Outcomes after reinitiating antiretroviral therapy in children randomized to planned treatment interruptions

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Background: Excess risks for death/opportunistic disease in adults randomized to CD4-driven planned treatment interruption (PTI) in the Strategies for Management of Antiretroviral Therapy (SMART) trial remained after antiretroviral therapy (ART) re-initiation. Risks for children following PTI were evaluated in long-term follow-up of children in the PENTA 11 trial.

Methods: Children with HIV RNA below 50 copies/ml and CD4 at least 30% (2–6 years) or at least 500 cells/μl (7–15 years) were randomized to continuous ART (cART) or PTI in PENTA 11 (ISRCTN 36694210). After the end of the trial, all were recommended to resume ART. Data were collected annually and analysed up to the second year of visit.

Results: One hundred and one (51 cART, 50 PTI; median baseline age 9.2 years) children had median overall follow-up 4.6 (range 3.7–5.0) years. During 2-year post-trial period, there were no deaths or new Centers for Disease Control and Prevention (CDC) stage B/C events. Rate of clinical grade of at least two events was similar between PTI and cART [relative risk (RR) 1.03; 95% confidence interval (CI) 0.43, 2.50; $P = 0.94$]. At 2 years, difference in absolute CD4% between PTI and cART was −1.6% (−4.5%; 1.3%; $P = 0.27$), and proportions with HIV RNA below 50 copies/ml were 82 versus 86% ($P = 0.57$), respectively; no differences in growth or fasting lipids were observed. Key predictors of greater CD4% recovery after re-initiating ART were higher CD4% at baseline ($P < 0.001$) and longer time since ART re-initiation ($P < 0.001$). During overall follow-up, 4 (8%) PTI versus 5 (10%) CT children switched ART for failure ($P = 0.75$) and 9 (18%) versus 1 (2%) ($P = 0.008$) substituted ART for simplification.

Conclusions: No adverse clinical, immunological or virological consequences of PTI were observed 2 years after the end of PENTA 11 trial. Although ART interruption is not generally recommended, it may be an acceptable option for children, particularly when there is high risk of unplanned treatment interruptions.

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Introduction

Several randomized studies of CD4-guided planned treatment interruption (PTI) strategies in HIV-infected adults have been conducted [1–3] with goals to reduce long-term drug toxicity of antiretroviral therapy (ART) and preserve future ART options. However, greater risks of AIDS, deaths, and unexpectedly, serious non-AIDS events, were observed during CD4-guided PTI compared to continuous ART (cART) in the large randomized Strategies for Management of Antiretroviral Therapy (SMART) trial, making PTI a nonviable treatment strategy option for adults [1,4]. The excess risks for opportunistic disease and death remained after patients randomized to PTI resumed ART [5]. Systemic inflammation induced by viraemia following PTI is postulated to be the underlying mechanism [6,7].

The Paediatric Eugropean Network for Treatment of AIDS (PENTA) 11 trial, the only paediatric randomized trial to date of PTI versus cART in children, did not find a greater risk of adverse clinical outcomes with PTI; however, its much smaller size compared to the SMART trial precluded making recommendations at this stage [8]. As detailed in the main study, when the SMART results were released (March 2006), the Trial Steering Committee and Data Monitoring Committee endorsed continuation of PENTA 11 but with an amendment which increased the safety of the trial [8], and the trial continued to the end of the planned trial on 29 May 2008. Revised criterion to restart ART during the trial was a confirmed CD4% below 20% or interruption of ART for more than 48 weeks; any child needing to restart ART within 10 weeks of interruption would not interrupt ART again [8]. At trial end, all children were recommended to re-initiate ART and were followed for possible long-term adverse consequences of PTI and further study of long-term detailed immunological [9] and neurodevelopmental [10] consequences of interruption in an extension phase. Here, we report on clinical, CD4 and virologic outcomes at 2 years following completion of the PENTA 11 main study, comparing between PTI and cART arms.

Methods

Study design and population

The PENTA 11 main trial (ISRCTN 36694210) has been previously described [8]. In brief, HIV-infected children were eligible if they had been on any combination ART regimen containing three or more drugs which had been taken for at least 24 weeks; had confirmed HIV RNA below 50 copies/ml and had two most recent CD4% at least 30% (age 2–6 years) or at least 25% and CD4 cell count at least 500 cells/μl (age 7–15 years). Randomization was stratified by whether a child started combination ART before 3 months of age; and if not by age ($<$ or $\geq$7 years) and by lowest recorded CD4% before starting ART (nadir CD4%, categorized as $<$ or $\geq$15%). Children were followed until the last randomized child had completed 72 weeks of follow-up.

At trial end on 29 May 2008, children in the PTI arm were recommended to restart ART. Routine annual data (ART, AIDS events, weight and height, CD4, HIV RNA and lipid levels) were collected from the end of main trial with approvals from local ethics committees of all sites (for total 5 years). Further ethics and regulatory approvals were requested to take blood stores and perform annual neurocognitive function tests; consent from caregivers/young people and assent from children, as appropriate and according to national guidelines, were obtained for this. US sites did not participate in any long-term follow-up.

Statistical analyses

Analyses presented here were based on data collected up to end of second year following the end of the main trial among children participating in long-term follow-up. Weight, height, CD4, HIV RNA and other laboratory measurements at 1 and 2 years from trial end were defined as those taken nearest to but within $\pm$3 months of these respective time points. Values at ART re-initiation following the most recent PTI were defined as the nearest measurements up to the ART restarting date which was taken within the preceding 3 months and while off therapy.

Comparison between the two randomized arms was according to intention-to-treat, adjusting for stratification factors in regression analyses. Rate of clinical events from end of the main trial up to last clinic visit was compared between arms using random-effects Poisson models, allowing more than one event(s) diagnosed per child. Virologic suppression below 50 copies/ml at 1 and 2 years was analysed using a modified Poisson regression approach (as recommended for binary outcomes which are common) [11]. Absolute values of CD4 percentage and count, weight-for-age and height-for-age z-scores, and lipid levels at 1 and 2 years were analysed using linear regression, adjusted for baseline values. Based on two-sided significance level of 0.05, the power of the study to detect a difference in CD4 percentage of 5, 4, 3 and 2% between arms was 83, 65, 42 and 21%, respectively. For ART outcomes, proportions were compared using chi-squared or Fisher's exact tests. Analyses at 1 and 2 years were repeated excluding children in PTI arm who were off ART at the end of main trial and had not been back on treatment for at least 3 months at each respective time point.

On the basis of all CD4% measurements in the PTI arm after each child restarted ART following the most recent PTI, effects of the following factors on CD4 recovery were assessed: baseline characteristics, CD4% and HIV

RNA at ART re-initiation, nadir CD4% (lowest recorded CD4% before starting combination ART), number of PTIs the child experienced and time since ART re-initiation. Longitudinal mixed models were fitted for absolute CD4% to account for repeated measures within the same child. Nonlinear effects of continuous covariates were assessed using cubic spline terms with knots at the 10th, 50th and 90th [12]. All analyses were undertaken using Stata version 11 (Stata Corp., College Station, Texas, USA).

Results

A total of 101 (51 cART, 50 PTI) of the 109 children in the main trial participated in long-term follow-up; all had year 1 and 95 had year 2 follow-ups (Fig. 1). Seventy-nine children were from Europe and 22 from Thailand. Of the remaining eight children not in long-term follow-up, four were from the US site, two were lost to follow-up, one withdrew consent during the main trial and one was transferred to adult care after the end of the main trial.

Among children participating in the long-term follow-up, median duration of follow-up from trial enrolment was 4.6 (range 3.7–5.0) years. Fifteen of the 50 children in the PTI arm had experienced a second PTI during the main trial, and none had a third PTI. Characteristics at PENTA 11 enrolment (pre-PTI) were similar between the two arms (Table 1). Almost half were male and the median baseline age was around 9 years. The majority initiated ART at a young age (median 2.0 years old), and had asymptomatic or mildly symptomatic HIV disease with median CD4% of 37% and CD4 cell count of 970 cells/μl. More cART children had HIV RNA less than 50 copies/ml at baseline (94 versus 86% in PTI).

Status at end of main trial

At the end of the main trial, one child in the cART arm was off ART. Forty-three (86%) of the 50 children in PTI were back on ART for a median duration 11.8 [interquartile range (IQR) 7.1–22.8] months since their last PTI. Among the remaining PTI children, six were still undergoing a PTI and one was off ART due to poor adherence. Compared to children in the cART arm, those in the PTI arm had lower CD4% (median 32 versus 36%; $P < 0.001$) and CD4 cell counts (792 versus 927 cells/μl; $P = 0.06$), and also were less likely to have viral load suppression below 50 copies/ml (60 versus 76%; $P < 0.001$) (Table 1). The cumulative ART exposures were 8.3 years in the cART arm and 7.0 years in the PTI arm.

Outcomes during the 2-year follow-up after the main trial

During the 2 years after trial end, no child died or had a new CDC stage B or C event. There were 21 clinical events diagnosed in 13 (25%) children in the cART arm and 20 events in 12 (24%) children in the PTI arm (all were grade 2 or above). The rates [95% confidence interval (CI)] of events per 100 child-years were 20.9

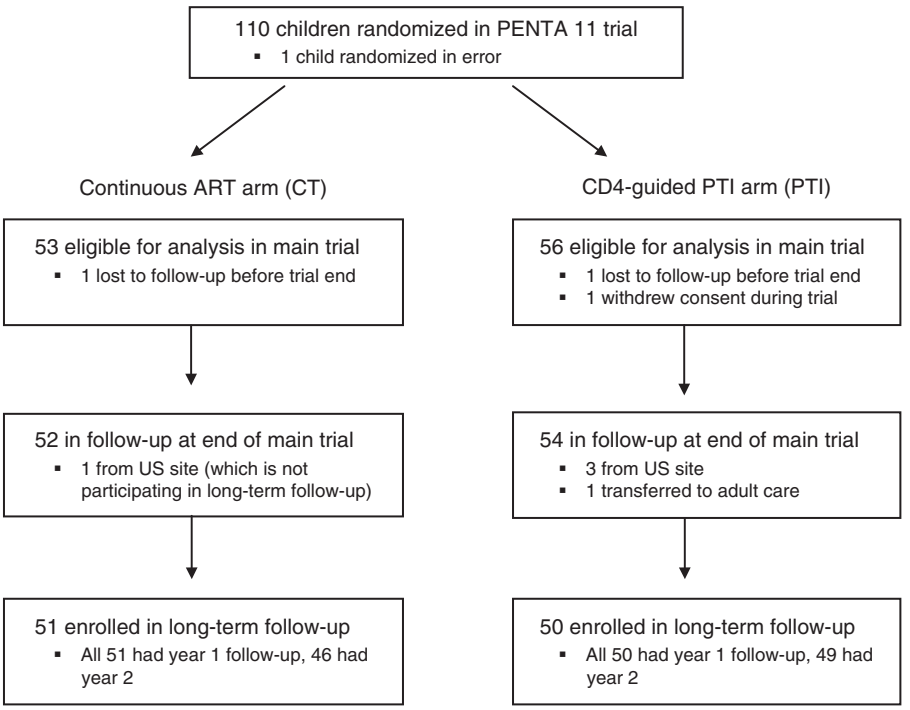

Fig. 1. Flowchart of children included in PENTA 11 long-term follow-up.

Table 1. Characteristics at baseline and end of main trial: children in long-term follow-up.

	At baseline		At end of main trial	
	cART ($n=51$)	PTI ($n=50$)	cART ($n=51$)	PTI ($n=50$)
Male (%)	21 (41%)	24 (48%)	–	–
Age (years), median (IQR)	9.8 (6.3, 12.0)	8.8 (6.1, 11.4)	12.1 (9.0, 14.6)	11.3 (9.0, 13.3)
%Ethnic origin				
White: black: Asian: others	31: 31: 24: 14%	40: 28: 20: 12%		
%CDC disease stage				
N: A: B: C	16: 22: 25: 37%	18: 32: 32: 18%	16: 22: 25: 37%	18: 32: 32: 18%
Number of children on ART (%)	51 (100%)	50 (100%)	50 (98%)	43 (86%)
CD4 parameters, median (IQR)				
Nadir CD4% before starting combination ART	18 (10, 27)	21 (12, 26)		
CD4%	37 (34, 40)	37 (33, 42)	36 (31, 42)	32 (28, 36)
CD4 cell count (cells/μl)	965 (738, 1222)	1013 (860, 1280)	927 (700, 1140)	792 (595, 1045)
HIV RNA <50 copies/ml	48 (94%)	43 (86%)	39 (76%)	30 (60%)
Age when started ART, years, median (IQR)	2.2 (0.4, 4.6)	1.8 (0.5, 4.3)		
Initial regimen mono/dual ART (%)	16 (31%)	14 (28%)		
Cumulative ART exposure, years, median (IQR)	6.0 (3.9, 8.8)	5.5 (2.9, 8.2)	8.3 (5.8, 11.2)	(4.7, 9.4)

ART, antiretroviral therapy; cART, continuous antiretroviral therapy; IQR, interquartile range; PTI, planned treatment interruption.

(13.6, 32.0) in the cART arm and 20.0 (12.9, 31.0) in the PTI arm (rate ratio comparing PTI versus CT of 1.03; 95% CI 0.43, 2.50; $P=0.94$), with similar type of events presenting in the two arms. The most common events were infections/infestations ($n=7$ total) and gastrointestinal disorders ($n=6$). The other events were respiratory symptoms ($n=5$), rash ($n=5$), hyperlipidaemia ($n=5$), anaemia/thrombocytopenia ($n=3$) and others ($n=10$). There were no differences in height-for-age and weight-for-age z-scores between arms at 1 and 2-year follow-up (Table 2). Mean CD4% was significantly lower in the PTI compared to the cART arms at 1 year from trial end (adjusted difference −3.5%; 95% CI −6.2%, −0.7%; $P=0.01$), but there was no evidence of any difference by 2 years (−1.6% [−4.5%, 1.3%]; $P=0.27$). Similar results were seen for CD4 cell count, with estimated difference at 2 years of −42 cells/μl (95% CI −149, 65 cells/μl; $P=0.44$). The proportions with HIV RNA below 50 copies/ml were 77% (36/47) in the PTI arm versus 90% (44/49) in the cART arm at 1 year from the end of the main trial ($P=0.07$); corresponding proportions at 2 years were 82% (37/45) versus 86% (37/43), respectively ($P=0.57$). No differences in lipid levels between the two arms were seen at 1 or 2 years follow-up. When analyses at 1 and 2 years were repeated excluding children in PTI arm who were off ART at end of main trial and had not been back on treatment for at least 3 months at each respective time point, the overall conclusions remained the same. In addition, the estimated differences between arms for CD4%, CD4 cell count and proportion with HIV RNA below 50 copies/ml were less compared with original analyses, as expected. Figure 2 shows the trend in absolute CD4% (Fig. 2a) and CD4 cell count (Fig. 2b) and proportion of children with HIV RNA below 50 copies/ml (Fig. 2c) over time from the beginning of the main trial and also from after main trial end.

Among those with complete relevant ART follow-up data, none of the children in the cART arm ($n=46$) were off ART at 2 years from trial end compared with 11% in PTI (5/47, three of whom had not restarted ART by this time following PTI, despite recommendation that all PTI children restart ART) ($P=0.06$). During overall follow-up from baseline, the number (%) of children in the PTI versus cART arms who changed at least two antiretroviral drugs simultaneously for treatment failure was four (8%) versus five (10%) ($P=0.75$), substituted at least three drugs simultaneously for toxicity was zero (0%) versus one (2%, for lipoatrophy) ($P=0.99$) and substituted at least three drugs simultaneously for simplification (mainly to once-daily and fixed-dose combination of tenofovir/emtricitabine or abacavir/lamivudine) was nine (18%) versus one (2%) ($P=0.008$), respectively. Six of the nine PTI children who substituted at least three drugs simultaneously for simplification did this when ART was resumed after PTI.

Predictors of greater CD4% recovery after restarting antiretroviral therapy

In multivariable analyses, independent predictors of higher absolute CD4% after restarting ART following the most recent PTI were higher baseline CD4% ($P<0.001$), higher CD4% at ART re-initiation ($P=0.02$) and longer duration of ART following re-initiation ($P<0.001$) (Table 3). Of note, CD4% increased mainly within the first 2 years back on treatment with only a modest change thereafter ($P<0.001$ for nonlinear trend). Also, the effect of CD4% at ART re-initiation on CD4 recovery was greatest soon after ART re-initiation and then decreased over time (P for interaction <0.001). Sex, ethnicity, baseline age, baseline CDC disease stage, baseline weight-for-age z-score, nadir CD4%, HIV RNA at ART re-initiation and number of PTIs did not predict long-term CD4 recovery.

Table 2. Summary of growth, virologic, immunologic, growth and laboratory outcomes at 1 and 2 years from the end of the main trial.

	At 1 year from end of main trial					At 2 years from end of main trial				
	n	cART Mean or proportion (SE)	*n*	PTI Mean or proportion (SE)	Difference or risk ratio comparing; PTI versus cART (95% CI)	*P*	*n*	cART Mean or proportion (SE)	*n*	PTI Mean or proportion (SE)	Difference or risk ratio comparing; PTI versus cART (95% CI)	*P*
Height-for-age z-score	48	−0.5 (0.1)	49	−0.6 (0.1)	−0.1 (−0.3, 0.1)	0.32	41	−0.5 (0.1)	46	−0.6 (0.1)	−0.2 (−0.4, 0.1)	0.23
Weight-for-age z-score	47	−0.2 (0.1)	49	−0.3 (0.1)	−0.1 (−0.4, 0.2)	0.43	44	−0.2 (0.1)	46	−0.3 (0.1)	−0.2 (−0.4, 0.1)	0.28
HIV RNA <50 copies/ml	49	90% (4%)	47	77 (6%)	0.85 (0.71, 1.02)[a]	0.07	43	86% (5%)	45	82% (6%)	0.95 (0.79, 1.14)[a]	0.57
CD4%	46	35.8 (1.0)	50	32.7 (1.0)	−3.5 (−6.2, −0.7)	0.01	47	36.0 (1.1)	49	34.6 (1.0)	−1.6 (−4.5, 1.3)	0.27
CD4 cell count (cells/μl)	45	925 (45)	47	808 (44)	−126 (−251, −1)	0.05	47	864 (39)	48	832 (39)	−42 (−149, 65)	0.44
Total cholesterol (mg/dl)	47	175.5 (5.2)	45	174.5 (5.3)	−1.0 (−15.5, 13.6)	0.90	43	166.8 (5.4)	44	17.6 (5.4)	4.0 (−11.6, 19.6)	0.61
LDL cholesterol (mg/dl)	28	97.9 (4.9)	30	97.7 (4.9)	−0.4 (−14.1, 13.4)	0.96	25	96.8 (4.8)	31	99.8 (4.4)	0.7 (−12.4, 13.9)	0.91
HDL cholesterol (mg/dl)	35	56.1 (2.2)	36	56.6 (2.2)	0.3 (−5.7, 6.4)	0.92	29	57.5 (2.2)	36	55.7 (2.0)	−2.6 (−8.2, 3.0)	0.36
Triglycerides (mg/dl)	46	104.7 (8.1)	44	107.7 (8.3)	4.4 (−18.8, 27.5)	0.71	41	97.5 (8.7)	44	101.5 (8.4)	5.2 (−18.8, 29.1)	0.67

ART, antiretroviral therapy; cART, continuous antiretroviral therapy; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PTI, planned treatment interruption.
[a]Estimated risk ratio.

Discussion

At 2 years after the end of the PENTA 11 trial, children who underwent CD4-guided PTI achieved similar clinical, immunologic and virologic outcomes compared to those who were on cART. ART interruption is not generally recommended, but the results of this study indicate that, in contrast to adults, PTI may be an acceptable therapeutic option in children because of their superior ability for CD4 recovery. Of note, higher CD4% before PTI and at the time of ART re-initiation, and longer time since ART re-initiation, were independently associated with greater CD4% recovery.

Treatment interruptions are sometimes necessary in children who experience side-effects to ART [13,14]. However, most interruptions are unplanned and are largely due to treatment fatigue and poor adherence, which are unfortunately common in carers administering ART to children, and particularly among adolescents who are increasingly responsible for their own medication as they get older. The inevitable increase in ART resistance and diminishing therapeutic options [15] is an important health issue and is very demanding on resources. In the US Adolescent Master Protocol, 25% of 444 children aged 7–16 years had at least one unsupervised ART interruption of 3 months or more [13] and in some settings the frequency of unplanned treatment interruption may be greater. In the light of such high levels of unplanned interruptions, carefully planned interruptions of up to a year in duration could be preferable.

CD4-guided PTI in adults with chronic HIV infection in the SMART trial was associated with an increased risk for deaths, and increases in both AIDS and non-AIDS events, largely attributable to lower CD4 cell counts and higher HIV RNA in the PTI compared to the cART group [5,16]. Whereas re-initiation of ART resulted in a 38% decrease in the rate of opportunistic disease and deaths during 18 months of post-trial follow-up in SMART, there was ongoing excess risk with the hazard ratio for such clinical events in PTI versus cART arms of 1.4 (95% CI 1.0–2.0; $P = 0.04$). Whereas data are far fewer in children, this has not been described in association with treatment interruptions in children [8,13]. During the 2 years follow-up after trial end in PENTA 11, we did not observe an excess in deaths, serious AIDS/non-AIDS or clinical events grades at least 2 in the PTI arm, although the study clearly had much lower power compared with the SMART trial.

There are multiple differences between children in PENTA 11 and adults in SMART. Firstly children, unlike adults, are at low risk for cardiovascular, renal and liver complications due to their younger age and lower incidence of traditional risk factors such as hypertension, diabetes mellitus and tobacco smoking [17]. Secondly,

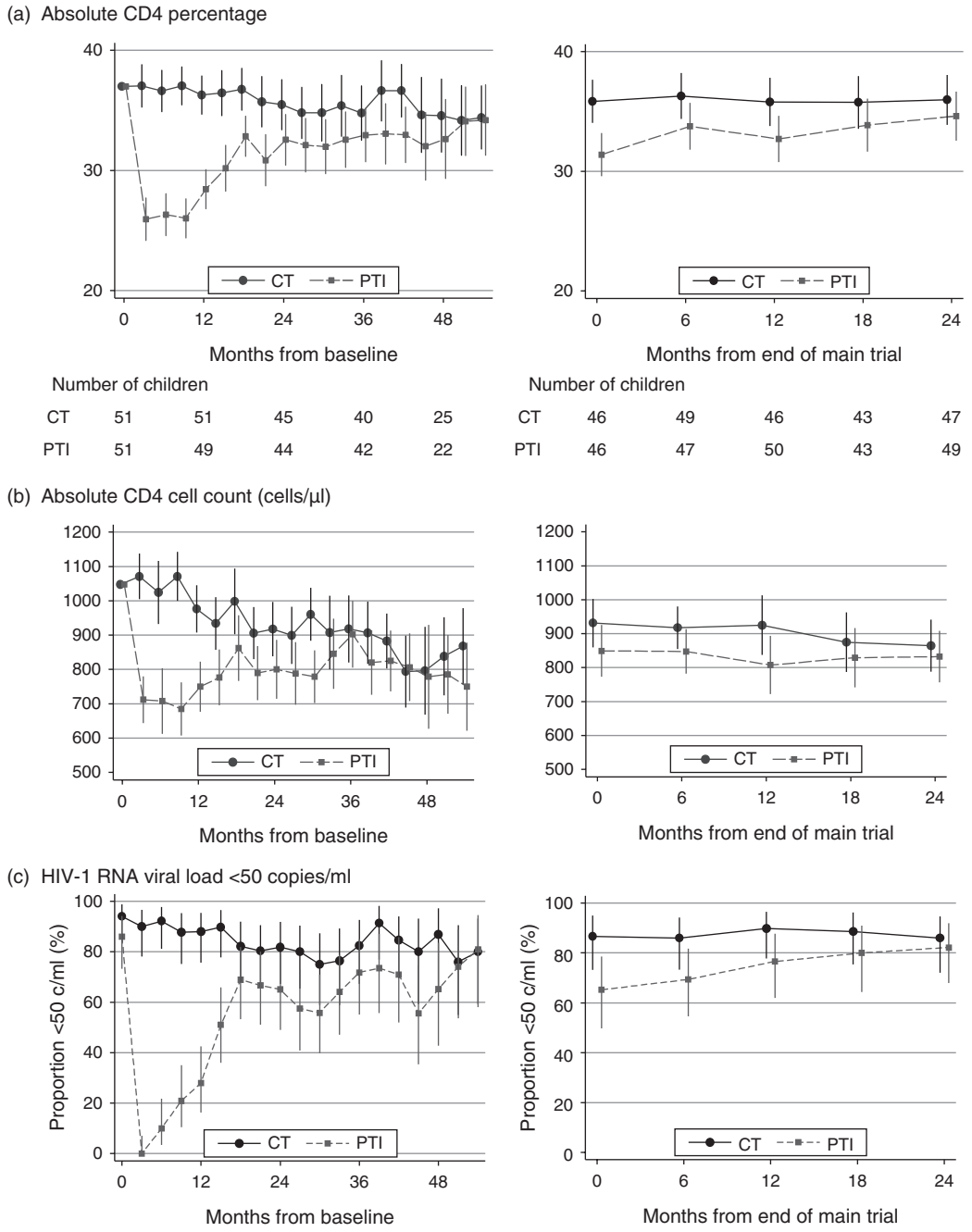

Fig. 2. Trends in CD4 percentage, CD4 cell count and HIV RNA over time firstly, from baseline of main trial (left-hand side) and secondly, from end of main trial (right-hand side). Trends in CD4 percentage and absolute CD4 cell count are adjusted for baseline measurements. The estimated mean values for each CD4 parameter at different time points corresponding to the overall respective mean baseline value for both arms combined (37% for CD4% and 1048 cells/μl for CD4 cell count) are presented. At each time point, the number of children with available measurements may vary slightly for CD4 percentage CD4 cell count and HIV-RNA viral load.

prior to ART re-initiation, none of the PENTA 11 children had experienced serious AIDS or non-AIDS events within the main trial; adults who experienced severe adverse events during the main SMART study had higher mortality rates in the ART re-initiation follow-up phase [5]. Thirdly, PTI children in PENTA 11 achieved similar CD4% and CD4 cell count as those on cART within 2 years of trial end: 35% and 832 cells/μl in PTI versus 36% and 864 cells/μl in cART. In SMART, at 18 months after the end of the trial, CD4 cell count was still 152 cells/μl (95% CI −0.167 to −0.136; $P < 0.001$) lower in the PTI compared to the cART arms [5]. Similarly, HIV RNA suppression rates after ART resumption were similar in both arms of PENTA 11

Table 3. Associations with CD4% recovery after restarting ART following the most recent PTI ($N = 48$[a]).

	Univariable analyses		Multivariable analyses	
Factors	Difference in mean absolute CD4% (95% CI)	*P*	Difference in mean absolute CD4% (95% CI)	*P*
Age at baseline	−0.3 (−0.9, 0.2) per year	0.25	−0.2 (−0.6, 0.2) per year	0.28
Sex				
Male	0	0.71	0	0.51
Female	−0.7 (−4.2, 2.8)		0.9 (−1.8, 3.7)	
Ethnicity				
White	0	0.75	0	0.08
Black	0.8 (−3.5, 5.0)		3.9 (0.8, 7.1)	
Asian	−2.1 (−6.9, 2.7)		3.3 (−0.3, 6.8)	
Other	−0.4 (−6.0, 5.2)		2.7 (−1.5, 7.0)	
Baseline disease stage				
A/N	0	0.39	0	0.56
B	−2.0 (−6.0, 2.0)		−0.8 (−3.8, 2.3)	
C	−2.0 (−6.7, 2.6)		1.1 (−2.6, 4.9)	
Cumulative ART exposure up to baseline	−0.1 (−0.7, 0.5) per year	0.74	0.0 (−0.6, 0.6) per year	0.93
Baseline weight-for-age z-score	−0.1 (−1.5, 1.3) per unit	0.86	−0.1 (−1.0, 0.9) per unit	0.92
Baseline CD4 percentage	6.1 (3.8, 8.3) per 10%	<0.001	5.4 (3.3, 7.5) per 10%	**<0.001**
Nadir CD4 percentage	1.6 (0.2, 3.1) per 10%	0.03	0.9 (−0.3, 2.1) per 10%[b]	0.13
CD4 percentage at ART re-initiation	3.9 (1.9, 5.9) per 10%	<0.001	2.3 (0.4, 4.2) per 10%	**0.02**
HIV RNA at ART re-initiation	(−1.6, 3.8) per $\log_{10}$ (copies/ml)	0.42	1.4 (−0.7, 3.6) per $\log_{10}$ (copies/ml)	0.18
Number of PTIs child have had				
1	0	0.05	0	0.51
2	3.8 (0.0, 7.5)		1.0 (−2.0, 4.1)	
Time since ART re-initiation[c]				
0	0	<0.001	0	**<0.001**
6 months	2.4 (2.0, 2.8)		2.3 (1.8, 2.7)	
1 year	4.5 (3.8, 5.2)		4.3 (3.5, 5.0)	
2 years	6.8 (5.9, 7.8)		6.6 (5.5, 7.6)	
3 years	7.1 (6.1, 8.0)		6.9 (5.9, 7.9)	

ART, antiretroviral therapy; CI, confidence interval; PTI, planned treatment interruption.
[a]Two of the 50 children in the PTI arm were excluded: one child was undergoing a PTI at end of main trial but was still off ART at last follow-up, and one child did not have any CD4 percentage measurements after restarting ART following their last PTI.
[b]The estimated effect of nadir CD4% without adjusting for CD4% at ART re-initiation was 1.4 (95% 0.3, 2.5; $P = 0.02$) per 10% and with adjustment was 0.9 (−0.3, 2.1; $P = 0.13$) per 10%.
[c]Time since ART re-initiation was fitted as a continuous covariate with a cubic spline (*P*-value for cubic term <0.001). To present the effect of time since re-initiation, the difference in CD4% at selected time points compared with time zero was estimated based on the fitted model.

(82% in PTI versus 86% in cART at 2 years post-trial), whereas in SMART, lower virologic suppression was seen in PTI adults (73% in PTI versus 84% in cART; $P < 0.001$) [5]. The highest risk of adverse events in SMART was observed in those with CD4 below 350 cells/μl and HIV RNA above 400 copies/ml [5]; of note, very few children in PENTA 11 ever had CD4 cell count falling below 350 cells/μl.

Several paediatric studies have shown varying rates of CD4 decline after treatment interruptions [13,14,18], but none have reported responses after ART was resumed. The rapid rise in CD4 after ART resumption in our PTI children was likely due to a combination of reduced CD4 cell death, along with a greater capacity for the thymus to repopulate the $CD4^+$ T-cell pool in children, and particularly in the very young [19]. This is in contrast to data from SMART and several adult trials showing a slow CD4 rise after ART re-initiation, with the majority failing to achieve pre-PTI CD4 cell counts [20–22]. In our study, higher baseline CD4 percentage as well as higher CD4 percentage at re-initiation were associated with greater CD4% recovery after ART re-initiation. Nadir CD4 percentage prior to ART did not have an independent effect once CD4 percentage at ART re-initiation was adjusted for (see footnote of Table 3); this suggests that the effect of nadir CD4 was mediated via CD4 percentage at ART re-initiation, given our previous finding that during PTI, CD4 nadir was an important determinant of the magnitude of CD4 decline and hence CD4 percentage at re-initiation [8]. Importantly, duration of ART following re-initiation was also a strong predictor for CD4% recovery, with CD4 increase occurring mainly within the first 2 years back on ART ($P < 0.001$ for nonlinear trend; see Table 3). This may be due to the inherently higher thymic output in children and possibly because of additional supplementation of the thymic output in response to ART [23]. This asymptotic pattern of CD4 cell recovery is in keeping with that seen following ART treatment of ART-naive children [24]. Studies in ART-naive children have shown that high baseline CD4%, virologic suppression, young age and female sex are associated with favourable CD4 recovery [25,26].

In the SMART trial, biomarkers of immune activation, IL-6, high-sensitivity C-reactive protein and soluble CD14 were raised in the PTI arm, particularly during periods of interruptions compared to the cART arm, and they were associated with risks for mortality, opportunistic diseases and cardiovascular and renal events [6,7,27]. Data from PENTA 11 have shown evidence of immune activation during PTI [9] but as yet, no evidence for associated clinical events, likely also due to small numbers. Whilst PTI did not appear to irreversibly impair CD4 recovery in our study, immune activation during PTI and possibly after PTI could have the potential to increase the risk for premature non-AIDS events when children reach early adulthood, and thus warrants long-term monitoring. However, it is interesting that other potential consequences of PTI were also not evident. For example, growth, which is an important and often sensitive measure of successful treatment in children and youth, were comparable between PTI and cART arms, and more recently we have reported no difference between cART and PTI arms in neurodevelopmental test scores performed cross-sectionally in the PENTA 11 children after the end of the trial [10]. Similarly, although a decline in total, low and high-density lipoprotein from baseline was seen in the first 12 weeks off ART among PTI children in the main trial [8], no differences in fasting lipids were observed between the two arms during long-term follow-up; in contrast, PTI was associated with increased low high-density lipoprotein levels in SMART [28].

Planned treatment interruption may have other consequences which may be advantageous. Children who experienced PTI were more likely to have their regimen simplified to once-daily and fixed-dose ART after restarting ART, suggesting that once time off ART has been experienced, there is an opportunity to request regimen simplification. The majority of carers (75%) and children (83%) in PENTA 11 also reported that PTI made life easier [29], and one could speculate that this might positively influence long-term adherence in a disease in which ART for life is much longer than in HIV acquired during adulthood. Others have also reported that simplification of ART by changing to a once-daily regimen enhanced treatment satisfaction, adherence and quality of life [30].

Our study has limitations including the small sample size and the lack of systematic sub-clinical evaluation for non-AIDS events such as cardiovascular complications. Our data may not be applicable to all children as we included mainly older children (median baseline age of 9 years old), the majority of whom maintained a relatively high CD4 level while on PTI. Younger children have a greater capability to regenerate $CD4^+$ T cells, but also have a more rapid HIV disease progression in the absence of ART [14]. Children who undergo unplanned PTI could be at greater risks for severe immunosuppression and HIV-related illnesses [13,18,31], although there was no evidence that children in the PTI arm adhered more poorly to ART after re-initiation [29]. Detailed immunologic and neurocognitive investigations are being undertaken annually in PENTA 11, with follow-up to 5 years post-trial. We await results of the Botswana/Baylor Antiretroviral Assessment trial in Botswana which was similar in design to PENTA 11 and also in chronic HIV infection. Results from the recently presented South African Children with HIV Early Antiretroviral Therapy (CHER) trial [32] also provide evidence that ART could be interrupted following treatment started at age 6–12 weeks, near the time of seroconversion. Early limited ART for 1 or 2 years was associated with better clinical and mortality outcomes after 5 years, than deferred ART, and one-third of children on ART for 2 years were still off medication at trial end; of note, however, an early continuous arm was not included in this trial [32].

In conclusion, 2 years after end of PENTA 11, children who had CD4-guided PTI achieved similar immune recovery and viral suppression to those who were maintained on cART and clinical outcomes did not differ between the two arms. These data provide reassurance that no obvious long-term harm resulted from CD4-guided PTI. This contrasts with adults and may be due to children's greater potential for immune recovery. Further research is warranted to explore ART strategies such as PTI, to limit the unacceptably high rate of unstructured treatment interruptions, especially in older children and young people. Whilst considered by many to be unacceptable, judicious use of PTI may actually reduce the risks of developing ART resistance and the consequent limitation of future therapeutic options during childhood, and particularly during adolescent years.

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Conflicts of interest

There are no conflicts of interest.

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