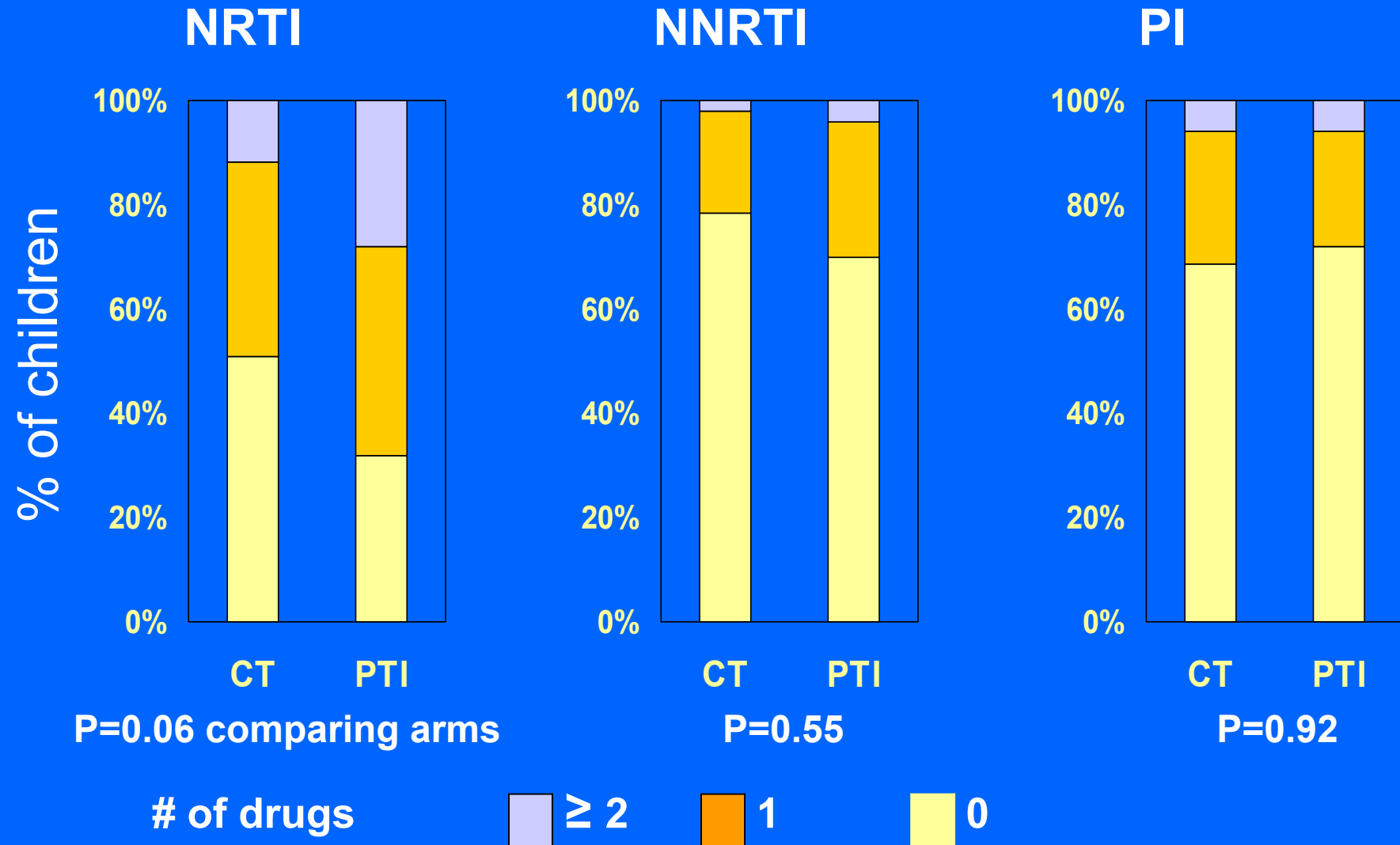
Switching ART regimen

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

New drugs never used before prescribed after baseline, by class



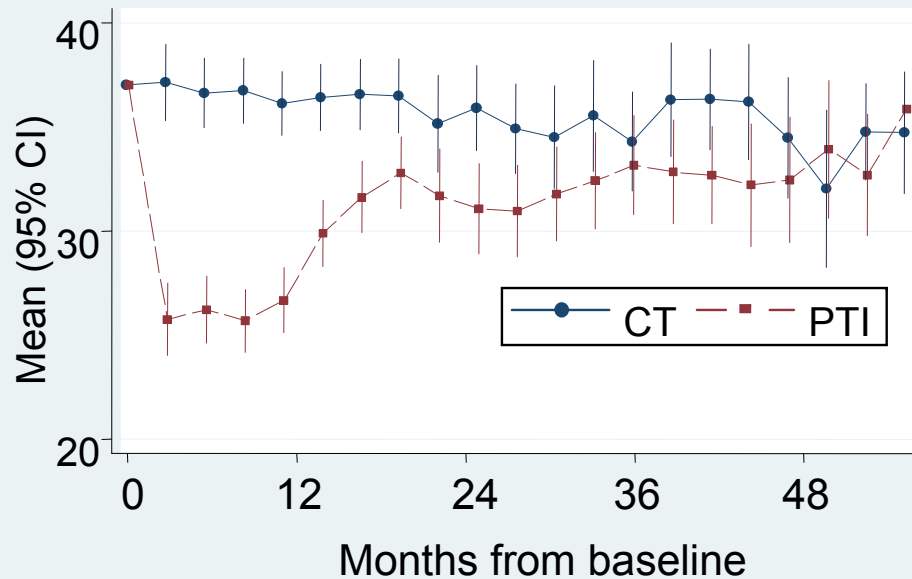
Immunological and virological outcomes at 12 and 24 months after end of trial

		Mean (SE) or proportion CT	Mean (SE) or proportion PTI	Difference or risk ratio (95% CI) comparing PTI vs CT	P-value
CD4%	12m	35.8 (1.0)	32.7 (1.0)	-3.5 (-6.3, -0.7)	0.014
	24 m	36.0 (1.1)	34.6 (1.0)	-1.6 (-4.5, 1.3)	0.27
CD4 count (cells/mm ³)	12 m	925 (45)	808 (44)	-126 (-251, -1)	0.048
	24 m	864 (39)	832 (39)	-42 (-149, 65)	0.44
CD8%	12m	33.6 (1.3)	36.6 (1.3)	3.3 (-0.5, 7.1)	0.085
	24 m	34.1 (1.5)	36.3 (1.4)	2.4 (-1.7, 6.5)	0.24
HIV-1 RNA <50 copies/ml	12 m	90% (44/49)	77% (36/47)	0.85 (0.71, 1.02)	0.074
	24m	86% (37/43)	82% (37/45)	0.95 (0.79, 1.14)	0.57

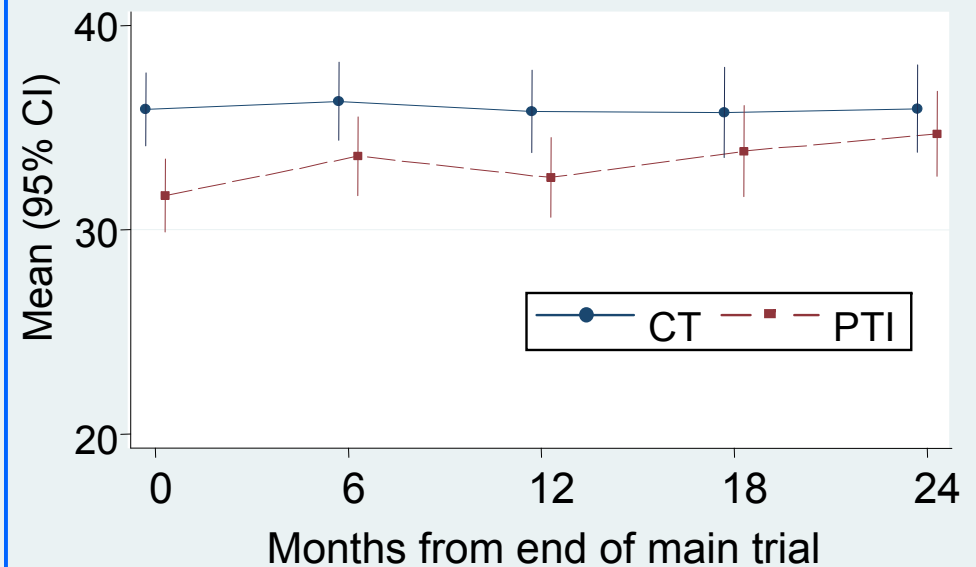


CD4 % over time

Mean CD4 % over time from baseline



Mean CD4% over time from end of main trial



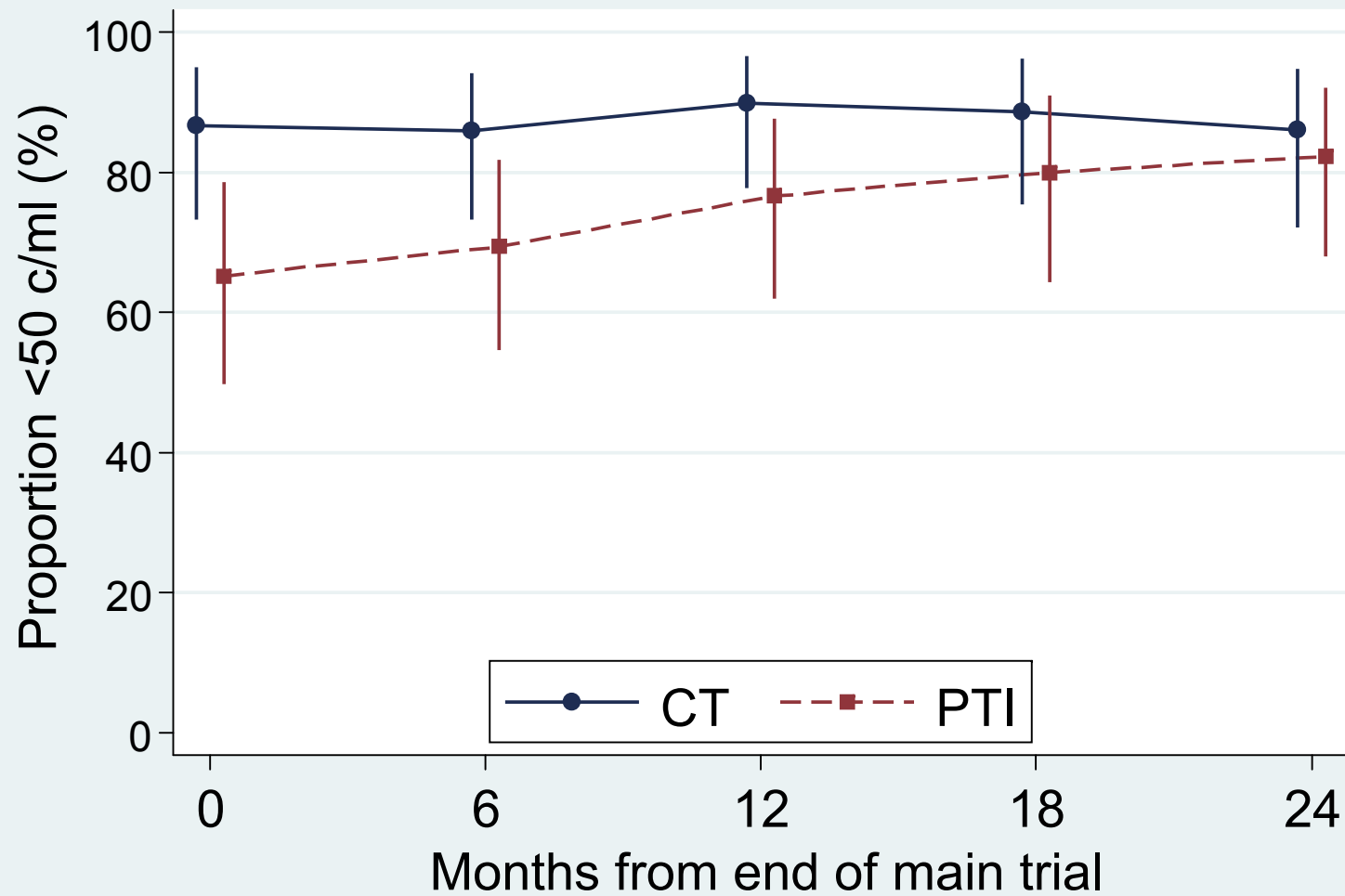
Number of children

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

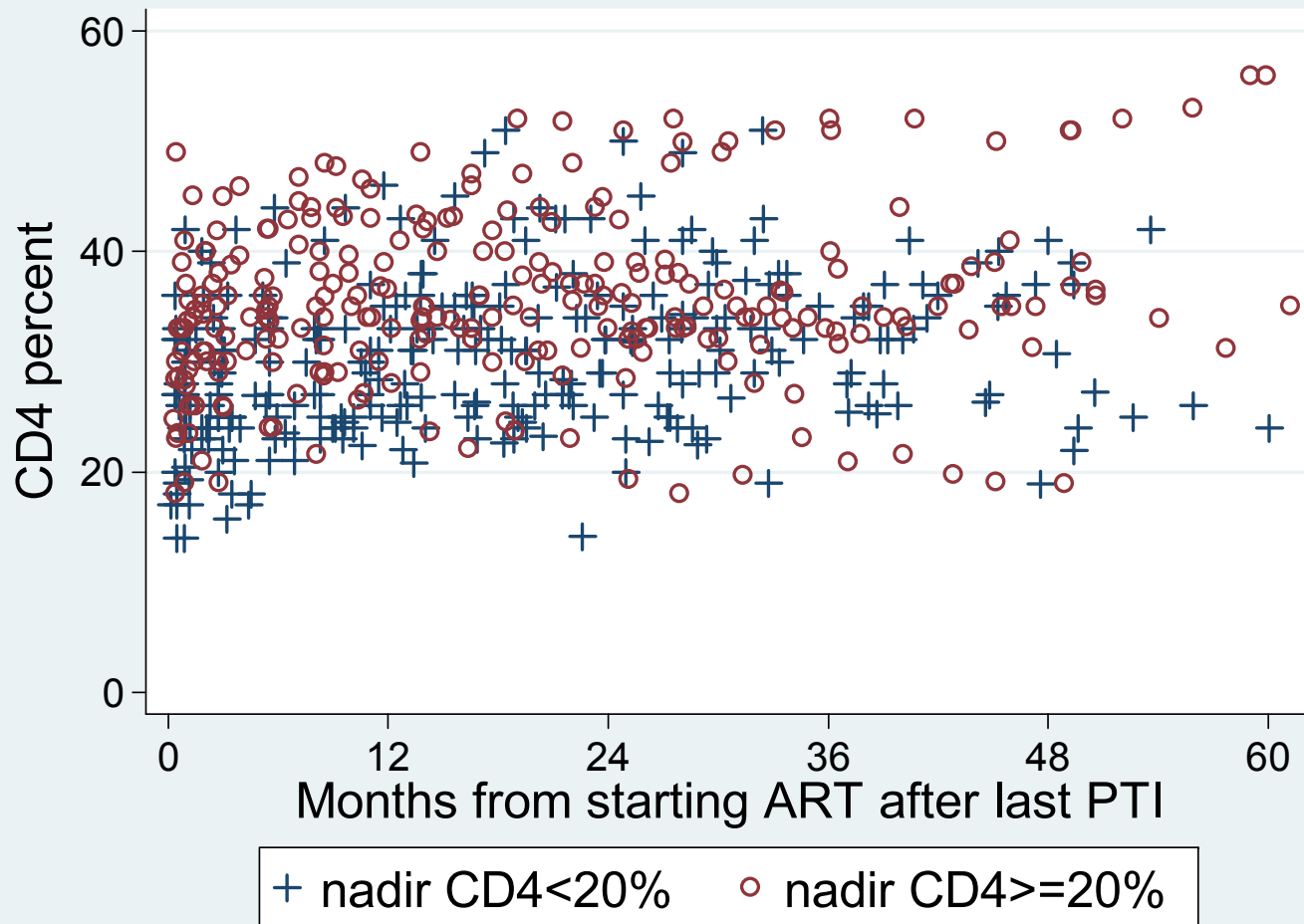
Number of children

CT	46	48	45	42	47
PTI	40	44	47	42	48

Proportion HIV-1 RNA <50 copies/ml from end of main trial



Association between nadir CD4 and CD4 recovery in PTI group



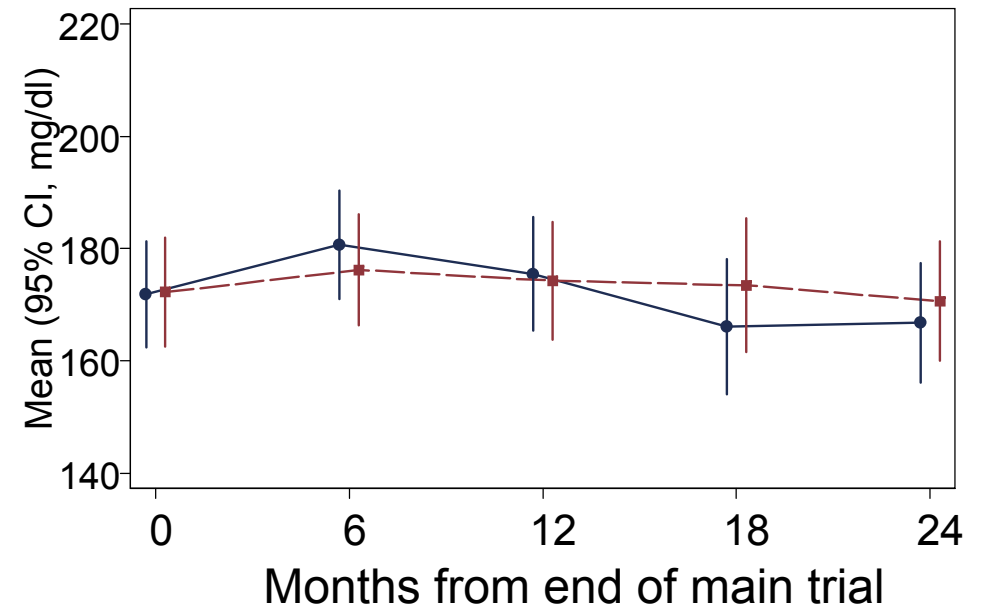
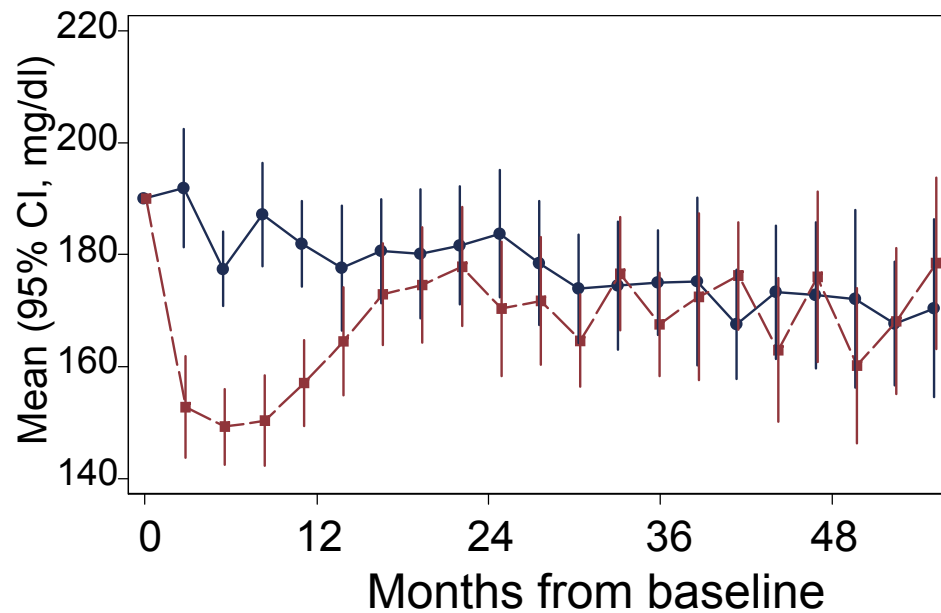
Based on measurements since child restarted ART after last PTI

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

Total cholesterol

Mean cholesterol over time from baseline

Mean cholesterol over time from end of main trial



—●— CT —■— PTI



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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