Response to planned treatment interruptions in HIV infection varies across childhood

Paediatric European Network for Treatment of AIDS

Objective: To evaluate clinical, immunological and virological consequences of CD4-guided antiretroviral therapy (ART) planned treatment interruptions (PTIs) compared with continuous therapy in children with chronic HIV infection in the Paediatric European Network for Treatment of AIDS 11 trial.

Design: This was a multicentre, 72-week, open, randomized, phase II trial.

Methods: One hundred and nine children with HIV-RNA below 50 copies/ml and CD4% of at least 30% (2–6 years) or at least 25% and CD4 cell count of at least 500 cells/μl (7–15 years) were randomized to continuous therapy (53) or PTI (56). In PTI, ART was restarted if confirmed CD4% was less than 20% or more than 48 weeks had been spent off ART. The primary outcome was Centers for Disease Control and Prevention (CDC) stage C event, death or CD4% less than 15% (and CD4 cell count less than 200 cells/μl for children aged 7–15 years).

Results: At baseline, median (interquartile range) age was 9 (6–12) years, CD4% 37% (33–41), CD4 cell count 966 (793–1258) cells/μl, nadir CD4% before combination ART 18% (10–27), time on ART 6 (3–6) years and 26% were CDC stage C. After median (range) 130 (33–180) weeks of follow-up, 4 versus 48% of time was spent off ART in continuous therapy and PTI, respectively. No child died or had a new CDC stage C event; one (2%) continuous therapy versus four (7%) PTI children had a primary outcome based on CD4%/cell count ($P = 0.2$). Lower nadir CD4% predicted faster CD4% decline after stopping ART. Younger age and higher nadir CD4% predicted being off ART for at least 48 weeks and better CD4% recovery following PTI.

Conclusion: In this first paediatric trial of PTI, there were no serious clinical outcomes. Younger children had better CD4% recovery after PTIs. Immunology substudies and long-term follow-up in Paediatric European Network for Treatment of AIDS 11 trial are ongoing. Further research into the role of treatment interruption in children is required, particularly, as guidelines now recommend early ART for all infected infants.

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Introduction

Trials evaluating treatment interruptions in adults have reported higher rates of AIDS events/deaths and serious non-AIDS events in those stopping antiretroviral therapy (ART) [1–6]. Therefore, current adult guidelines recommend continuous ART. No paediatric trials of planned treatment interruptions (PTIs) have been reported. However, response to PTIs may be different in children infected with HIV perinatally compared with adults; although children acquire HIV when the immune system is immature, they have greater potential for immune regeneration after starting ART, as the thymus is more active in childhood [7]. In children, immune reconstitution also occurs from naive cells [8] rather than through proliferation of memory populations, as in adults.

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The risk–benefit balance of continuous ART versus PTIs may also be different in children, as they will take ART for much longer than adults, with accompanying greater potential for long-term drug toxicity. Fewer licensed drugs and suitable formulations add to the challenge of sustained adherence in young children, and this, combined with greater potential for inadequate drug dosing [9] and lower viral suppression rates [10], increases the risk that children will acquire multidrug-resistant HIV before reaching adulthood. Finally, many children will interrupt ART for personal reasons, particularly during adolescent years.

Paediatric European Network for Treatment of AIDS (PENTA) 11 trial (Treatment Interruption in Children with Chronic HIV infection, TICCH) was, therefore, designed as a pilot study to evaluate the role of CD4-guided PTIs in the management of HIV-infected children who have responded well to ART.

Methods

Trial design

PENTA 11 was an open, multicentre, randomized, phase II trial (ISRCTN 36694210) in HIV-infected children aged 2–15 years on any ART regimen containing at least three drugs, which they had taken for at least 24 weeks. Eligibility to participate also required that the two most recent plasma HIV-1 RNA were less than 50 copies/ml and two most recent CD4% were at least 30% (ages 2–6 years) or at least 25% and CD4 cell count at least 500 cells/μl (ages 7–15 years). Children were randomized in a 1 : 1 ratio to either continue ART (continuous therapy) or to a strategy of CD4-guided PTI, and followed for at least 72 weeks (Fig. 1). The protocol was approved by the ethics committee for each participating centre. All parents/guardians gave written consent, and children gave written assent, according to their age and knowledge of HIV status.

Randomization was stratified by age (<7 or ≥ 7 years) or whether a child had started three or four-drug ART before 3 months of age, and by lowest recorded CD4% before starting combination ART (nadir) (<15 or $\geq 15\%$). For children allocated to PTI, ART was to be stopped immediately, or if currently receiving a nonnucleoside reverse transcriptase inhibitor and/or lamivudine, stopped using a protocol-defined replacement or staggered stop strategy to minimize the risk of development of resistance when stopping drugs with a long half-life [11]. Children randomized to continuous therapy continued on their current ART. Follow-up was 12-weekly until the last child randomized reached 72 weeks (29 May 2008), with extra visits at weeks 2, 4 and 8 for children randomized to PTI.

During the trial, in early 2006, six randomized trials assessing ART interruption strategies in adults [1–6] were presented with varying results. Three trials [2,3,6] were stopped early due to a significantly greater risk of AIDS/death in the interruption arms (although absolute risks of AIDS/death were low). Following an immediate review by the PENTA 11 Independent Data Monitoring Committee (IDMC), it was decided to continue the trial, but with changes in the design, to further minimize any potential risks to children (Fig. 1). As the treatment interruption strategy in the PENTA 11 trial was based on considerably higher CD4 cell count thresholds than the Strategies for Management of Antiretroviral Therapy (SMART) [3] and Trivacan [2] trials, and also given the age of children, it was expected to be associated with lower risks of disease progression.

Outcome measures and sample size

The primary outcome was a composite of a CD4%/cell count outcome (CD4% $<15\%$ at ages 2–6 years or CD4% $<15\%$ and CD4 cell count <200 cells/μl at ages 7–15 years) or new Centers for Disease Control and Prevention (CDC) stage C diagnosis or death. Secondary outcomes included changes in ART regimen, ART-related toxicity, resistance mutations, adherence and acceptability.

The trial was powered to exclude substantial clinical or immunological disadvantages to the PTI group. If no child in the continuous therapy group experienced the primary outcome (0%), then 50 children per group provided 80% power to exclude an increase to more than 15% in the PTI group (one-sided $\alpha = 0.05$).

Statistical analysis

All analyses were performed as intention-to-treat; statistical tests were two-sided and adjusted for stratification factors. The difference between groups in the number of primary outcomes (i.e. a binary outcome) was tested using logistic regression. Overall event rate and rate ratios were estimated using Poisson regression. Changes from baseline in CD4%, CD4 cell z score and continuous laboratory outcomes were estimated using normal regression of actual measurements adjusting for baseline. Piecewise longitudinal mixed normal models [12] were used to assess the effect of baseline characteristics on the decline in CD4% after stopping ART in the PTI group, adjusting for repeated measures and censoring the data when ART was restarted or at the last follow-up; random effects allowed for CD4% decline (split into before and after 10 weeks after stopping ART, based on the best model fit) to vary across children. Multivariate analyses, adjusted for age, were used to assess the effect of baseline characteristics and nadir CD4% on CD4% decline and recovery 24 weeks after restarting ART. Similar analyses were performed to assess the recovery of CD4 cell z score. The difference between groups in the number of resistance mutations was tested using Wilcoxon rank sum test. All analysis used Stata statistical software, version 10.1 (StataCorp., College Station, Texas, USA).

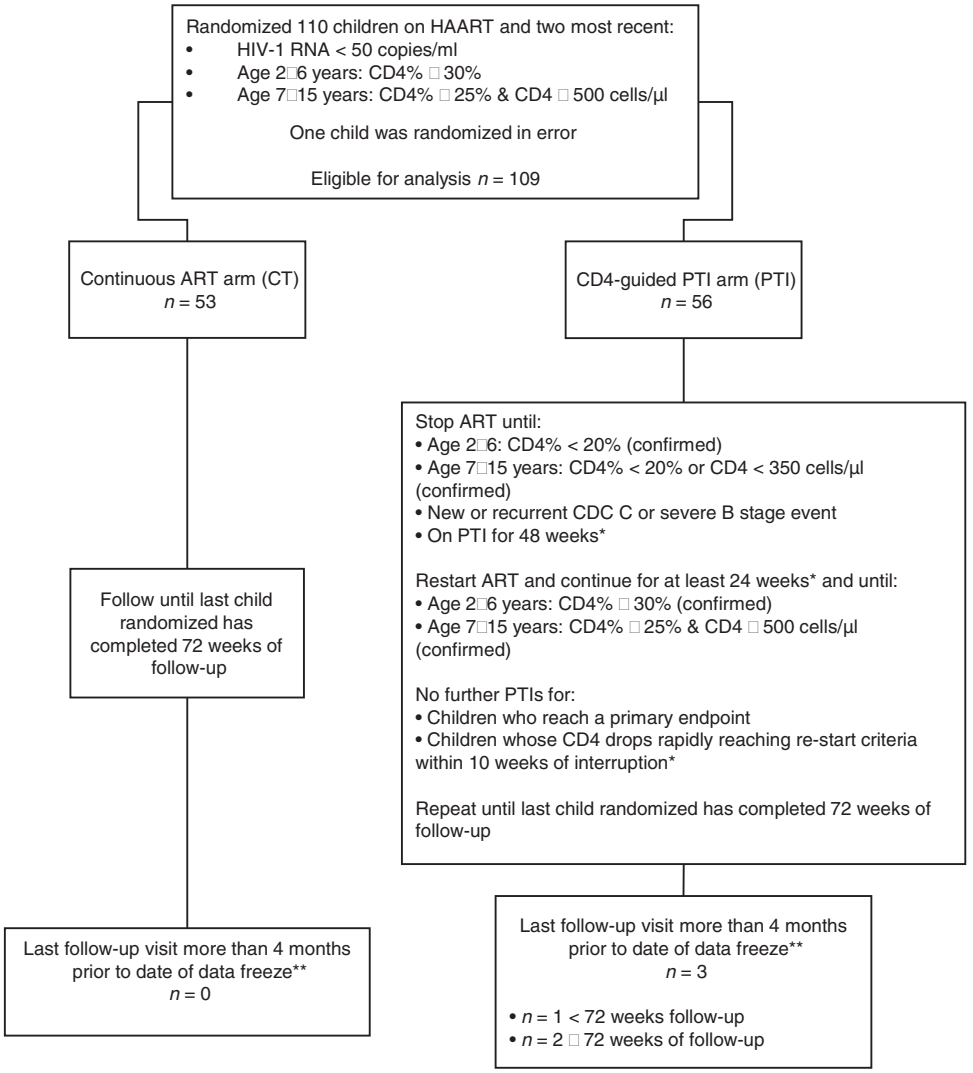

Fig. 1. Schematic diagram of the design of the Paediatric European Network for Treatment of AIDS 11 trial and participant flow. ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; CT, continuous therapy; PTI, planned treatment interruption. *Changes to the trial design in March 2006 to further minimize the risk to children after the results of adult treatment interruptions trials. **Date of when the last child randomized reached 72 weeks of follow-up (29 May 2008).

Clinical events included events reported as definitely or possibly HIV-related (clinical categories were assigned according to the CDC classification [13]) and adverse events not related to HIV (graded according to an adapted Division of AIDS classification [14]). CD4 cell count for age (*z* score) was calculated with reference to uninfected European children born to HIV-infected mothers [15]. For the proportion of children with HIV-1 RNA of less than 50 copies/ml, measurements recorded as undetectable, but less than an assay quantification limit of at least 50 copies/ml (e.g. <100 copies/ml), were assumed to be at least 50 copies/ml. Drug resistance was assessed in the first of two consecutive samples with HIV-1 RNA above 100 copies/ml on the same drug regimen. In the PTI group, resistance was also measured in the first sample having more than 100 copies/ml after stopping ART, and in the sample nearest to 4 weeks after restarting ART (if >100 copies/ml). Major resistance mutations were defined according to the 2008 International AIDS Society (IAS)-USA guidelines [16].

Results

Baseline characteristics

One hundred and ten children, from 29 centres in nine countries, were randomized (continuous therapy 53 and PTI 57) between November 2004 and December 2006: UK (28 children), Thailand (23 children), Italy (19 children), Spain (17 children), France (10 children), Germany (four children), USA (four children), Poland (three children) and Switzerland (two children). One child (randomized in error) with screening HIV-1 RNA

of at least 50 copies/ml was excluded (Fig. 1), leaving 109 children (53 continuous therapy and 56 PTI) included in the analysis; only one child was lost to follow-up before 72 weeks. The randomized groups were similar at study entry (Table 1).

Antiretroviral therapy received after baseline

Over a median follow-up of 130 weeks (range 33–180 weeks), 4 and 48% of time was spent off ART in continuous therapy versus PTI groups, respectively. Of 56 children randomized to PTI, 19 (34%) reached the CD4-guided ART restart criteria between 6 and 42 weeks after stopping ART (11 within 10 weeks). Of 37 children who did not reach the restart criteria, 32 (57% of total) restarted ART only because they had been off ART for 48 weeks, four restarted for other reasons (CD4% or cell count decline not meeting restart criteria, 'flu symptoms', thrombocytopenia and child uncomfortable off ART) and one child did not restart ART for social reasons (off ART at last follow-up). Sixteen children had a second PTI, and no child had a third PTI.

Excluding ART used for replacement/stopping strategies [11] in the PTI group, nine (8%) children (four continuous therapy and five PTI) changed their ART regimen (defined as switching at least three drugs for any reason or two drugs for treatment failure). In the continuous therapy group, two children switched following virological failure and resistance test results, one substituted for toxicity and one to simplify the ART regimen. In the PTI group, one child switched because of poor virological response and adherence after restarting ART following the first PTI and four substituted drugs to simplify the ART regimen after a PTI. On nine other occasions, one or two drugs were substituted for simplification (five continuous therapy and four PTI).

Primary outcome

One child (2%) in the continuous therapy group and four (7%) in the PTI group [difference 5%, 95% confidence interval (95% CI) −2 to +13%, $P = 0.2$] reached a CD4%/cell count outcome (zero continuous therapy versus three PTI for children aged <7 years; one continuous therapy versus one PTI for children aged ≥7 years). No child died or had a new CDC stage C diagnosis.

Clinical outcomes

There were 50 clinical events reported in 29 (52%) PTI children compared with 26 in 15 (28%) continuous therapy children (rate ratio 2.4, 95% CI 1.3–4.4, $P = 0.004$) (Table 2), including only one CDC stage B event (osteomyelitis, PTI) and one grade 3/4 ART-related event (grade 3 migraine, possibly related to efavirenz restarted after a second PTI). Excess events in the PTI group were haematological/lymphatic system disorders (zero continuous therapy, 10 PTI, mainly lymphadenopathy, 9/10 while off ART), dermatological (rashes) (three continuous therapy, nine PTI; 5/9 off ART) and central nervous system (CNS)/psychiatric disorders, most commonly headache (one continuous therapy, seven PTI; 3/7 off ART) (Table 2). Infections were reported with similar frequency in both groups. Overall, 37 events occurred when the child was off ART [2/26 (8%) continuous therapy and 35/50 (70%) PTI].

There were 18 admissions to hospital (five continuous therapy and 13 PTI) in 16 (five continuous therapy and 11 PTI) (15%) children (rate ratio 2.4, 95% CI 0.8–6.8, $P = 0.09$). Most admissions were of less than 2 days duration, and total inpatient days were very similar in continuous therapy (47) and PTI (42) groups. Of four children admitted for more than 7 days, three (encephalopathy, impetigo and suicide attempt) were in the continuous therapy group and one (osteomyelitis) in the PTI group.

Immunological outcomes

After 72 weeks of following a CD4-guided PTI strategy, changes from baseline in CD4% and CD4 cell z score were greater in the PTI than in the continuous therapy group [mean standard error (SE) −0.4% (0.9) CD4% and −0.3 (0.2) z score in continuous therapy compared with −5.3% (0.9) and −1.0 (0.2) in PTI, respectively]. However, not all children in the PTI group were back on ART at 72 weeks and were at different stages of their PTI cycle, making comparisons with the continuous therapy group hard to interpret. Over total follow-up, 96% of child-years in the continuous therapy group versus 92% of child-years in the PTI group were spent with CD4% of at least 20%, and 98% of child-years in continuous therapy versus 96% of child-years in PTI with a CD4 cell count of at least 350 cells/μl.

In the PTI group, CD4%, cell count and z score values decreased sharply in the first 10 weeks off ART and then stabilized. In adjusted analysis, CD4% decline in the first 10 weeks was greater in children with lower nadir CD4% ($P = 0.005$) (Fig. 2). Children who reached the CD4-guided restart criteria had lower nadir CD4%, were older and had started ART at an older age than those who restarted ART only because they reached 48 weeks off ART (Table 3); in adjusted analysis, only lower nadir CD4% and older age were independently associated with higher odds of reaching the restart criteria [adjusted odds ratio nadir CD4% 0.88 (95% CI 0.80–0.97) per 1% increase, $P = 0.007$; age 1.23 years (95% CI 0.99–1.56) per 1-year increase, $P = 0.07$]. Recovery of CD4% after 24 weeks back on ART following the first PTI was better in younger children ($P = 0.09$) and in those with a higher nadir CD4% ($P = 0.04$). For example, comparing CD4% nadir of at least 20% versus less than 20% by age gave mean (SE) CD4% changes from baseline of −0.3% (1.5) versus −4.5% (1.7) in children less than 7 years of age, −3.1% (1.4) versus −7.2% (1.4) in children 7–11 years of age and −5.0% (1.8) versus −9.2% (1.5) in children at least 11 years of age. CD4 cell z score analyses gave similar results:

Table 1. Baseline characteristics.

	CT ($n=53$)	PTI ($n=56$)	Total ($n=109$)
Male (%)	22 (42)	27 (48)	49 (45)
Age (years)			
Median (IQR)	9.9 (6.4–12.3)	9.0 (6.7–11.9)	9.3 (6.7–12.0)
≥2 to <7 years (%)	15 (28)	17 (30)	32 (29)
≥7 to <11 years (%)	18 (34)	22 (40)	40 (37)
≥11 to <16 years (%)	20 (38)	17 (31)	37 (34)
Ethnic origin			
Percentage of white/black/Asian/other[a]	32/32/23/13	37/30/20/12	35/31/21/13
CDC disease stage			
Percentage of N/A/B/C	17/23/26/34	20/34/28/18	18/28/28/26
CD4 parameters, median (IQR)			
CD4%	37 (34–40)	37 (33–42)	37 (33–41)
CD4 cell count, cells/μl	965 (741–1222)	967 (844–1302)	966 (793–1258)
CD4 cell z score	−0.5 (−1.3 to +0.1)	−0.5 (−0.9 to 0.4)	−0.5 (−1.1 to 0.2)
Nadir[b] CD4%[c]	18 (9–28)	19 (11–25)	18 (10–27)
Nadir[b] CD4 cell count (cells/μl)[d]	534 (309–888)	766 (320–1350)	627 (320–1050)
Nadir[b] CD4 cell z score[d]	−2.8 (−4.1 to −1.7)	−2.1 (−4.0 to −1.1)	−2.4 (−4.1 to −1.5)
HIV-1 RNA			
≥50 copies/ml at baseline[e] (%)	3 (6)	8 (14)	11 (10)
Number of classes exposed to:			
All three classes (%)	19 (36)	14 (25)	33 (30)
NRTIs + PIs only (%)	11 (21)	17 (30)	28 (26)
NRTIs + NNRTIs only (%)	22 (42)	25 (45)	47 (43)
NRTIs only (%)	1 (2)	0 (0)	1 (1)
Number of different ART drugs ever received, median (IQR)	4 (3–6)	4 (3–6)	4 (3–6)
Cumulative ART exposure, years, median (IQR)	6.6 (3.9–8.9)	5.6 (3.2–8.3)	5.7 (3.4–8.7)
Age when started ART, years, median (IQR)	2.2 (0.4–4.6)	2.1 (0.6–5.5)	2.2 (0.5–5.1)
Initial regimen mono/dual ART (%)	18 (34)	15 (27)	33 (30)
Lipids (fasting), median (IQR)			
Total cholesterol (mg/dl)[f]	179 (162–208)	182 (169–228)	181 (166–211)
LDL cholesterol (mg/dl)[g]	98 (85–116)	112 (86–137)	107 (86–122)
HDL cholesterol (mg/dl)[h]	58 (45–68)	62 (50–71)	60 (47–71)
Total/HDL ratio[h]	3.0 (2.7–3.8)	3.1 (2.7–4.3)	3.1 (2.7–4.0)
Platelets (10^9/l)[d], median (IQR)	295 (266–358)	315 (268–378)	310 (268–359)

ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; CT, continuous therapy; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PTI, planned treatment interruption.
[a]Nine children (five CT and four PTI) were Hispanic/Mulato, four (two CT and two PTI) were mixed black/white and one (PTI) was American Indian.
[b]Before starting combination ART.
[c]Missing for 11 children (six CT and five PTI); column percentages are of nonmissing values.
[d]Missing for 12 children (seven CT and five PTI); column percentages are of nonmissing values.
[e]All children had HIV-1 RNA less than 50 copies/ml at screening and prescreening. HIV-1 RNA was assumed to be at least 50 copies/ml at baseline for 11 children [six children (two CT and four PTI) <100 copies/ml, two children (one CT and one PTI) <200 copies/ml and three children (PTI) ≥200 copies/ml: range 240–2430 copies/ml].
[f]Missing for one (PTI) child; column percentages are of nonmissing values.
[g]Missing for 23 children (14 CT and nine PTI); column percentages are of nonmissing values.
[h]Missing for 13 children (nine CT and four PTI); column percentages are of nonmissing values.

for example, children less than 7 years of age with CD4 cell z score nadir of at least −3 had 0.0 (0.3) mean (SE) change from baseline versus−1.8 (0.3) in children at least 11 years of age with nadir less than −3.

HIV-1 RNA and drug resistance

In the PTI group, HIV-1 RNA increased rapidly in the first weeks off ART; 100 and 98% of children had HIV-1 RNA of at least 50 and at least 400 copies/ml at 12 weeks, respectively, compared with 10 and 2%, respectively, in the continuous therapy group. Suppression of viral load to less than 50 copies/ml following the first PTI was achieved for 77% (38/49) of children by 24 weeks back on ART, 96% (47/49) were less than 400 copies/ml. Of the 11 children with viral load of at least 50 copies/ml, nine subsequently attained viral load suppression of less than 50 copies/ml.

In the PTI group, among 68 samples tested for resistance at a median [interquartile range (IQR)] of 4 (2–5) weeks after interruption and 30 samples at 4 (3–5) weeks after restarting ART, 30 (31%) samples had at least one major resistance mutation. All except one mutation appeared to be associated with previous rather than current ART regimens; the exception was a child who developed a new K103N mutation after stopping efavirenz during a second PTI (HIV-1 RNA at the time of assay 10 691 copies/ml); plasma concentrations of efavirenz were still detectable 2 weeks after stopping efavirenz during the first PTI. The protocol was subsequently amended to recommend that

Table 2. Clinical events of grade 2 or above.

	CT	PTI	Total
Children randomized and included (%)	53 (100)	56 (100)	109 (100)
CDC stage B events: osteomyelitis	0	1	1
Blood/lymphatic system	0	10	10
Lymphadenopathy		7	7
Parotid enlargement		1	1
Splenomegaly		1	1
Thrombocytopenia purpura		1	1
Gastrointestinal disorders	4	6	10
Abdominal pain/nausea/vomiting/diarrhoea/enterobiasis	3	5	8
Stomatitis	1		1
Toothache		1	1
General disorders	0	3	3
Fatigue/pyrexia		2	2
Amenorrhoea		1	1
Infections and infestations	15	12	27
Lower respiratory tract infection	1	1	2
Upper respiratory infection	7	9	16
Otitis media	5		5
Skin infections	2	1	3
Discitis		1	1
Central nervous system/psychiatric disorders	1	7	8
Facial palsy		1	1
Headache/migraine		3	3
Muscle spasticity/paresis	1	1	2
Attention deficit/hyperactivity disorder		1	1
Sleep disorder		1	1
Respiratory	3	2	5
Asthma/cough	2	1	3
Pharynglaryngeal pain	1		1
Snoring		1	1
Skin/subcutaneous tissue	3	9	12
Alopecia		1	1
Cutaneous vasculitis	1		1
Dermatitis	1	2	3
Henoch–Schonlein purpura		1	1
Lipodystrophy	1		1
Rash		4	4
Swelling face		1	1
Total events	26	50	76
Total children (%)	15 (28)	29 (52)	44 (40)
Event rate (per 100 child-years) (95% CI)	15.9 (9.6–26.5)	37.5 (26.1–54.0)	25.7 (19.1–34.5)
		Rate ratio 2.4 (95% CI 1.3–4,4), $P = 0.004$	

CDC, Centers for Disease Control and Prevention; CI, confidence interval; CT, continuous therapy; PTI, planned treatment interruption.

efavirenz should be replaced with lopinavir/ritonavir for 4 weeks before interrupting all drugs.

While on ART, 19 (17%) children (10 continuous therapy and nine PTI) had confirmed HIV-1 RNA of more than 100 copies/ml. Two (one continuous therapy and one PTI) children had HIV-1 RNA between at least 400 copies/ml and less than 1000 copies/ml and five (two continuous therapy and three PTI) had at least 1000 copies/ml. Resistance test results were available for 13 children; six (three continuous therapy and three PTI) children had nonamplifiable ($n = 3$) or missing ($n = 3$) samples. Ten (five continuous therapy and five PTI) children had at least one major resistance mutation; the median (range) number of mutations was five (2–8) in the continuous therapy and three (2–4) in the PTI group ($P = 0.1$). In the continuous therapy group, four children had multiple thymidine analogue mutations [all had previous mono/dual-nucleoside reverse transcriptase inhibitor (NRTI) therapy] as well as mutations associated with individual drugs in their current regimen. In the PTI group, three children had new resistance mutations associated with drugs in the regimen they restarted after their first PTI, which had not been present on a sample tested after interruption. At the last follow-up, two of these 10 children (one continuous therapy and one PTI) had HIV-1 RNA of less than 50 copies/ml.

Laboratory outcomes

There were no significant differences between groups in the number of laboratory grade 2 (86%) or 3 (14%) events (continuous therapy: 23 events in 11 (21%) children and PTI: 34 events in 15 (27%) children; rate ratio 1.4, 95% CI 0.7–3.1, $P = 0.3$). Total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol (nonfasting) decreased from baseline by mean (SE) −37 (5) mg/dl, −17 (7) mg/dl and −14 (2) mg/dl, respectively, in the first 12 weeks off ART among children on

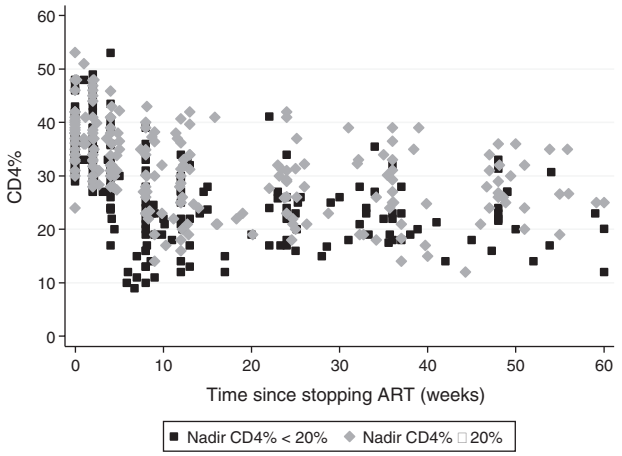

Fig. 2. CD4% decline in children in the planned treatment interruption group off antiretroviral therapy by nadir CD4% before starting combination antiretroviral therapy. The graph represents actual CD4% measurements recorded off ART in the PTI group. Measurements were censored when ART was restarted or at the last follow-up. ART, antiretroviral therapy; PTI, planned treatment interruption.

PTI, although the change in the total/HDL ratio was small [+0.2 (0.3)]. Platelets also decreased by mean (SE) −60 (10) 10^9/l. No significant changes were observed in haemoglobin, white blood cell or neutrophil values.

Discussion

HIV-infected children acquire HIV when the immune system is developing and start ART early compared with adults. Therefore, they may respond differently to PTIs. Here, we observed no major disadvantages of PTIs guided by CD4%/cell count thresholds; however, there was a significant excess of reported minor clinical events in the PTI group. Events, such as lymphadenopathy and mild skin complaints, may well have been related to immune activation with HIV viraemia after stopping ART; of note, there was no evidence of an increase in any infections in the PTI group. The only grade 3 ART-related adverse event report of headache could have been related to restarting ART with efavirenz after a PTI. Even if not serious, the occurrence of minor clinical symptoms in the PTI group after stopping ART may have been problematic for children and families, and questionnaires

Table 3. Baseline characteristics of children in the planned treatment interruption group by whether they reached the CD4-guided restart criteria or restarted antiretroviral therapy after 48 weeks off antiretroviral therapy.

	Reached CD4-guided restart criteria ($n=19$[a])	Restarted ART after 48 weeks off ART ($n=32$[a])	P*
Male (%)	8 (42)	16 (50)	0.8
Age (years)			
Median (IQR)	11.4 (8.1–14.3)	8.3 (5.9–10.7)	0.03
≥2 to <7 years (%)	3 (16)	12 (37)	0.04
≥7 to <11 years (%)	6 (32)	14 (44)	
≥11 to <16 years (%)	10 (53)	6 (19)	
Ethnic origin			
Percentage of white/black/Asian/other[b]	16/37/31/16	50/28/9/13	0.06
CDC disease stage, percentage of N/A/B/C	16/37/26/21	19/34/31/16	1.0
CD4 parameters, median (IQR)			
CD4%	34 (31–38)	37 (34–43)	0.04
CD4 cell z score	−0.5 (−1.2 to 0.1)	−0.4 (−0.7 to 0.4)	0.2
Nadir[c] CD4%[d]	13 (8–17)	23 (18–32)	<0.001
Nadir[c] CD4 cell z score[d]	−4.0 (−5.6 to −2.1)	−1.5 (−2.7 to −0.8)	0.009
Number of classes exposed to			
All three classes (%)	4 (21)	10 (31)	0.09
NRTIs + PIs only (%)	3 (16)	12 (37)	
NRTIs + NNRTIs only (%)	12 (63)	10 (31)	
Number of different ART drugs ever received, median (IQR)	4 (3–5)	4 (4–6)	0.1
Cumulative ART exposure, years, median (IQR)	5.4 (2.9–9.1)	5.9 (4.2–8.3)	0.8
Age when started ART (years), median (IQR)	3.3 (2.0–6.8)	1.3 (0.4–3.8)	0.01
Initial regimen mono/dual ART (%)	6 (32)	8 (25)	0.7
Lowest CD4 parameters off ART, median (IQR)			
Lowest CD4% off ART[e]	14 (11–17)	23 (20–37)	<0.001
Lowest CD4 cell z score off ART[e]	−4.4 (−5.9 to −2.9)	−2.5 (−3.4 to −1.5)	0.001

ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PTI, planned treatment interruption.
[a]Four children who restarted ART for other reasons and one child did not restart ART are not included in this table.
[b]Seven children: four Hispanic/Mulato, two mixed black/white and one American Indian.
[c]Before starting combination ART.
[d]Missing for five children; column percentages are of nonmissing values.
[e]Lowest CD4%/cell z score count off ART on first PTI.
*Univariate analysis. Fishers exact test was used for categorical variables and Wilcoxon rank sum test for continuous variables.

completed during the trial on acceptability of PTI versus continuous therapy are currently being analysed. Because the allocation to treatment strategy was not masked, reporting bias among both families and paediatricians could have contributed to the excess reporting of minor clinical events. Children on PTIs were also reviewed in clinic more often than children on continuous therapy, increasing the opportunity for reporting events, particularly in the initial weeks of PTI. Lack of blinding could also have contributed to a lower threshold for admitting children to hospital in the PTI group; the number of short-term admissions was greater among PTI children, although total admission days were very similar in both the groups.

Despite relatively advanced disease before starting combination ART, nearly 60% of children in the PTI group only restarted ART because they reached the predefined 48 weeks off ART. In addition, in the PTI group, only 4% of follow-up time was spent with a CD4 cell count of less than 350 cells/μl. This compares with 32% of time in the interruption arm in the adult SMART trial, which had lower CD4 cell count thresholds for starting and stopping ART [3]. As the average age of children at entry into the PENTA 11 trial was around 9 years and 90% were more than 5 years of age, CD4 cell counts would have similar predictive value for disease progression as young adults for most children [17], suggesting that any clinical risks, not observed due to small numbers in this trial, would likely be lower than in the SMART trial.

All four children in the PTI group who reached a CD4%/cell count outcome did so within 12 weeks after stopping ART, as did two-thirds of all children who reached CD4%/cell count threshold values to restart ART. As also reported in PTI studies in adults, we observed a rapid initial decline in CD4%, which was predicted by nadir CD4% before starting combination ART [18–20]. Nadir CD4% and cell z score were also a predictor of CD4% and cell z score recovery respectively following interruption, as was age, with children of less than 7 years of age and with good nadir CD4% and cell z score able to recover CD4% and CD4 cell z score values within 24 weeks of restarting ART. CD4 cell count declines naturally with age in HIV-uninfected children [15], and the dynamics of CD4 cell count response to ART in HIV-infected children varies considerably with age [21]; interpretation of results is, therefore, complex and requires adjustment for age, as failure to return to preinterruption CD4 cell count values might be expected as a consequence of older age alone. Only 11 children in the PENTA 11 trial were less than 5 years old, and therefore, although encouraging, our findings in young children remain exploratory. As it is now recommended that all infants start ART as soon as they are diagnosed with HIV, a focus for future research should be the role of PTIs in younger children starting early ART; CD4 cell count and% predict disease progression most poorly in this age group [22,23], and maintaining long-term ART is also most difficult.

The high proportion of children with suppressed viral load after 24 weeks back on ART in the PTI group precludes investigation of predictors of re-suppression of viral load. There was no evidence of more drug resistance in the PTI group than in the continuous therapy group; if anything, there was a tendency towards a higher number of mutations in the continuous therapy group. One child in the PTI group developed a new mutation to efavirenz, which prompted recommendation of 'protease inhibitor replacement' (as is currently recommended in adult guidelines) rather than 'staggered stop' strategy for children on efavirenz.

Only small (mainly observational) studies have so far reported on treatment interruptions in the management of HIV-infected children [24], including one small, randomized, pilot trial [25] of 30 children in whom no AIDS events or deaths were reported in either the interruption (guided by viral load rather than CD4%/cell count) or continuous ART arm. Two large interruption trials in children are ongoing in Africa: the South African Children with HIV Early anti-Retroviral therapy trial (CHER) is addressing the question of early limited ART (starting ART before 12 weeks of age and stopping at first or second birthday) in around 400 infants. The Bana trial in Botswana (600 children with chronic HIV infection) has a similar design to the PENTA 11 trial, but lower CD4% thresholds for stopping (25%) and restarting (15%) ART in the PTI arm. The results from the PENTA 11 trial provide reassurance for continuation of these trials (at the recent IDMC meetings, continuation was recommended for both trials; A Violari and M. Kline, personal communication). Five-year follow-up of all children in the PENTA 11 trial, who were recommended to take ART continuously at the end of the main follow-up of the trial, is ongoing, and along with the results of CHER and Bana trials, should help to determine the extent of CD4% and cell count recovery after longer periods back on ART after PTI, and whether this occurs across all ages in childhood or only in the youngest children. Of note, at 18 months after re-initiation of ART in adults (median age 43 years) in the SMART trial, mean CD4 cell counts were still statistically significantly lower (152 cells/μl lower, 95% CI 136–167, $P < 0.001$) in those initially randomized to CD4-guided PTI compared with those on continuous therapy [26].

The overall aim of paediatric HIV management is to ensure that children reach adulthood not only with no adverse clinical outcomes, optimal growth, good cognitive development and intact immune systems but also with minimal HIV drug resistance and toxicity. Results of the PENTA 11 trial so far provide useful information for paediatricians and families about children

who may undergo unplanned interruptions of ART for a variety of reasons but cannot be used to advocate PTIs at the moment. The balance of risks and benefits of HIV and lifelong ART is clearly different in vertically HIV-infected children starting ART early compared with adults. The long-term consequences of PTIs in the PENTA 11 trial as well as the results from the ongoing African trials will hopefully clarify whether PTIs have a future role in paediatric HIV management.

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