Treatment interruption after 2-year antiretroviral treatment initiated during acute/early HIV in infancy

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Objective: Treatment interruption has been well tolerated and durable in some pediatric studies but none have compared treatment interruption with continued antiretroviral treatment (ART) following ART initiation in early HIV. The objective of this study was to compare outcomes in treatment interruption versus continued ART among early-treated infants.

Design: Randomized trial (OPH-03; NCT00428116).

Methods: The trial included HIV-infected infants who initiated ART at less than 13 months of age, received ART for 24 months, and, if eligible (CD4% >25%, normal growth), were randomized to treatment interruption versus continued ART. Children in the treatment interruption group restarted ART if they met WHO ART-eligibility criteria. During 18-months postrandomization, primary outcomes were incidence of serious adverse events and growth. CD4%, viral load, morbidity, and growth were compared.

Results: Of 140 infants enrolled, 121 started ART, of whom 75 completed at least 24 months ART and 42 were randomized (21 per arm). ART was initiated at median age 5 months and randomization at 30 months. Among 21 treatment interruption children, 14 met ART restart criteria within 3 months. Randomization was discontinued by Data and Safety Monitoring Board due to low treatment interruption durability. At 18 months postrandomization, growth and serious adverse events were comparable between arms; hypercholesteremia incidence was higher in the continued arm ($P = 0.03$). CD4% and viral load did not differ between arms [CD4% 35% and median viral load undetectable (<150 copies/ml) in both arms, $P = 0.9$ for each comparison]. No infants had post-treatment viral control.

Conclusion: Short treatment interruption did not compromise 18-month CD4%, viral control, growth, or morbidity compared with continued ART among infants who started ART in early HIV infection.

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Introduction

Early antiretroviral treatment (ART) is recommended for HIV-infected infants based on significant benefits of early versus eligibility-deferred ART [1]. Prior to widespread ART use, some HIV-infected untreated children had long-term nonprogression (LTNP) [2]. It is plausible that some children who would be LTNP without therapy, as well as others who control virus following early ART, could benefit from treatment interruption after immune recovery. This approach could reduce ART toxicity or resistance and preserve ART regimens for later in life.

There are several differences between pediatric and adult treatment interruption. In children, it is frequently possible to diagnose HIV soon after infection, which makes treatment during primary HIV infection more feasible than in adults. Initiation of ART during primary HIV may enable sustained treatment interruption with post-treatment virologic control (PTC) as observed in the 'Mississippi baby' and in a teen from France [3,4]. The ANRS VISCONTI study noted durable PTC among adults who started ART during primary HIV [5] and had treatment interruption, although PTC may be infrequent [6,7]. Immune outcomes and safety of treatment interruption may also differ between children and adults. The presence of functional thymus in infants could enhance immune recovery following early ART [8]. Although some adult treatment interruption studies, notably the SMART trial, observed increased cardiovascular mortality risk with treatment interruption, these findings have not been replicated in children [9–12]. In a large pediatric treatment interruption trial, PENTA-11, more than half of children randomized to treatment interruption completed a 48-week period of treatment interruption without meeting criteria to restart ART [12]. Importantly, 2-year follow-up noted no differences in long-term outcomes, including cognitive or growth outcomes in children with treatment interruption versus continued ART in this trial [13]. In adults, ART plays a dual role in treatment and prevention and treatment interruptions could undermine HIV prevention; however, this is not the case for children until adolescence [14,15]. High rates of unplanned treatment interruptions, poor adherence, and resistance are noted in children, leading to the possibility of exhausting regimens for children who start lifelong ART in infancy [16–18]. Thus, on balance, strategic treatment interruptions may permit a longer life period in which ARTs are effective for some children.

We hypothesized that infants treated early in HIV infection may safely sustain treatment interruption, making this a viable approach to preserving limited ART options for infants. We conducted a randomized clinical trial (RCT) to compare outcomes of children who were treated in the first year of life and randomized following 2-year ART to a single treatment interruption versus continued treatment.

Methods

Study design, ethical approvals, and trial data and safety monitoring

The optimizing pediatric HIV-1 (OPH-03) treatment study (NCT00428116) was an RCT in which HIV-infected infants, who completed at least 2 years ART and attained immune reconstitution and normalized growth, were randomized to treatment interruption or continued ART. Written informed consent was obtained from caregivers of children. The study received ethical approval from the Institutional Review Boards at the University of Washington and the Ethical Review Committee at Kenyatta National Hospital (KNH). An independent Data and Safety Monitoring Board (DSMB) reviewed the study at 6-month intervals.

Recruitment of trial participants

HIV-infected infants were identified from prevention of mother-to-child HIV transmission (PMTCT) sites in Nairobi, KNH wards, and the KNH HIV Treatment Clinic. Initial eligibility criteria restricted to infants less than 4 months of age were extended to less than 13 months to include infants who may have acquired postnatal HIV and infants already on ART who started at less than 13 months. For these children, pre-ART clinical, $CD4^+$ cell count and CD4%, and growth data were abstracted from medical records.

Enrollment and prerandomization follow-up

At enrollment, a questionnaire was administered and physical examination was performed; blood was collected for $CD4^+$ cell count and CD4%, viral load, lipids, and liver function tests. Children were initiated on ART (PMTCT-exposed children received lopinavir/ritonavir, lamivudine, and zidovudine; children with no prior PMTCT exposure received nevirapine, lamivudine, and zidovudine; later enrollees received abacavir instead of zidovudine). Generic antiretroviral medications were provided by PEPFAR. These medications are on the WHO pre-qualified list meeting US FDA standards. Children were seen monthly for clinical assessment and anthropometry with 3-month interval blood collections for $CD4^+$ cell count and CD4% (6-monthly), HIV RNA, complete blood count, lipids (6-monthly), and liver transaminases.

Randomization

After 24 months of ART, infants were randomized to continue ART (continued arm) or interrupt ART (TI arm) and followed for 18 months. Prior to randomization, caregivers were counseled using a standard script and re-consented for randomization. Eligibility criteria for randomization included: normal growth [weight-for-height (WHZ > -0.5) and weight-for-age (WAZ > -1.65 or 5th percentile) with no recent weight loss (crossing two major weight-for-age percentiles in the last 3 months)], CD4% $\geq$ 25%, no recent

opportunistic infections including tuberculosis, and willingness for randomization. Block randomization was conducted with variable block sizes generated using Stata 8.0 ralloc.ado v2.2.1 (StataCorp, College Station, Texas, USA). Treatments were allocated in 1 : 1 ratio. All study investigators were blinded to block number, block size, and sequence in the block. Treatments were assigned in preprepared sealed, opaque envelopes ordered in the sequence of treatment assignments. Once an infant's eligibility was determined, the first available allocation envelope was assigned to the infant.

Treatment interruption

To prevent resistance, nucleoside reverse transcriptase inhibitors (NRTIs) were continued for 2 weeks after stopping non-nucleoside reverse transcriptase inhibitors (NNRTIs) to allow for NNRTI decay.

Postrandomization follow-up

After randomization, children were reviewed after 2 weeks and monthly to 18 months with anthropometric measurements, WHO staging, and adverse event determination. Blood was collected at 3-month intervals for $CD4^+$ cell count and CD4% and viral load.

Restart of antiretroviral treatment in the treatment interruption arm

Criteria for ART restart were CD4% less than 20–25% (CD4% threshold changed from 20 to 25% in November 2010 following a change in WHO guidelines for ART initiation) or a decrease greater than one-third of the peak $CD4^+$ cell count or CD4%, more advanced WHO stage, or weight loss (drop in weight-for-age percentile to less than 5th percentile or weight crossing more than 2 major weight-for-age percentiles). Once a child restarted ART, there was no further interruption.

Sample size

The targeted sample size was 150 enrolled children, of which 100 would be randomized. Using data from a previous perinatal HIV study in Nairobi, the average weight-for-height *z*-score (WHZ) among HIV-uninfected and HIV-infected children at ~20 months was −0.7002 with a SD of 0.8529 [19]. Assuming the mean WHZ among the continuous ART children was −0.7002, the same SD for both groups, a two-sided test, significance level of 0.05, and 10% loss to follow-up: with 50 children in each trial arm (45 with complete follow-up), there was an estimated 80% power to exclude differences in WHZ of 0.50 or larger between RCT arms.

Laboratory methods

$CD4^+$ cell counts were determined at the University of Nairobi using FACSCount (BD Biosciences, Franklin Lakes, New Jersey, USA) and CD4% using the Humalyser hematology analyzer. HIV RNA measurements were conducted at the Fred Hutchinson Cancer Research Center in Seattle, using the Gen-Probe HIV-1 RNA assay (Gen Probe, San Diego, California, USA). Genotypic resistance testing was conducted in Nairobi using a population-based Sanger sequencing method described previously [20]. Interpretation of the sequences conferring resistance utilized the Stanford University HIV Drug resistance Database (http://hivdb.stanford.edu/).

Statistical analysis

All analyses were conducted using Stata SE version 12 (StataCorp, College Station, Texas, USA). To assess adequacy of randomization, baseline characteristics were compared between trial arms using the Wilcoxon rank sum tests and Fisher's exact tests. The primary outcome was comparison of growth and serious adverse events (SAEs) postrandomization between arms. Plasma HIV RNA, $CD4^+$ cell count and percentage, and morbidity were also compared. Growth was measured as weight-for-age *z*-scores (WAZ), WHZ, and height-for-age *z*-scores (HAZ). Primary outcomes were compared using the Wilcoxon rank sum tests (continuous variables) and Cox regression (time-to-event variables) with Anderson-Gill methods for recurrent events, as appropriate. Time to death was compared using the log-rank statistic.

Results

Baseline characteristics and prerandomization follow-up

Between September 2007 and August 2010, 140 HIV-infected children were enrolled, and 121 enrolled children initiated ART (80 initiated ART in study, 41 previously on ART), of whom 18 died, 8 were lost to follow-up, 3 withdrew prior to randomization, 75 completed 2 years of ART, and 17 had not completed 2-year ART (Fig. 1). The prerandomization cohort has been described [21]. Among infants enrolled prior to ART, pre-ART mortality was high despite short median time to ART (2 weeks from diagnosis) [20]. Of 75 children who completed 2-year ART, 29 did not meet randomization eligibility criteria or had evidence of nonadherence, treatment switch, or unplanned treatment interruption; four children were pending randomization when the DSMB recommended stopping the study. Forty-two children were randomized.

Characteristics of randomized children

Pre-ART (over 2 years before randomization), median age of the 42 infants was 5.0 months and the pre-ART CD4% was 23 and 19% in the continued and treatment interruption arms, respectively ($P = 0.2$) (Fig. 1, Table 1). Initial ART regimens (38% received protease inhibitor and the remainder NNRTI regimens) and anthropometric measures pre-ART were comparable between arms.

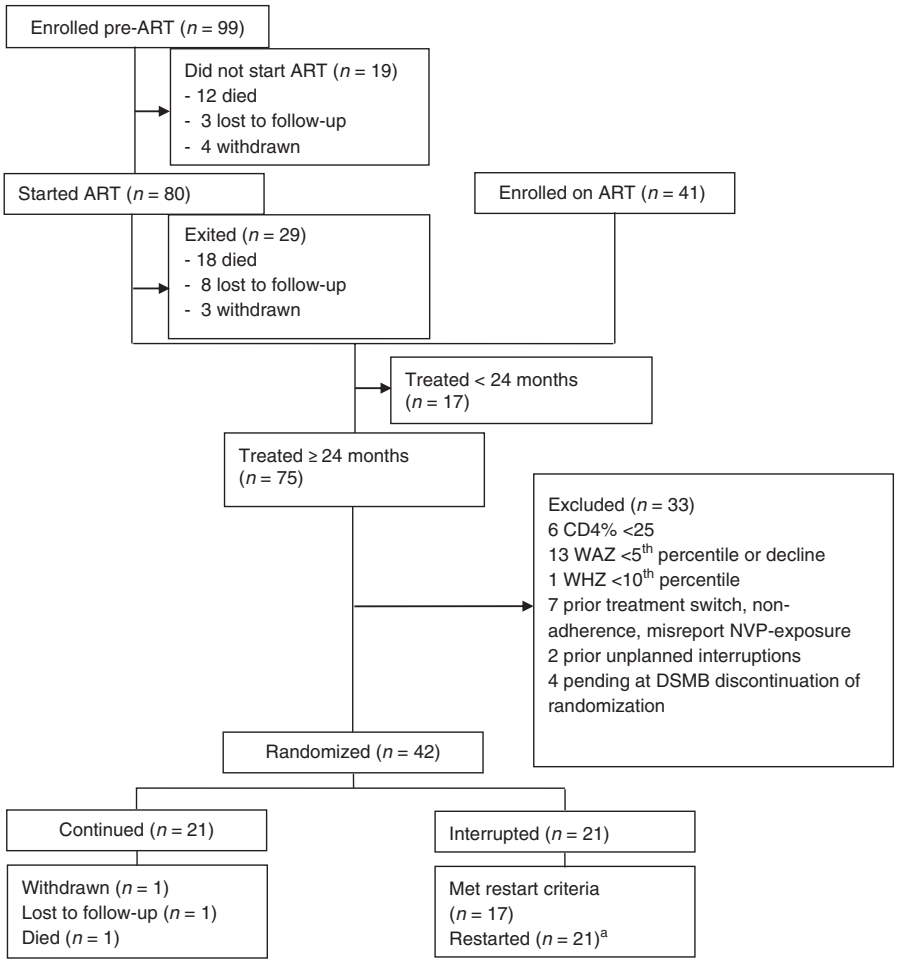

Fig. 1. CONSORT diagram of trial. [a]Four children did not meet antiretroviral treatment restart criteria but were started due to caregiver's preference (2) or study team advice (2).

At randomization, time on ART, clinical, immunologic, virologic, and growth characteristics were similar between trial arms. Median CD4% was 33 versus 34% in the continued versus treatment interruption arm, respectively ($P = 0.9$). Plasma viral load was comparable with each arm median less than 150 copies/ml.

Data safety monitoring board discontinuation of randomization

In July 2011, the DSMB determined that although randomization into the treatment interruption arm was safe, most children met ART restart criteria at 3-months post-treatment interruption. The DSMB recommended stopping randomization due to low treatment interruption durability and that randomized children complete 18-month follow-up with the option of restarting ART depending on caregiver preference.

Postrandomization follow-up

There were 30.6 person-years of follow-up in the continued arm and 32.1 person-years of follow-up in the treatment interruption arm. There was one loss to follow-up and one withdrawal, both in the continued arm. Among 21 children randomized to treatment interruption, 17 (81%) met criteria for ART restart. Fourteen (66%) experienced a CD4% drop to 25% or less within 3 months and one child after 6 months; one child met criteria of a greater than one-third drop from peak CD4% at 15 months, and one had a worsened WHO stage at 15 months post-treatment interruption. Four children (19%) never met ART restart criteria. Following the DSMB recommendation, two caregivers restarted ART at 9 and 12 months, whereas two children remained on treatment interruption till 12 and 15 months until the team advised restart due to inability to monitor children following study completion. Median time off treatment for children in the treatment interruption arm was 4.3 months (interquartile range, 3.7, 9.7).

Immunologic responses following treatment interruption and restart

Following treatment interruption, median CD4% dropped from 34 to 23% at 3-months postrandomization (Table 2). Median CD4% was significantly lower in the

Table 1. Baseline characteristics by randomization arm.

Characteristics	Continued; Median (IQR) or *n* (%); *N* = 21	Treatment interruption; Median (IQR) or *n* (%); *N* = 21
Pre-ART characteristics		
Age at ART initiation (months)	5.0 (4.4, 7.5)	5.0 (4.0, 7.1)
Male	6 (29)	13 (62)
Ever breastfed	16 (76)	19 (90)
Growth (*N* = 20, 21)		
WAZ	−2.31 (−3.02, −0.72)	−1.34 (−2.85, −0.79)
HAZ	−2.23 (−3.02, −1.52)	−1.03 (−2.34, −0.35)
WHZ	−0.62 (−1.88, 0.39)	−0.96 (−1.65, −0.02)
WHO stage (*N* = 18, 16)[a]		
I	8 (44)	8 (50)
II	3 (17)	1 (6)
III	7 (39)	5 (31)
IV	0 (0)	2 (13)
WHO stage III/IV (*N* = 18, 16)[a]	7 (39)	7 (44)
CD4%	23 (14, 29)	19 (15, 23)
$CD4^+$ cell count (cells/μl)	1370 (830, 1939)	1385 (738, 1941)
Plasma HIV RNA $\log_{10}$ copies/ml (*N* = 17, 15)[a]	6.50 (6.12, 7.25)	6.59 (5.98, 6.93)
ART initial regimen		
LPV/r-based regimen	8 (38)	8 (38)
Characteristics at Randomization		
Age at randomization (months)	29.9 (28.9, 33.8)	30.0 (29.3, 34.9)
Time on HAART (months)	25.2 (24.9, 25.5)	25.2 (24.9, 27.4)
Regimen at randomization		
LPV/r; 3TC; ZDV	10 (48)	14 (67)
LPV/r; 3TC; ABC	6 (29)	2 (10)
NVP; 3TC; ZDV	4 (19)	5 (24)
NVP; 3TC; ABC	1 (5)	0 (0)
LPV/r-based regimen	16 (76)	16 (76)
Growth		
WAZ	−0.47 (−0.87, −0.02)	−0.34 (−0.63, 0.47)
HAZ	−1.33 (−2.04, −1.03)	−0.91 (−1.66, −0.16)
WHZ	0.52 (0.19, 0.79)	0.67 (0.15, 1.18)
WHO stage 1	21 (100)	21 (100)
CD4%	33 (30, 40)	34 (32, 38)
$CD4^+$ cell count (cells/μl)	1750 (1547, 2299)	1654 (1300, 1924)
Plasma HIV RNA copies/ml	150 (150, 440)	150 (150, 515)
Plasma HIV RNA $\log_{10}$ copies/ml	Undetectable[b] (2.18, 2.64)	Undetectable[b] (2.18, 2.71)

ART, antiretroviral treatment; HAZ, height-for-age *z*-scores; IQR, interquartile range; WAZ, weight-for-age *z*-scores; WHZ, weight-for-height *z*-score.
[a]Excludes infants already on ART at enrollment who did not have this information.
[b]Below level of detection is 2.18 (<150 copies/ml).

treatment interruption arm at 3-months postrandomization (median 23 versus 37% in treatment interruption versus continued, $P < 0.001$). Among the 17 children who met ART restart criteria, median increase in CD4% was 8% at 3 months following ART restart (Fig. 2a). CD4% was identical between trial arms at 18 months (CD4% 35% in each arm, $P = 0.92$).

Growth and morbidity

At 6, 12, and 18 months postrandomization, the median WAZ was −0.42, −0.54, and −0.57 in the continued arm, respectively and −0.30, −0.29, and −0.17 in the treatment interruption arm, respectively (Table 2, Fig. 2c). There were no significant differences in WAZ, WHZ, and HAZ between arms (Fig. 2c–e).

Incidence of serious adverse events

SAEs were infrequent and did not differ between arms. In the continued arm, one infant died (incidence 3.3 per 100 person-years). In the treatment interruption arm, one infant was hospitalized for cellulitis (Grade 3) (incidence 3.1 per 100 person-years) (Table 2). Children in the treatment interruption arm had a trend for higher incidence of lymphadenopathy, whereas children on continued ART had significantly higher incidence of hypercholesterolemia. During 6-months postrandomization, those with shorter treatment interruption had a higher incidence of lymphadenopathy (135.8 cases per 100 person-years), than those with longer treatment interruption had less lymphadenopathy (31.2 cases per 100 person-years) ($P = 0.125$), and those on the continued arm had a rate of lymphadenopathy of 20.2 cases per 100 person-years.

Virologic response and resistance compared postrandomization

Plasma viral loads rose sharply in the treatment interruption arm compared with continued arm to a

Table 2. Summary of postrandomization CD4%, viral load, growth, and morbidity by arm.[a]

Characteristics	Continued; Median (IQR) or *n* (%); *N* = 21	Treatment interruption; Median (IQR) or *n* (%); *N* = 21	*P* value
CD4%			
Randomization (*N* = 21, 21)	33 (30, 40)	34 (32, 38)	0.950
3-month (*N* = 21, 21)	37 (29, 42)	23 (18, 27)	<0.001
6-month (*N* = 21, 20)	34 (26, 41)	26 (24, 37)	0.155
9-month (*N* = 21, 21)	34 (27, 41)	29 (26, 34)	0.170
12-month (*N* = 19, 21)	35 (25, 42)	30 (28, 35)	0.303
15-month (*N* = 19, 20)	37 (30, 44)	32 (29, 38)	0.172
18-month (*N* = 18, 21)	35 (27, 42)	35 (33, 37)	0.921
Plasma $\log_{10}$ viral load			
Randomization (*N* = 21, 21)	2.18 (2.18, 2.64)	2.18 (2.18, 2.71)	0.655
3-month (*N* = 20, 21)	2.18 (2.18, 5.30)	6.02 (5.42, 6.37)	<0.001
6-month (*N* = 21, 19)	2.28 (2.18, 5.29)	3.21 (2.69, 5.27)	0.174
9-month (*N* = 21, 21)	2.18 (2.18, 5.36)	3.07 (2.18, 4.87)	0.506
12-month (*N* = 19, 21)	2.18 (2.18, 4.24)	2.76 (2.18, 3.82)	0.398
15-month (*N* = 17, 20)	2.18 (2.18, 4.38)	2.30 (2.18, 4.35)	0.618
18-month (*N* = 18, 21)	2.18 (2.18, 4.03)	2.18 (2.18, 2.96)	0.920
% With viral load >1000 copies/ml			
Randomization (*N* = 21, 21)	5 (24)	5 (24)	1.000
3-month (*N* = 20, 21)	7 (35)	19 (90)	<0.001
6-month (*N* = 21, 19)	8 (38)	12 (63)	0.205
9-month (*N* = 21, 21)	8 (38)	11 (52)	0.536
12-month (*N* = 19, 21)	6 (32)	9 (43)	0.527
15-month (*N* = 17, 20)	5 (29)	7 (35)	1.000
18-month (*N* = 18, 21)	6 (33)	5 (24)	0.723
WAZ			
Randomization (*N* = 21, 21)	−0.47 (−0.87, −0.02)	−0.34 (−0.63, 0.47)	0.155
3-month (*N* = 21, 21)	−0.54 (−0.96, −0.07)	−0.31 (−0.53, 0.70)	0.105
6-month (*N* = 21, 21)	−0.42 (−0.93, −0.13)	−0.30 (−0.81, 0.47)	0.297
12-month (*N* = 20, 21)	−0.54 (−0.98, −0.19)	−0.29 (−0.71, 0.29)	0.141
18-month (*N* = 17, 20)	−0.57 (−0.88, −0.28)	−0.17 (−0.56, 0.37)	0.148
HAZ			
Randomization (*N* = 21, 21)	−1.33 (−2.04, −1.03)	−0.91 (−1.66, −0.16)	0.155
3-month (*N* = 21, 21)	−1.32 (−1.91, −0.93)	−0.94 (−1.67, −0.42)	0.232
6-month (*N* = 21, 21)	−1.31 (−1.75, −0.96)	−1.00 (−1.76, −0.21)	0.237
12-month (*N* = 20, 21)	−1.14 (−1.87, −0.73)	−0.92 (−1.67, −0.13)	0.498
18-month (*N* = 17, 20)	−1.04 (−1.58, −0.59)	−0.78 (−1.62, 0.00)	0.446
Morbidity and adverse events	Incidence per 100 child-years (number of cases)	Incidence per 100 child-years (number of cases)	
Follow-up time since randomization, months	18.3 (18.0, 18.4)	18.4 (18.3, 18.5)	
Clinical severe adverse events (per 100 child-years)	3.3 (1)	3.1 (1)	0.972
Upper respiratory tract infection	324 (99)	334 (107)	0.875
Rash	68.7 (21)	84.3 (27)	0.569
Anemia	29.4 (9)	31.2 (10)	0.957
High cholesterol	58.9 (18)	34.3 (11)	0.032
Diarrhea	45.8 (14)	40.6 (13)	0.774
Pneumonia	13.1 (4)	9.37 (3)	0.603
Lymphadenopathy	22.9 (7)	50.0 (16)	0.087
Death	3.3 (1)	0 (0)	0.293

HAZ, height-for-age *z*-scores; IQR, interquartile range; WAZ, weight-for-age *z*-scores.
[a]Intent-to-treat analyses.

median of 6.02 $\log_{10}$ copies/ml versus undetectable 2.18 $\log_{10}$ copies/ml (<150 copies/ml) at 3-months postrandomization ($P < 0.001$), Fig. 2b. Following ART restart, median plasma viral load dropped by 3.49 $\log_{10}$ copies/ml after 6-months postrestart. By 18 months, median viral levels were undetectable in continued and treatment interruption arms ($P = 0.92$); however, 6 of 18 (33%) children in the continued arm had viral load more than 1000 copies/ml versus 5 (24%) of 21 children in the treatment interruption arm ($P = 0.72$) (Table 2). Prerandomization, 5 children in the continued arm had viral load more than 1000 copies/ml, of whom one did not amplify, two tested without resistance, and two tested with resistance (M46I, I54V, V82F, Y188L, H221Y, M184V, D67N; and M184V, K103N); five children in the treatment interruption arm had viral load more than 1000 copies/ml, of whom two were not tested, one tested without resistance, and two tested with resistance (Y181C, M184V; and A98AG, K101AE, G190A, M184V). Postrandomization, 10 in the continued arm

Table 3. Comparison of treatment interruption children who met antiretroviral treatment restart criteria at 3 months to those with met antiretroviral treatment restart criteria later.

Characteristics	Median (IQR) or *n* (%); Met ART-restart criteria at 3 months $N=14$	Median (IQR) or *n* (%); Did not meet ART-restart criteria at 3 months; $N=7$	*P* value
Age at ART (months)	4.8 (3.8, 7.1)	5.3 (4.4, 7.3)	0.654
Growth			
Pre-ART WAZ	−1.64 (−2.51, −0.79)	−1.34 (−2.98, −0.60)	0.852
Randomization WAZ	−0.29 (−0.63, 0.47)	−0.34 (−0.65, 0.62)	1.000
Pre-ART HAZ	−1.01 (−2.24, −0.19)	−1.14 (−3.73, −0.35)	0.794
Randomization HAZ	−0.76 (−1.18, −0.13)	−1.89 (−2.17, −0.76)	0.073
Pre-ART WHZ	−1.15 (−2.93, 0.21)	−0.54 (−1.62, 0.02)	0.478
Randomization WHZ	0.58 (−0.09, 0.69)	0.98 (0.45, 1.41)	0.101
CD4%			
Pre-ART CD4%	19 (15, 23)	19 (14, 23)	0.822
CD4% nadir	16 (10, 19)	18 (14, 23)	0.525
Randomization CD4%	33 (29, 36)	39 (33, 41)	0.043
$CD4^+$ cell count			
Pre-ART $CD4^+$ cell count (cells/ml)	1365 (738, 1760)	1572 (596, 2140)	0.654
Randomization $CD4^+$ cell count (cells/μl)	1390 (1177, 1887)	1747 (1654, 2238)	0.073
HIV-1 viral load			
Pre-ART viral load (log_{10}) ($N=9$, 6)[a]	6.63 (6.30, 6.93)	6.28 (5.52, 6.83)	0.556
Randomization viral load	150 (150, 325)	150 (150, 343 305)	0.328
Enrollment WHO stage 3/4 ($N=10$, 6)[a]	4 (40)	3 (50)	1.000
Randomization WHO stage I	14 (100)	7 (100)	–
Randomization regimen			
Protease inhibitor regimen	12 (86)	4 (57)	0.280
NNRTI-regimen	2 (14)	3 (43)	

ART, antiretroviral treatment; HAZ, height-for-age *z*-scores; IQR, interquartile range; WAZ, weight-for-age *z*-scores; WHZ, weight for height *z*-score.
[a]Excludes infants already on ART at enrollment who did not have this information.

had a viral load more than 1000 copies/ml, of whom four were tested and had no resistance; all 21 in the treatment interruption arm had at least one viral load more than 1000 copies/ml, of whom 11 tested without resistance and two tested with resistance (K103N; and A98AG, K101AEKT, G190AG, M184MV).

Characteristics of children who sustained longer treatment interruption

Although most children rapidly met ART restart criteria following treatment interruption, seven (one-third) sustained longer treatment interruption (>5 months). Patterns of viral load and CD4% before, during, and after treatment interruption are summarized in Fig. 3. Because viral loads were measured retrospectively and were not part of eligibility criteria, some children were not virally suppressed at randomization. Two children with viremia prior to treatment interruption had minimal changes in CD4% after treatment interruption (nos. 041 and 045). In children with longer treatment interruption, ID nos. 010 and 076 had viral load decline after initial high levels. All children had rapid viral decline following restarting ART.

Children in the treatment interruption arm who sustained treatment interruption longer than 3 months had similar nadir pre-ART CD4% to those who restarted ART by 3 months after treatment interruption but had a higher CD% at randomization (randomization CD4%: 39 versus 33% for treatment interruption more than 3 versus less than 3 months; $P=0.04$) (Table 3).

Discussion

In this study (OPH), which involved infants who started ART before 13 months of age, received at least 2 years of ART, and were randomized to treatment interruption versus continued ART, most children in the treatment interruption arm met criteria for restarting ART within 3 months of treatment interruption. During postrandomization follow-up, treatment interruption was safe and 18-month CD4%, viral load, incidence of severe adverse events, and growth in children in the treatment interruption arm did not differ from those who continued ART. These findings complement those from the PENTA-11 trial that evaluated treatment interruption in older children and the CHER trial that evaluated treatment interruption among children who started ART in infancy, but lacked a continued ART comparison group. Collectively, these studies suggest that monitored short-term treatment interruption does not increase adverse effects over 1–2 years following the treatment interruption and ART restart period.

We observed a lower proportion of children (<20%) sustaining treatment interruption (not meeting ART restart criteria for more than 3 months) compared with the CHER study [median treatment interruption duration 70 weeks in CHER at trial end among children with a similar duration of early ART prior to treatment interruption (96 weeks) as in our study] or the PENTA-11 study (60% had treatment interruption up to 48 weeks)

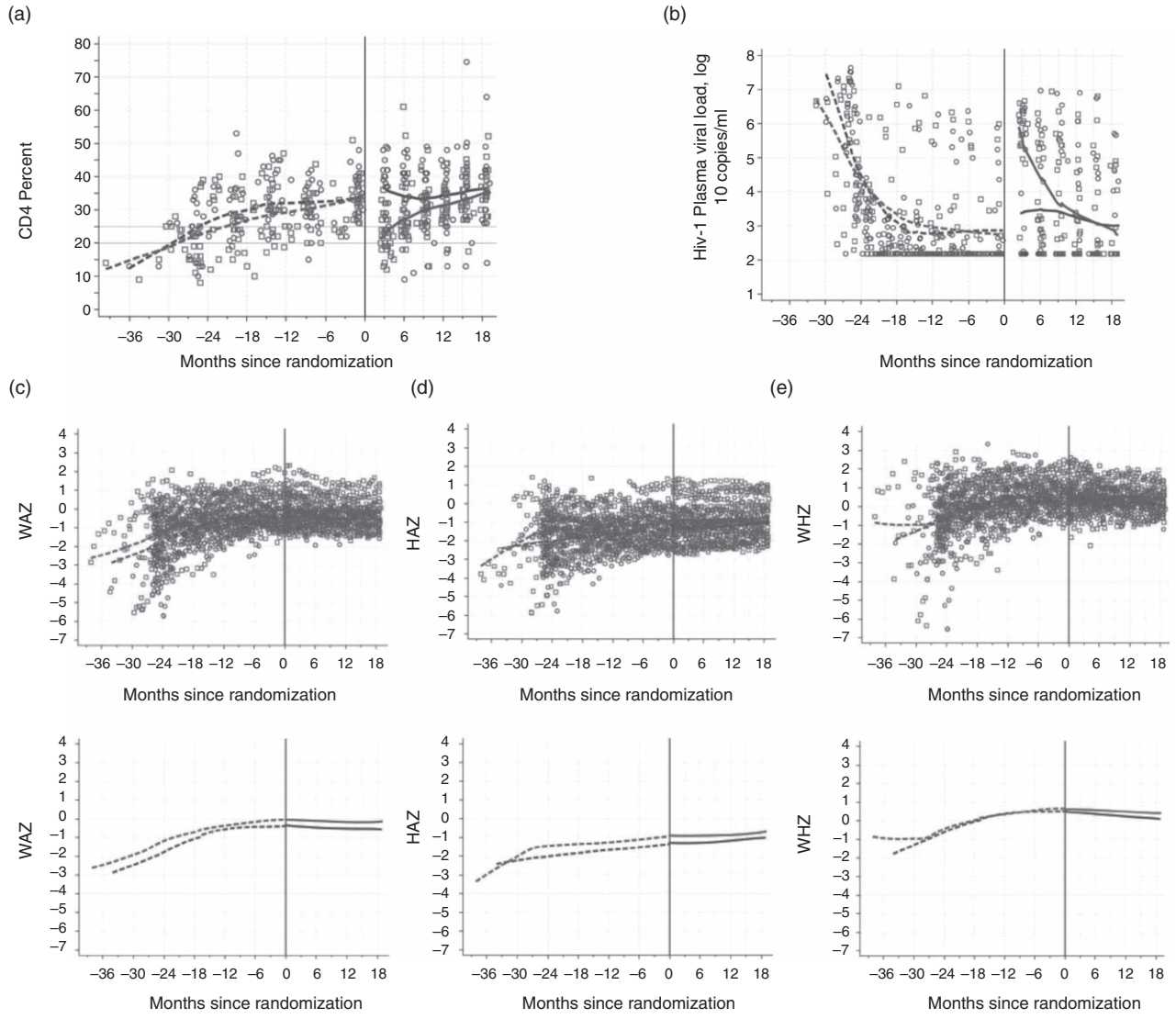

Fig. 2. CD4 percentage, viral load, and growth changes by randomization arm. (a) CD4% by randomization arm. *Note:* Individual observations for continued (circles) and interrupted (squares) are plotted. Lowess curves of prerandomization data (dashed lines) and of postrandomization (solid lines) for continued (navy) and interrupted (maroon) are included. (b) Viral loads for randomized study participants by arm. (c) Weight-for-age *z*-scores (WAZ) since randomization, by arm. (d) Height-for-age *z*-scores (HAZ) since randomization, by arm. (e) Weight-for-height z-scores (WHZ) since randomization, by arm.

[10,12]. One reason for our observed shorter treatment interruption is that our CD4% criterion for ART restart was higher (25%) to align with later WHO recommendations [22], whereas PENTA-11 and CHER used CD4% of 20% eligibility for ART restart. Small pediatric treatment interruption studies have observed CD4% increase following initial decline as HIV-1 specific immunity increases in response to viremia emerging after treatment interruption [23]. Lower CD4% criteria for ART restart may permit time to develop HIV-specific immunity to contain virus and regain immune reconstitution. Another potential reason for shorter treatment interruption in the OPH cohort is the more advanced HIV disease pre-ART. CHER infants started ART while being asymptomatic with CD4% more than 25% [1]. In OPH, over half of children had CD4% less than 25% and WHO stage 3–4 at ART initiation. Children in OPH were older at ART initiation (median 5 versus 1.9 months in CHER). We extended age-eligibility to broaden generalizability to postpartum-infected and later-diagnosed infants with the hypothesis that infants treated in the first year of life could restore immune function. Consistent with this hypothesis, we found that nadir pre-ART CD4% was not as predictive of treatment interruption duration as CD4% following 2-year ART, suggesting that some infants may safely sustain treatment interruption despite a low nadir CD4%.

In the PENTA-11 trial, 60% completed treatment interruption for 48 weeks with no serious adverse effects

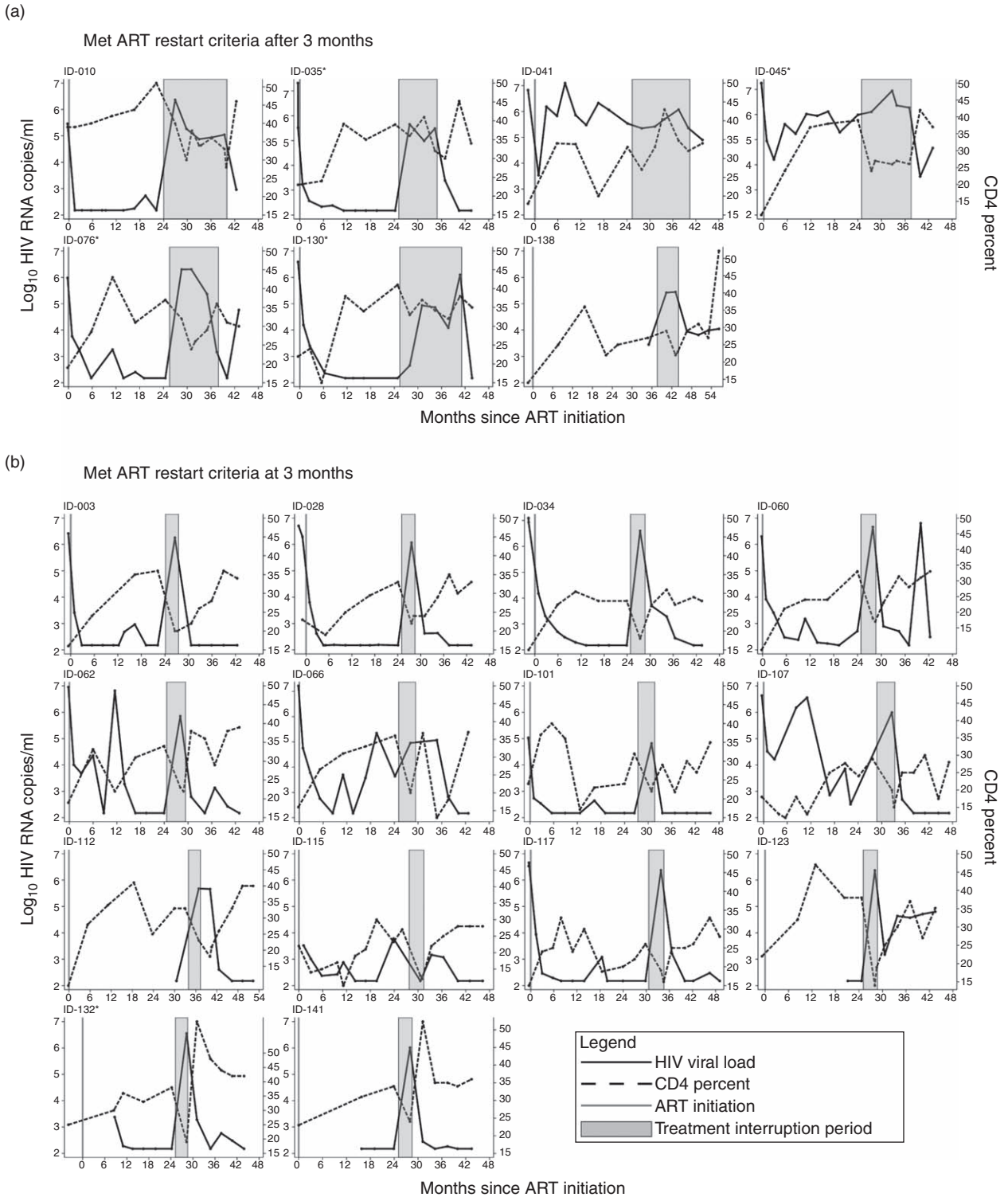

Fig. 3. CD4% and viral load changes among infants before, during and after treatment interruption. (a) Restarted antiretroviral treatment after 3 months. (b) Restarted antiretroviral treatment before 3 months.

[12]. Children in PENTA-11 were older (median age 9 years) and received ART longer (median 6 years) than in our study. Although the period of treatment interruption in OPH was shorter, we also observed prompt CD4% recovery and viral suppression following reinitiation of ART with no discernable differences in viral control or CD4% in treatment interruption children at 18 months post-treatment interruption. The incidence of serious clinical events in OPH was not elevated in the treatment interruption arm, suggesting that treatment interruption

can be safe in the short-term with close monitoring. A higher CD4% at treatment interruption, rather than nadir CD4%, predicted treatment interruption durability in OPH, in contrast to PENTA-11 and SPARTAC (an adult treatment interruption trial following ART in primary HIV) studies, which observed that pre-ART immune status predicted treatment interruption durability or PTC [12,24]. This suggests that both pre-ART and post-ART immune function may influence treatment interruption durability and PTC [25,26].

We did not identify post-treatment virologic controllers. This differs from the VISCONTI ANRS cohort [5], but is consistent with other adult studies [6,7] and preliminary data from children in the CHER study [27]. Most studies have had limited statistical power to estimate frequency of PTC (estimated 0–15%) [7]. We used immune, growth, and clinical criteria rather than viral suppression to identify children for treatment interruption and our data underscore limitations of a clinically guided approach to pediatric treatment interruption. Given the timing of ART initiation and slow suppression on ART in our cohort, children likely had large viral reservoirs at treatment interruption, which correlate with rapid rebound. In contrast to adults, in whom PTC has been observed following ART initiation within months of acute HIV, rapid progression in infants suggests need for more accelerated detection and treatment. Although our study suggests clinical safety of short treatment interruption, children with limited viral reservoirs following very early ART could have more to lose from treatment interruption than children such as those in our cohort, with more established reservoirs, because of potential to expand their viral reservoir [28]. Studies to determine whether shorter treatment pauses can safely reveal PTC are ongoing.

Several issues are uniquely relevant to pediatric treatment interruption. Children appear not to have morbidity risks noted in adult treatment interruption trials, with comparable morbidity in treatment interruption versus continued ART. Poor viral control and unplanned treatment interruptions contribute to poor outcomes in infants on ART, lending conceptual appeal to strategic treatment interruption to preserve regimen efficacy. We observed prompt declines in viral load following ART restart. Long-term virologic failure postrandomization was not uncommon (33%) in the continued arm and actually more frequent than in the treatment interruption arm (24%), although underpowered for comparison. This illustrates the challenges of ART adherence in children. Our data suggest safety of short treatment interruption; however, it does not provide evidence to support longer treatment interruption in this population.

Limitations of our study include a small sample size and the short duration of treatment interruption. Thus, we may not have realized longer term risks or benefits of treatment interruption. Despite limited numbers, prevalence of hypercholesterolemia was higher in children in the continued arm. Increased incidence of lymphadenopathy in children with treatment interruption is consistent with an acute infection-like syndrome and has been consistently observed in treatment interruption studies. Incidence of lymphadenopathy was highest among those with short treatment interruption, suggesting that lymphadenopathy occurred in parallel with rapid CD4% decline and consequent ART restart in this group.

In summary, our study provides clinical trial evidence that children who initiate ART during early HIV do not have clinically discernable long-term adverse outcomes from brief-monitored treatment interruption. Our study did not identify any post-treatment controllers among infants started on ART. Complementary strategies such as immune therapies may be necessary to enhance likelihood of PTC [29]. The study also underscores need for improved ART regimens for young children [30].

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Conflicts of interest

There are no conflicts of interest.

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