LONG-TERM CONSEQUENCES OF PLANNED TREATMENT INTERRUPTION IN HIV-1-INFECTED CHILDREN.

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Poster N°:919

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Background: Planned Treatment Interruption (PTI) in HIV-1 infected patients has been introduced over the past years to reduce long-term drug toxicity and to preserve different ART options for the future. PENTA 11 was the first trial that studied the response to 48 weeks CD4-guided PTI in HIV-1 infected children [1]. PTI arm showed a rapid increase in HIV-1 plasmaviremia over the first 4 ART-off weeks. CD4 cell count fell in the first 12 ART-off weeks, with a decrease in both naive and memory cells. CD8 cell count increased in the first 8 ART-off weeks and this increase was mainly due to CD8 memory cells. PTI was also associated with rapid and sustained increase in CD4 cells expressing activation markers Ki67 and HLA-DR and increased levels of HIV-1 proviral DNA [2]. Despite these changes, no adverse clinical serious events have been observed. After the end of main trial (EOT), all children were advised to resume ART. The aim of this study was to assess the long-term immunological and virological outcomes of the PTI strategy in children up to 4 years after EOT.

Methods: 54 children (randomized at main trial baseline: 23 to CT and 31 to PTI arm) entered the long-term viro-immunological substudy (Fig. 1). Immunophenotyping of CD4 and CD8 memory and naive cell subsets, thymic output by means of TREC quantification, cell-associated HIV-1 DNA and HIV-1 RNA were analyzed on available samples at EOT, 1, 2, 3, and 4 years after EOT.

Statistical Analyses: Each continuous variable was analysed using a longitudinal mixed model to account for repeated measures within the same subject. The significance of the fixed effects and the difference between CT and PTI at each time assessment were tested using the F statistic. Relationships between variables were explored by means of the Spearman rank correlation coefficient. For all the analyses mean and 95% CI have been calculated. All tests were two-sided, and a $P < 0.05$ was considered statistically significant.

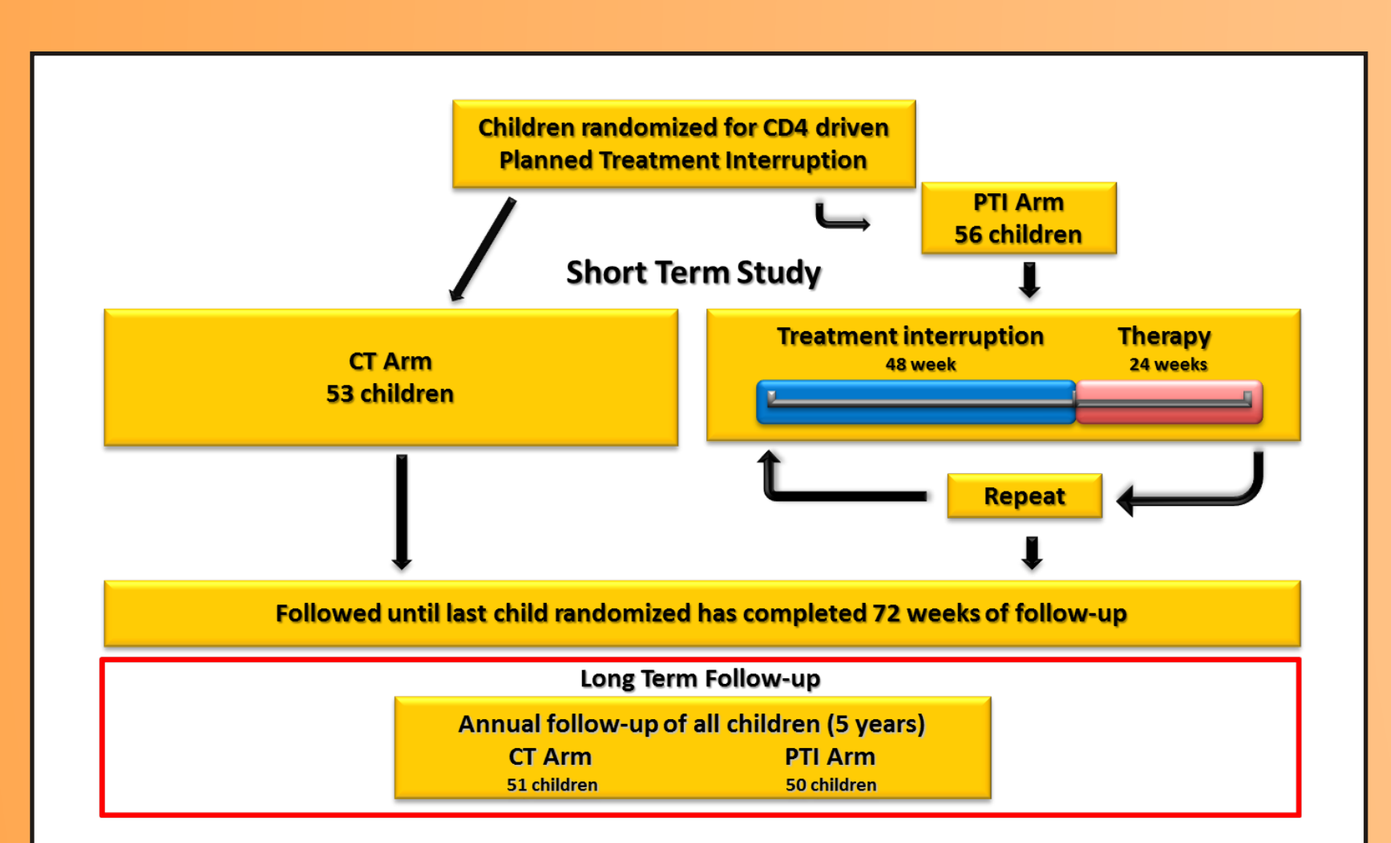

Figure 1: **Schematic design of PENTA11 main trial and long-term follow-up.** A total of 109 children were enrolled in the main trial and randomized in PTI and CT arms. The PTI group experienced 48 weeks of treatment interruption, followed by 24 weeks of therapy resumption. After the end of the main trial (EOT), 54 children entered the long-term viro-immunological substudy.

Table a. Comparison of baseline characteristics between main trial and substudy

	Main trial CT (n=53)	Main trial PTI (n=56)	Substudy CT (n=23)	Substudy PTI (n=31)	Substudy p-value CT vs PTI	Overall p-value Main trial vs substudy
Male (%)	22 (42 %)	27 (48 %)	9 (39 %)	14 (45 %)	0.66	0.78
Age (years)						
Median (IQR)	9.9 (6.4, 12.3)	9.0 (6.7, 11.9)	10.1 (7.0, 11.1)	9.0 (6.0, 10.9)	0.37	0.84
≥2 years to <7 years	15 (28 %)	17 (30 %)	4 (17 %)	10 (32 %)		
≥7 years to <11 years	18 (34 %)	22 (40 %)	11 (48 %)	14 (45 %)	0.40	0.48
≥11 years to <16 years	20 (38 %)	17 (30 %)	8 (35 %)	7 (23 %)		
CDC stage						
% N/A/B/C	17/23/26/34	10/34/29/18	22/26/22/30	13/39/32/16	0.39	0.91
HIV-RNA						
≥50 copies/ml at baseline	3 (5.7 %)	8 (14.3 %)	2 (8.7 %)	6 (19.4 %)	0.28	0.38
CD4 parameters, median (IQR)						
CD4 % of total lymphocytes	37 (34, 40)	37 (33, 42)	38 (36, 43)	37 (33, 43)	0.58	0.20
CD4 (cells/mm^3)	965 (741, 1222)	967 (844, 1302)	1050 (715, 1228)	969 (873, 1318)	0.52	0.77
CD8 parameters, median (IQR)						
CD8 % of total lymphocytes	31 (27, 34)	33 (26, 37)	30 (25, 36)	31 (24, 35)	0.81	0.36
CD8 (cells/mm^3)	790 (592, 1020)	870.5 (615, 1070)	790 (576, 940)	710 (544, 1057)	0.99	0.31
CD3 parameters, median (IQR)						
CD3 % of total lymphocytes†	71 (69, 75)	73 (69, 78)	73 (69, 76)	73 (66, 78)	0.92	0.44
CD3 (cells/mm^3) ‡	1785 (1347, 2200)	1860 (1668, 2146)	1882 (1504, 2272)	1883 (1662, 2135)	0.76	0.85

†11, 13, 2 and 6 missing values from CT, PTI (main trial), CT, PTI (substudy) respectively ‡11, 15, 2 and 7 missing values from CT, PTI (main trial), CT, PTI (substudy) respectively

Table b. Comparison of clinical parameters at end of trial between all participants entering the long-term follow-up and participants in the substudy

	At end of main trial, entering LTFU (n=101) n	CT (n=51)	n	PTI (n=50)	Substudy (n=54) n	CT (n=23)	n	PTI (n=31)	Substudy p-value CT vs PTI	Overall p-value Main vs substudy
Age (years) Median (IQR)		12 (9, 15)		11 (9, 13)		12 (9, 14)		12 (9, 13)	0.546	0.793
Age group (n, %)										
≥2 years to <7 years		4 (8 %)		4 (8 %)		1 (4 %)		3 (10 %)		
≥7 years to <11 years		19 (37 %)		17 (34 %)		8 (35 %)		9 (29 %)	0.883	0.850
≥11 years to <16 years		23 (45 %)		25 (50 %)		12 (52 %)		16 (52 %)		
Over 16 years of age at EOT		5 (10 %)		4 (8 %)		2 (9 %)		3 (10 %)		
CDC stage										
% N/A/B/C		16/22/25/37 %		18/32/32/18 %		17/26/22/35 %		13/35/35/16 %	0.348	0.907
HIV-RNA										
≥50 copies/ml at EOT	45	6 (13 %)	46	16 (34 %)	22	3 (14 %)	30	11 (37 %)	0.064	0.716
CD4 parameters, median (IQR)										
CD4 (cells/mm3)	46	927 (700, 1140)	40	792 (595, 1045)	22	834 (667, 1097)	25	800 (600, 1006)	0.516	0.527
CD4 % of total lymphocytes	46	36 (31, 42)	46	32 (28, 36)	22	40 (32, 44)	30	32 (28, 35)	0.006	0.671
CD8 parameters, median (IQR)										
CD8 (cells/mm3)	44	773 (649, 973)	39	910 (688, 1281)	20	714 (584, 808)	24	900 (722, 1162)	0.027	0.397
CD8 % of total lymphocytes	44	31 (27, 37)	44	39 (32, 43)	20	31 (27, 36)	28	39 (32, 42)	0.029	0.971
CD3 parameters, median (IQR)										
CD3 (cells/mm3)	36	1774 (1455, 2124)	33	1883 (1510, 2383)	18	1553 (1434, 2002)	23	1830 (1277, 2250)	0.351	0.526
CD3 % of total lymphocytes	35	73 (67, 78)	33	76 (71, 79)	18	74 (71, 78)	22	76 (69, 79)	0.817	0.916

Characteristics at baseline and at EOT of children included in this subgroup are comparable to those of children enrolled in the main trial (Table a,b). The median baseline age was 9.55 years (range 6.0-11.1) and median follow-up was 6.6 years (IQR 5.8-7).

During the long term substudy, all CT children were on ART, while in the PTI arm proportion of children on ART were 84% at EOT, 84%, 87%, 89%, 93% at 1,2,3 and 4 years follow-up, respectively.

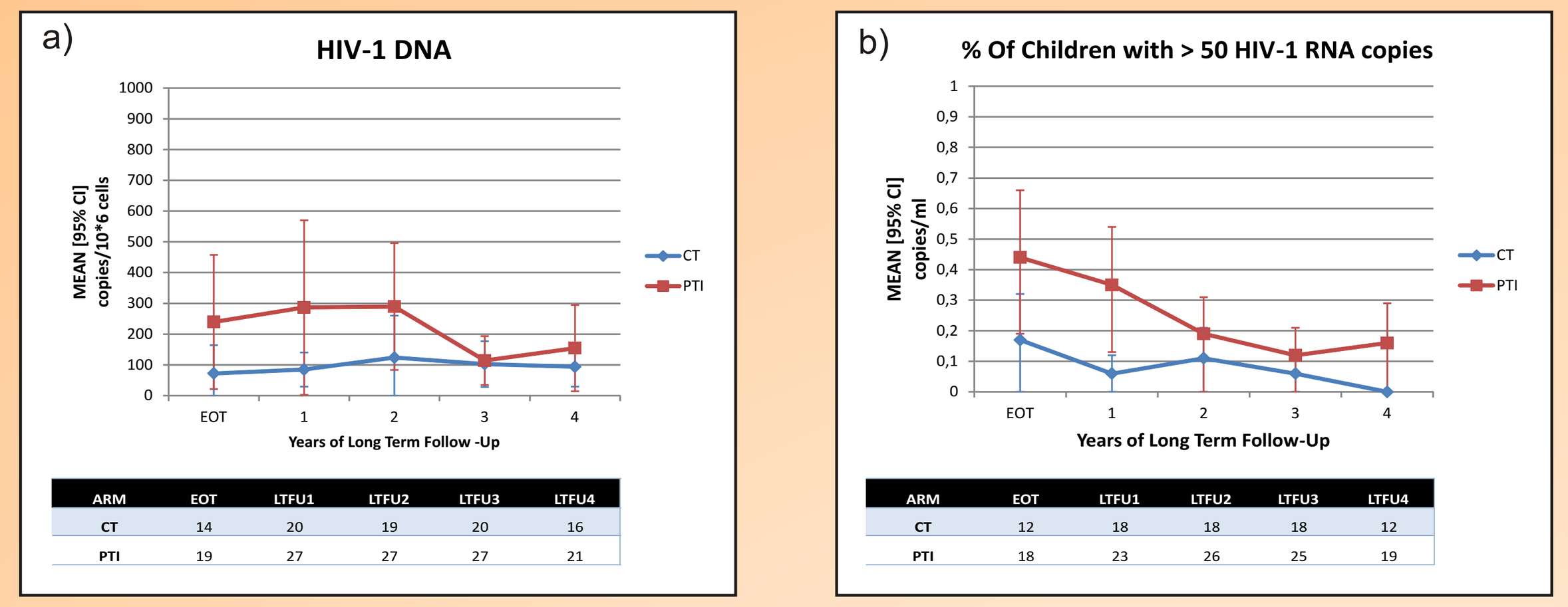

Figure 2: **Cell associated HIV-1 DNA and HIV-1 RNA plasmaviremia during the 4 years follow-up after the end of main trial (EOT).** Trends were estimated using normal linear regression with overall mean values for the reference category.

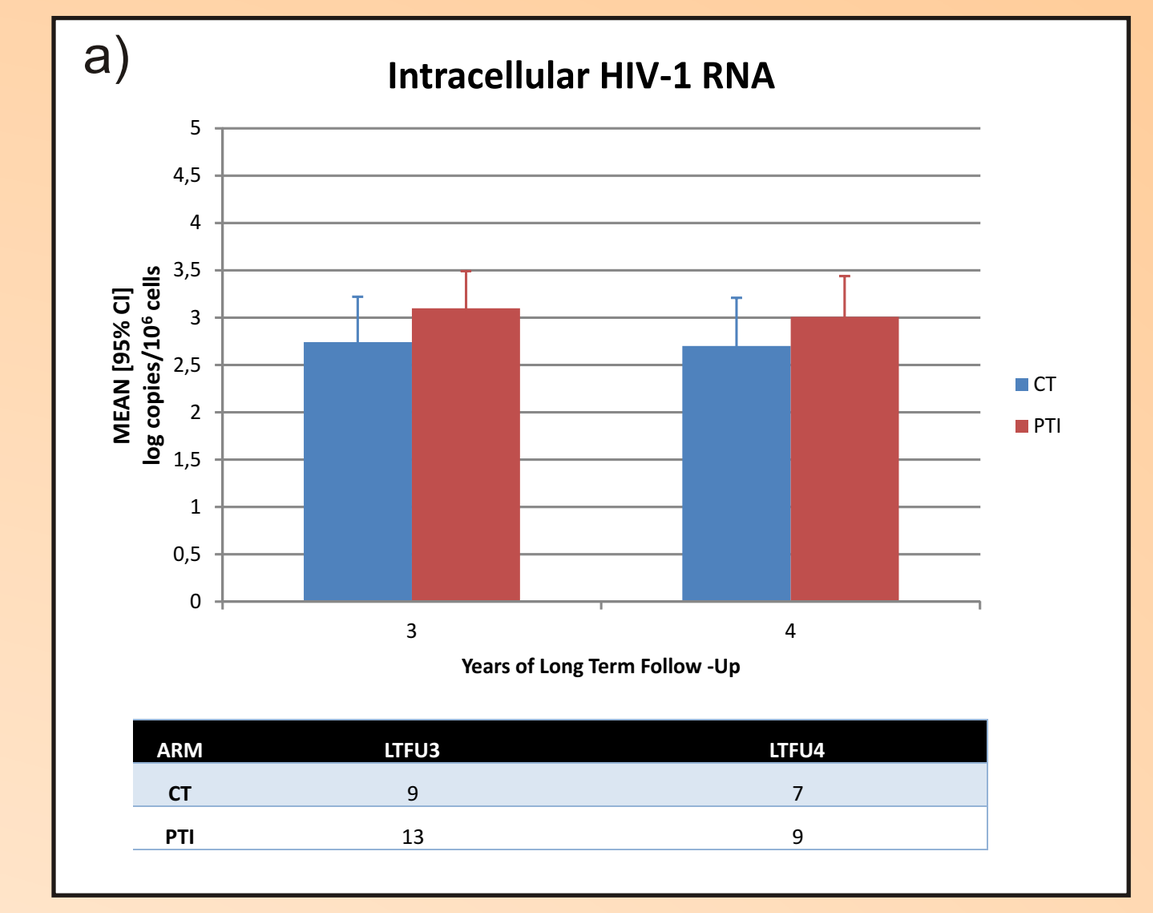

Figure 3: **Intracellular HIV-1 RNA levels. These data were obtained in available samples at 3 and 4 years follow-up (a).**

At EOT, HIV-1 DNA levels, as well as children with detectable HIV-RNA plasmaviremia, were higher in PTI than CT arm (Fig. 2a-b). At 1-year follow-up, levels of cell-associated HIV-DNA were still higher in PTI than in CT children (295 va 70 copies/10*6 cells; p=0.035), as was the proportion of children with detectable HIV-1 RNA in plasma (35% vs 6%; Fig. 2b). Cell-associated HIV-1 DNA and plasmaviremia slightly decreased during follow-up in the PTI arm. Cell-associated HIV-1 RNA was higher in PTI than CT children (3.01 vs 2.70 $\log_{10}$ copies/10^6 cells), consistent with a higher level of productive infection in the former (Fig. 3a).

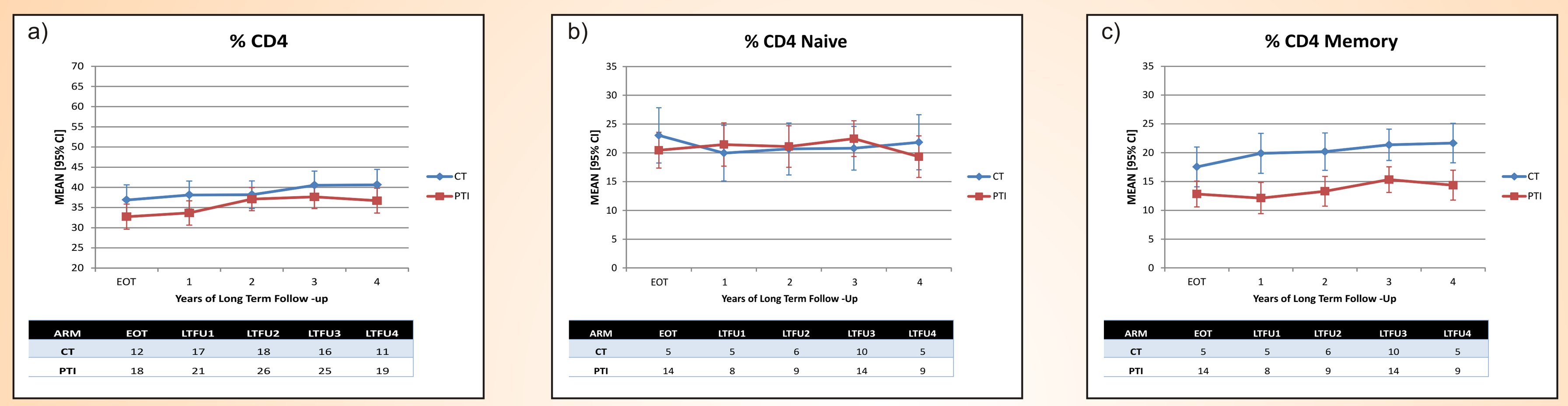

Figure 4: **CD4%, naive CD4% and memory CD4% during the 4 years follow-up after the end of main trial (EOT).** Trends were estimated using normal linear regression with overall mean values for the reference category.

At EOT CD4% is lower in PTI than CT; at 1 year follow-up mean [95% CI] CD4 cells were lower in PTI than CT (708 [578-837] vs 876 [738-1014] cells/mm^3; p=0.082) as were the CD4% (33.66 [30.63-36.69] vs 38.36 [34.76-41.95]; p=0.049)(Fig. 4a). Of interest, %CD4 naïve cells did not differ between the two groups (Fig. 4b), while CD4 memory cells remained persistently lower from EOT up to 4 years follow-up in the PTI arm (p=<0.0001; Fig. 4c).

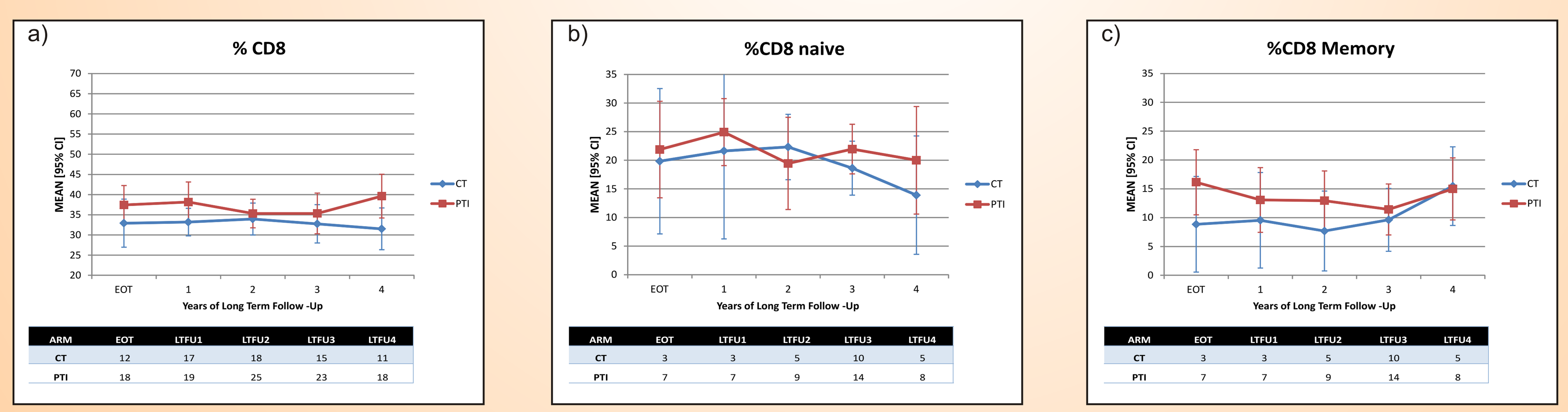

Figure 5: **CD8%, naive CD8% and memory CD8% during the 4 years follow-up after the end of main trial (EOT).** Trends were estimated using normal linear regression with overall mean values for the reference category.

At EOT CD8% is higher in PTI than CT; at 1 year follow-up CD8% was higher in PTI than CT (38.07 [34.39-41.74] vs 32.39 [28.28-36.50]; p=0.044)(Fig. 5a). In this population %CD8 naïve cells did not differ between the two groups (Fig. 5b), while %CD8 memory cells were persistently higher in PTI than in CT (Fig. 5c).

CD4/CD8 ratio, tended to be lower in PTI than CT at EOT and during the follow-up although not at significant level (Fig. 6a). TREC levels were higher at 1and 2 year follow-up in CT than in PTI (1 year: 2551 [2049-3054] vs 1855 [1283-2428] copies 10^5 cells; p=0.073)(Fig. 7a).

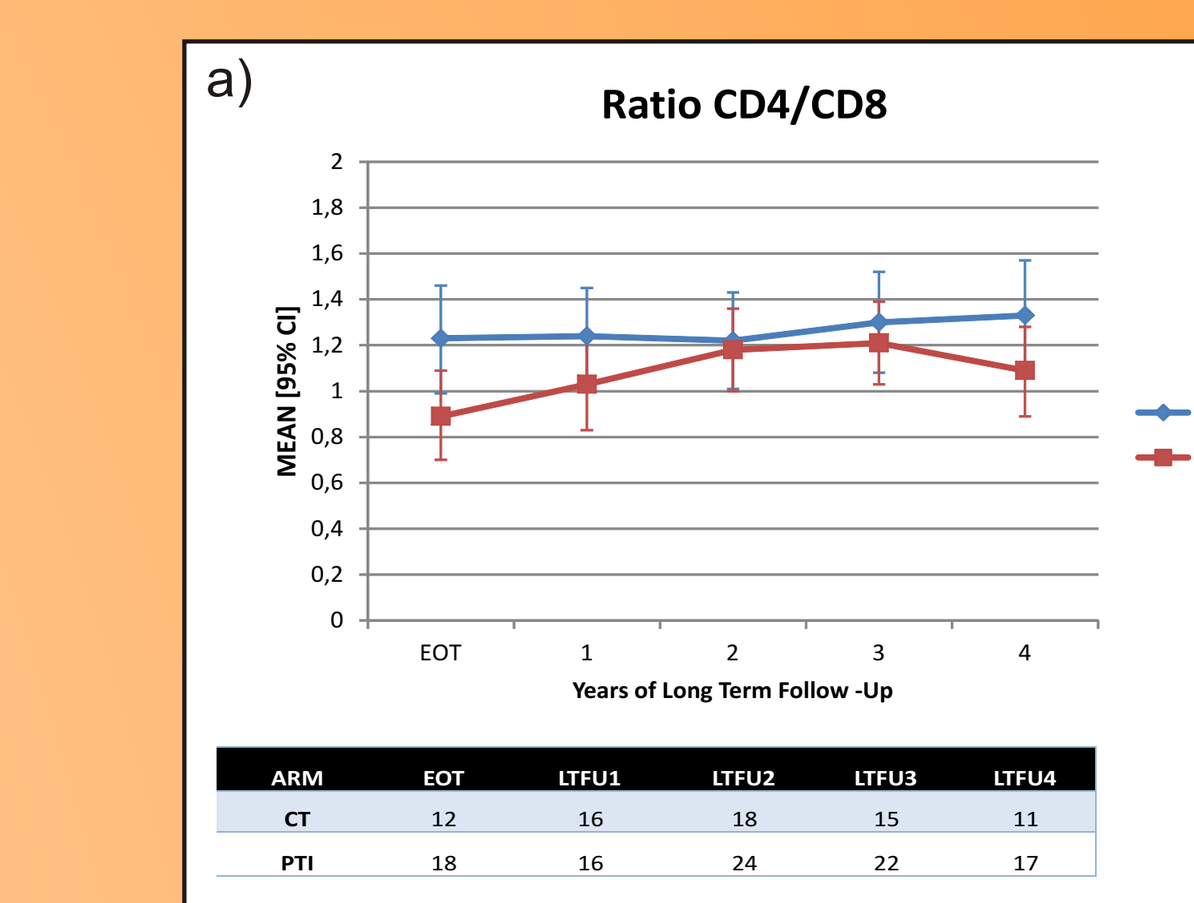

Figure 6: **CD4/CD8 ratio during the 4 years follow-up after the end of main trial (EOT).** Trends were estimated using normal linear regression with overall mean values for the reference category.

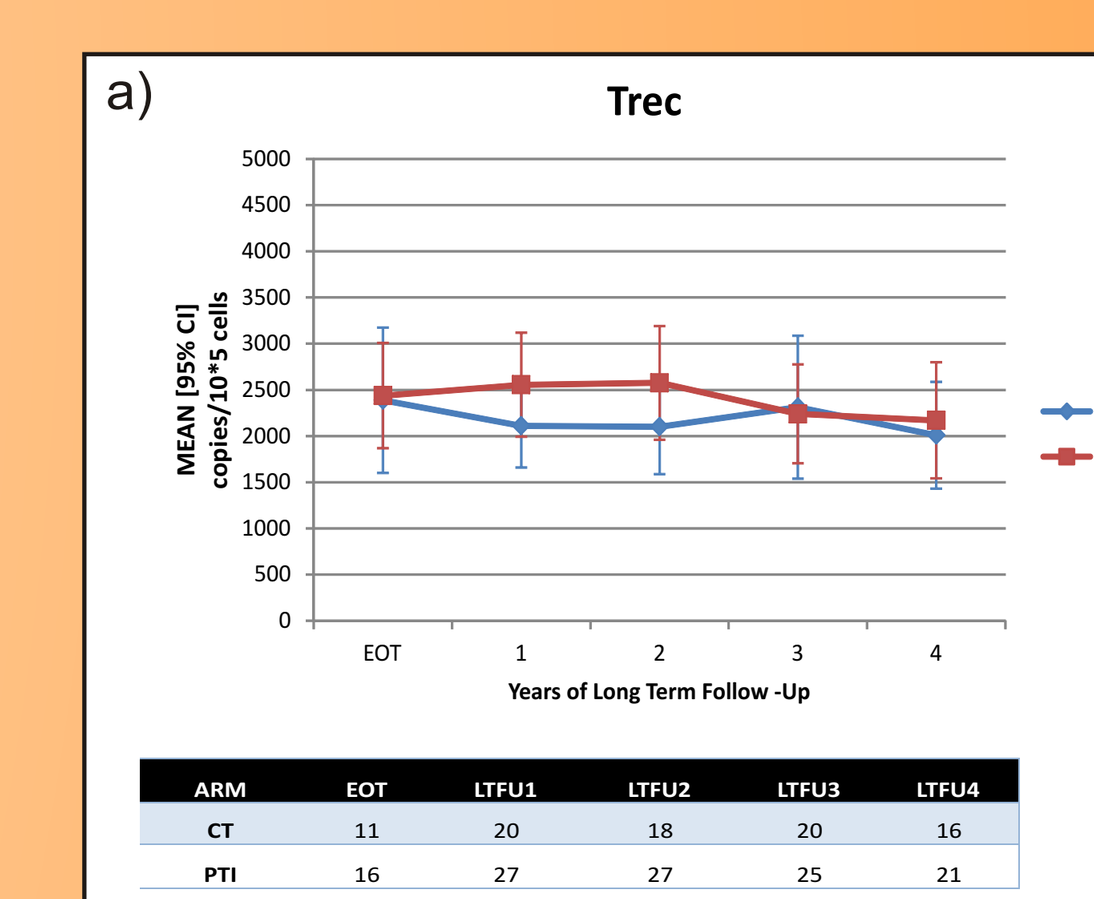

Figure 7: **TREC levels during the 4 years follow-up after the end of main trial (EOT).** Trends were estimated using normal linear regression with overall mean values for the reference category.

Conclusions: Most of the short term immunological and virological consequences of PTI were still present 1 year after the end of the trial, but no longer detectable after 2 years follow-up. Interestingly, CD4 memory cells continued to be lower in PTI children. While thymic output may compensate for loss of naive CD4 cells, the persistent depletion of CD4 memory cells from higher residual productive infection in PTI than in CT children. In this sub-group of patients, lower adherence to ART in PTI arm may partially explain the viro-immunological changes observed after the end of main trial.

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