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(DTG + 3TC: n=716; DTG + TDF/FTC: n=717)[1]

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TIVICAY + lamivudine was studied in HBV-negative adult patients with screening viral loads up to 500,000 copies/mL. Suitable for patients with no known or suspected viral resistance to integrase inhibitors or lamivudine.

Reference: 1. Cahn P et al. Published online November 9, 2018. *Lancet*. doi:10.1016/S0140-6736(18)32462-0.

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ORIGINAL RESEARCH

CD4 recovery following antiretroviral treatment interruptions in children and adolescents with HIV infection in Europe and Thailand

The European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) Study Group in EuroCoord*

Objectives
The aim of the study was to explore factors associated with CD4 percentage (CD4%) reconstitution following treatment interruptions (TIs) of antiretroviral therapy (ART).

Methods
Data from paediatric HIV-infected cohorts across 17 countries in Europe and Thailand were pooled. Children on combination ART (cART; at least three drugs from at least two classes) for > 6 months before TI of ≥ 30 days while aged < 18 years were included. CD4% at restart of ART (r-ART) and in the long term (up to 24 months after r-ART) following the first TI was modelled using asymptotic regression.

Results
In 779 children with at least one TI, the median age at first TI was 10.1 [interquartile range (IQR) 6.4, 13.6] years and the mean CD4% was 27.3% [standard deviation (SD) 11.0%]; the median TI duration was 9.0 (IQR 3.5, 22.5) months. In regression analysis, the mean CD4% was 19.2% [95% confidence interval (CI) 18.3, 20.1%] at r-ART, and 27.1% (26.2, 27.9%) in the long term, with half this increase in the first 6 months. r-ART and long-term CD4% values were highest in female patients and in children aged < 3 years at the start of TI. Long-term CD4% was highest in those with a TI lasting 1 to <3 months, those with r-ART after year 2000 and those with a CD4% nadir ≥ 25% (all $P < 0.001$). The effect of CD4% nadir during the TI differed significantly ($P = 0.038$) by viral suppression at the start of the TI; in children with CD4% nadir < 15% during TI, recovery was better in those virally suppressed prior to the TI; viral suppression was not associated with recovery in children with CD4% nadir ≥ 25%.

Conclusions
After restart of ART following TI, most children reconstituted well immunologically. Nevertheless, several factors predicted better immunological reconstitution, including younger age and higher nadir CD4% during TI.

Keywords: antiretroviral therapy, paediatric, treatment interruption

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Introduction

Life-long antiretroviral treatment (ART) is presently recommended in patients with HIV infection, and long-term adherence is often compromised by pill burden, toxicity and interference with everyday life, particularly in adolescents [1]. Consequently, randomized trials on the safety of planned treatment interruptions (TIs) in adults and children with HIV infection have been undertaken. Several studies have clearly shown a detrimental effect of TIs in adults, with patients experiencing a greater incidence of infections and higher mortality rates on recommencement of ART, compared with those on continuous ART [2–7]. TIs are therefore not recommended in adult treatment guidelines.

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Only two trials have evaluated the consequences of planned TIs in children. The first, Paediatric European Network for Treatment of AIDS (PENTA) 11, was a randomized trial of continuous ART compared with CD4-guided planned TIs in children with suppressed viral load and good immunological status at enrolment [8]. The second, the Children with HIV Early Antiretroviral (CHER) randomized trial, compared outcomes in children in whom ART was deferred to those in children who were treated early but then commenced TIs at 1 or 2 years of age [9]. Both studies reported no serious clinical or immunological outcomes during TIs. Additionally, PENTA 11 showed increased CD4 cell recovery after ART restart in younger children, while adult trials reported no age effect [10]. These two paediatric trials suggest that TIs may be more suitable for children than adults, possibly as children experience a different immunological course of HIV infection from adults. In the first years of life, children experience moderate immunosuppression, but following ART initiation their immune reconstitution is stronger than in adults [11,12] as a consequence of different immunological kinetics as a result of functional thymus activity in children [13].

Unplanned TIs continue to occur in routine clinical practice, often because of a patient's decision to stop treatment or poor adherence, suggesting that the virological and immunological status of patients at the point of unplanned interruptions may be poorer than those in experimental trials. In France, the risk of TIs of $\geq$ 3 months' duration among 483 children was 7% after 1 year of ART, rising to 30% at 5 years [14]. Children were matched to a control group who did not interrupt treatment using age at start of TI. During follow-up, severe immunosuppression, defined as CD4 percentage (CD4%) < 15%, occurred earlier in those who had a TI than in the control sample. Four years after the TI, 53% of children who had been back on ART for $\geq$ 6 months had a CD4% > 25% compared with 74% in the continuous ART group. However, there was no difference in AIDS-free survival. In a second study from the USA which examined the impact of unplanned TIs in 405 children, of whom 17% had a TI, the largest declines in CD4 off ART occurred in those who had experienced the largest gains while on treatment pre-TI, but CD4 recovery after ART restart was not investigated [15].

Here, we describe immunological outcomes of TIs in a large collaboration of paediatric cohorts from 17 countries in Europe and Thailand. We hypothesized that characteristics before and during the TI, in particular age and nadir CD4%, would be associated with immunological recovery following TI. Identification of children and adolescents at risk of poor recovery is important to ensure that treatment is restarted in a timely manner for those most at risk. Our aim was therefore to investigate factors that might predict improved immunological recovery after ART restart.

Methods

Nineteen cohorts from 17 countries in the European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) contributed patient-level data. Anonymized demographic, clinical, laboratory and treatment-related data were provided, following a standard operating procedure, and merged using a modified HIV Cohorts Data Exchange Protocol (http://www.hicdep.org) [16]. All cohorts had local ethics approval to transfer anonymized data for this study.

Children were included in this analysis if they were on a combination ART (cART) regimen, defined as at least three drugs from at least two classes or three nucleoside reverse transcriptase inhibitors (NRTIs), for $\geq$ 6 months before a TI. TIs were defined as a period off treatment of $\geq$ 30 days which commenced while < 18 years of age. Subsequent TIs were defined as further interruptions of $\geq$ 30 days where the previous TI had ended $\geq$ 30 days previously. Where there were < 30 days between two TIs of $\geq$ 30 days, the time between the start of the first TI and the end of the subsequent TI was considered as a single TI. Children were excluded if they had participated in TI trials, were followed up for < 30 days following restart of ART after the first TI, or had no CD4% measurements in the 24 months after restart of ART (or before the start of the second TI, if within 24 months).

Statistical analysis

Characteristics of children at ART initiation and first TI were described. CD4% response following restart of ART up to 24 months after the first TI was modelled using nonlinear asymptotic mixed effects models, with all CD4% measurements in this period included with the exception of those occurring after the start of a subsequent TI. Such models have previously been shown to describe CD4 response after ART initiation well [17–19].

The model is parameterized in terms of an intercept (int_i), representing CD4% at restart of ART, an asymptote (asy_i), representing the longer term, stable CD4%, and a rate parameter (c_i), which represents the speed at which change in CD4% occurs. CD4% for child i at time t is described by $\text{CD4\%}_{ij} = \text{asy}_i - (\text{asy}_i - \text{int}_i)\text{e}^{-c_i t_{ij}} + \varepsilon_{ij}$ where ε_{ij} is the residual error. The change parameter c can be used to calculate the time for half the CD4% recovery (i.e. time to half the difference between the intercept and asymptote) to take place as: In(2)/c.

In univariable models, the unadjusted associations between the intercept, asymptote and rate of change, *c*, and a number of factors were explored. These included sex and age (0 to < 3, 3 to < 6, 6 to < 11 or ≥ 11 years) at each of the following time-points: (1) initiation of any ART (not necessarily cART), (2) initiation of first cART, (3) start of first TI and (4) first restart of ART. The effects of being treatment naïve versus experienced at initiation of the first cART regimen; not being seen in the clinic versus being seen during the TI; the length of the TI (1 to < 3, 3 to < 6, 6 to < 24 or ≥ 24 months); the calendar year of the first ART restart (< 2000, 2000–2004, 2005–2009 or ≥ 2010); starting versus not starting a new class of drug at restart; and having planned versus unplanned TI were explored. Planned TI was defined as stopping ART because of the physician's decision (for reasons other than treatment/virological failure), noncompliance or side effects/toxicity. Viral load (< 400 or ≥ 400 HIV-1 RNA copies/mL) at the start of the TI; nadir CD4% (< 15%, 15 to < 25% or ≥ 25%) (1) prior to any ART, (2) before initiation of the first cART and (3) during the first TI; CD4% at the start of the first TI and mean CD4% during the first TI were also considered.

With the exception of age at ART initiation, age at first restart of ART (to avoid issues of multicollinearity), viral load and CD4% before and during TI, any variables that were significant at the 0.1 level in univariable analysis were considered for inclusion in the first multivariable model. A forward selection procedure was used to build the model with the variables added one at a time to either the intercept, asymptote or *c*, with entry probability = 0.1.

A second multivariable model was then fitted, in the subset of children with CD4% and viral load data available, which included all variables in the first model along with nadir CD4% prior to initiation of the first cART, nadir CD4% during TI and viral load at the start of TI. CD4% at the start of TI was not included as it is highly correlated with nadir CD4% during the TI; nadir CD4% during the TI was felt to be more clinically useful to a physician potentially faced with a decision regarding when to restart treatment. Interactions between nadir CD4%, viral load suppression and age at TI were also explored and included in the model where significant. In sensitivity analyses, modelling was repeated in only those who initiated ART on a cART regimen and again including only TIs of ≥ 3 months.

Characteristics of children were described using STATA/IC 15.1 (StataCorp, College Station, TX, USA) and models were fitted using the nlme package in R v3.3.2 [20].

Results

A total of 7358 children started ART, of whom 901 (12%) had a TI. Of these 901, 122 were excluded [22 were trial participants (12 in PENTA 11, nine in PENPACT1 and one in both), 85 had no CD4% in 24 months after ART restart, and 15 had < 30 days of follow-up after the restart of ART], leaving 779 included in this analysis (Fig. S1). Characteristics of the 779 included children, along with 6457 who never had a TI, are summarized in Table 1. The median duration of follow-up after first ART initiation was 13.1 [interquartile range (IQR) 9.6, 15.8] years and the median duration of follow-up from restart of ART after the first TI was 4.6 (IQR 2.5, 7.5 years).

For children who had a TI, 31% had more than one, with the first lasting a median of 9.0 (IQR 3.5, 22.5) months and occurring at a median age of 10.1 (IQR 6.4, 13.6) years. Age at and duration of first and subsequent TIs are summarized in the bottom half of Table 1 along with ART regimens used before and after the first TI. All subsequent results are based on the first TI only.

At the time of the first TI, 426 (55%) were taking a protease inhibitor (PI) + NRTI regimen and 294 (38%) were on a nonnucleoside reverse transcriptase inhibitor (NNRTI) + NRTI regimen; the reason for the TI did not differ significantly between patients on a PI and those on an NNRTI ($P = 0.082$). Following the TI, 392 (50%) restarted a regimen containing a different class of drug, while 126 (16%) restarted on the pre-TI regimen. For the remainder, 67 (9%) had a change in the backbone NRTIs only and 194 (22%) changed drug within a class other than NRTI. Those who were on an NNRTI prior to the TI were significantly more likely to start a new class after the TI (210 of 294; 71%) than those on PIs (173 of 426; 41%; $P < 0.001$). Three deaths occurred within 24 months of restarting ART [one at 3 months in 2005 (invasive bacterial infection), one at 4 months in 2000 (AIDS-defining event; unspecified), and one at 15 months in 2008 (HIV-related)].

CD4% recovery after restarting ART

Median calendar year of ART restart after the first TI was 2006 (IQR 2003, 2009). At the start of the first TI, the mean CD4% was 27% (SD 11%), which fell to a mean nadir of 17% (SD 9%) during the TI. Half of the children had a CD4% at the time of restart, for whom the mean was 18% (SD 10%). A CD4% was available for 546 at 12 (± 3) months after ART restart, at which point the mean was 25% (SD 10%), and in 425 with a measurement at 24 (± 3) months the mean was 27% (SD 10%). Observed

Table 1 Characteristics of children who did and did not interrupt treatment

	Interrupted treatment	Did not interrupt treatment
	n (%) or median (IQR)	
All	779	6457
Female gender	414 (53)	3307 (51)
Perinatally acquired infection	723 (93)	5730 (89)
Cohort		
UK and Ireland	264 (34)	1267 (20)
Italy	134 (17)	1261 (20)
France	131 (17)	443 (7)
Spain	95 (12)	754 (12)
Romania	38 (5)	418 (6)
Thailand	38 (5)	809 (12)
Other*	79 (10)	1505 (23)
Age at ART initiation (years)	2.5 (0.5, 6.4)	4.2 (1.0, 8.7)
Age at cART initiation (years)	5.3 (2.1, 8.7)	6.3 (2.2, 10.4)
Initiated ART on cART	374 (48)	3979 (62)
Initial cART regiment		
PI + NRTI	433 (56)	2587 (44)
NNRTI + NRTI	260 (33)	2614 (40)
NRTI only	55 (7)	213 (3)
PI + NNRTI	31 (4)	139 (2)
Other	0	6 (0)
No cART regimen initiated	0	628 (10)
Calendar year of first cART regiment	1999 (1998, 2003)	2004 (2000, 2007)
Nadir CD4% prior to any ART initiation		
< 15%	203 (35)	1996 (42)
15–24%	171 (30)	1532 (32)
≥ 25%	200 (35)	1257 (26)
Missing	*205* (26)	*1672* (26)
Number of TIs		
1	540 (69)	
2	168 (22)	
3	53 (7)	
≥ 4	18 (2)	
Age at start of TI (years)		
1st IT	10.1 (6.4, 13.6)	
2nd TI	13.8 (9.9, 15.9)	
3rd TI	14.8 (10.8, 16.0)	
4th TI	15.8 (14.1, 16.9)	
Duration of TI (months)		
1st IT	9.0 (3.5, 22.5)	
2nd TI	6.7 (3.0, 12.5)	
3rd TI	5.5 (3.0, 8.5)	
4th TI	3.9 (3.0, 7.8)	
Reason for first TI		
Patient decision/noncompliance	280 (49)	
Treatment failure	126 (22)	
Physicians decision	95 (17)	
Side effects/toxicity	53 (9)	
Other	21 (4)	
Missing	*204* (26)	
Regimen immediately prior to first TI		
PI + NRTI	426 (55)	
NNRTI + NRTI	294 (38)	
PI + NNRTI + NRTI	59 (8)	
Regimen at restart following first TI		
PI + NRTI	456 (60)	
NNRTI + NRTI	165 (21)	
3 NRTIs	72 (9)	
PI + NNRTI + NRTI	86 (11)	
Restarted on a different class after TI	392 (50)	

ART, antiretroviral therapy; cART, combination antiretroviral therapy; IQR, interquartile range; PI, protease inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; TI, treatment interruption.
*Other cohorts contributing < 5% of patients with TI were from Switzerland (n = 23 with TI, 129 without), Belgium (n = 17 with TI, 115 without), the Netherlands (n = 14 with TI, 259 without), Russia (n = 10 with TI, 149 without), Portugal (n = 5 with TI, 46 without), Sweden (n = 4 with TI, 88 without), Ukraine (n = 4 with TI, 622 without) and Poland (n = 2 with TI, 57 without). Additionally, Greece and Germany each had 20 children without TIs and none with.

CD4% values up to 24 months after restart of ART following first TI are presented in Figure 1. During this period, 4023 CD4% measurements were recorded with a median of 5 (IQR 3, 7) measurements (range 1–22) per child.

The overall estimated intercept was 19.2% (95% CI 18.3, 20.1%) and the asymptote was 27.1% (95% CI 26.2, 27.9%), indicating a modelled average CD4% of 19% at restart rising to 27% in the long term. The rate parameter was estimated as 0.119 (95% CI 0.104, 0.133) which corresponds to a time of 6 months [ln (2)/c = ln (2)/0.119 = 5.8 months] for half the CD4% recovery to take place. Univariable associations between demographic and treatment characteristics and CD4% up to 24 months following restart of ART are shown in Table 2.

In the first multivariable model, including all children but not laboratory data (Table 3), female sex and younger age at first TI were independent predictors of higher CD4% at restart (intercept) and in the long term (asymptote). Estimated mean CD4% values after ART restart for male and female patients of different ages are shown in Figure 2. Earlier year of first restart of ART and TI length of 3 to <6 months were also associated with lower long-term CD4%. None of the variables were associated with the rate of recovery (C).

The second multivariable model included 365 children with nadir CD4% prior to first cART, nadir CD4% during TI and viral load at the start of TI. These children were more likely to be from the UK/Ireland (45% versus 24% or those with incomplete data) and to have a longer TI [median 11.9 (IQR 5.1, 27.6) versus 5.6 (IQR 2.6, 17.0) months for those with incomplete data] but did not

differ by other characteristics listed in Table 1. In this model (Table 3), the only factors from model 1 to remain significant were the effects of year of ART restart, age at TI and length of TI on the long-term CD4%. The higher long-term CD4% in younger children implies better CD4% recovery compared with older children who restarted ART with a similar CD4%. Conversely, the lack of difference between male and female patients suggests that, after adjusting for higher average CD4% in female individuals, there was no difference in the rate of recovery between the sexes.

Lower CD4% nadir prior to cART was associated with lower CD4% at restart only. Lower CD4% nadir during the TI was also associated with lower CD4% at restart, as well as lower long-term CD4%. However, there was a statistically significant interaction between CD4% nadir during the TI and viral suppression prior to the TI ($P = 0.038$) and consequently the magnitude of the long-term effect of nadir CD4% during the TI differed by viral load suppression at TI start (Fig. 3). In children with CD4% nadir < 15% during the TI, those who had an undetectable viral load at the start of the TI reached a higher long-term CD4% than those without suppression (Fig. 3a and b); viral suppression was not associated with recovery in those with CD4% nadir ≥ 25% (Fig. 2e and f). Two hundred and sixty-two children included in the model had a CD4% available prior to the TI (< 2 months prior to stopping treatment). Predicted long-term CD4% was highly correlated with pre-TI CD4% ($r = 0.63$; $P < 0.001$; Fig. S2).

In a sensitivity analysis which included 374 children who were treatment naïve at cART start (Table S1), and 675 who had a TI of ≥ 3 months (Tables S2 and S3), results were broadly similar to those of the first and second models.

Discussion

ART interruptions occurred in just over 1 in 10 children and adolescents living with HIV. In our large data set from several cohorts in Europe and Thailand, we found that 12% of children who started ART had a TI. The first TI occurred at an average age of 10 years after 5.5 years on cART, with 21% having a further TI. This proportion of children with a TI is lower than that reported in a French cohort (42%) [14] and in a US cohort (18%) in 2008 [15]. Duration of TIs varied from a median of 9 months in our study, to 12 months in the French study and 14 months in the US study. Moreover, TIs occurred at a median age of 10.1 versus 8 years in the French cohort and 12.8 years in the US cohort. Detailed comparisons among studies are difficult and differences in definitions of TI (we defined a TI as a 1-month interruption, while the other studies defined it as a 3-month interruption), availability of treatment and calendar period of enrolment may explain differences in the proportions

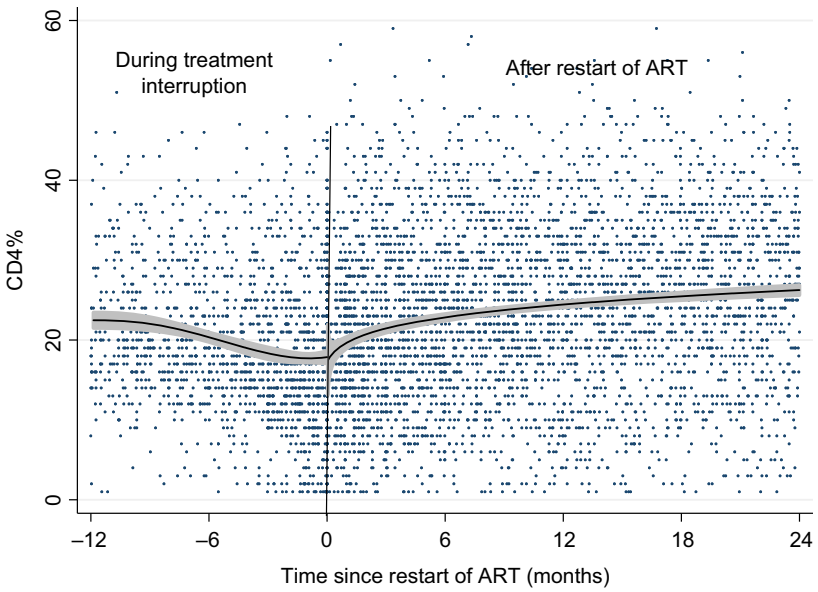

Fig. 1 Observed CD4 percentage (CD4%) during first treatment interruption (TI) and in the 24 months following restart of antiretroviral therapy (ART).

Table 2 Univariable associations between patient characteristics and CD4 percentage (CD4%) at restart of antiretroviral therapy (ART) (intercept) and up to 24 months after restart of ART (asymptote), and speed of recovery (*C*) following first treatment interruption (TI)

		Intercept (CD4% at restart)		Asymptote (long-term CD4%)		*C* (speed of recovery)	
	n (%)	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value
Sex							
Male	365 (47)	Ref		Ref		Ref	
Female	414 (53)	3.8 (2.0, 5.6)	< 0.001	4.23 (2.52, 5.93)	< 0.001	−0.002 (−0.032, 0.028)	0.892
Age at ART initiation							
0 to < 3 years	415 (53)	Ref		Ref		Ref	
3 to < 6 years	151 (19)	−2.7 (−5.1, −0.4)	< 0.001	−4.9 (−7.1, −2.7)	< 0.001	0.019 (−0.024, 0.063)	0.678
6 to < 11 years	154 (20)	−4.3 (−6.6, −2.0)		−5.4 (−7.6, −3.2)		0.021 (−0.019, 0.061)	
≥ 11 years	59 (8)	−6.0 (−9.4, −2.6)		−9.0 (−12.3, −5.6)		0.006 (−0.059, 0.071)	
Initiated ART on cART							
No	405 (52)	Ref		Ref		Ref	
Yes	374 (48)	0.0 (−1.8, 1.8)	0.994	0.3 (−1.5, 2.0)	0.762	0.007 (−0.023, 0.037)	0.631
Age at cART initiation							
0 to < 3 years	243 (31)	Ref		Ref		Ref	
3 to < 6 years	192 (25)	−3.6 (−6.0, −1.3)	< 0.001	−5.2 (−7.4, −3.0)	< 0.001	−0.004 (−0.042, 0.034)	0.813
6 to < 11 years	247 (33)	−5.7 (−7.9, −3.5)		−7.3 (−9.4, −5.2)		0.011 (−0.025, 0.047)	
≥ 11 years	97 (13)	−7.3 (−10.2, −4.3)		−10.6 (−13.5, −7.8)		0.019 (−0.041, 0.137)	
Age at first TI							
0 to < 3 years	63 (8)	Ref		Ref		Ref	
3 to < 6 years	113 (15)	−3.9 (−7.7, 0.0)	< 0.001	−4.7 (−8.3, −1.1)	< 0.001	0.045 (−0.010, 0.100)	0.120
6 to < 11 years	259 (33)	−5.7 (−9.09, −2.4)		−5.9 (−9.2, −2.6)		0.007 (−0.034, 0.049)	
≥ 11 years	344 (44)	−8.1 (−11.4, −4.9)		−11.6 (−14.8, −8.4)		0.039 (−0.005, 0.083)	
Age at first restart of ART							
0 to < 3 years	33 (4)	Ref		Ref		Ref	
3 to < 6 years	82 (11)	−1.0 (−5.8, 3.9)	< 0.001	−2.2 (−7.0, 2.6)	< 0.001	0.023 (−0.040, 0.087)	0.612
6 to < 11 years	212 (27)	−6.6 (−11.0, −2.2)		−5.2 (−9.6, −0.8)		0.022 (−0.030, 0.075)	
≥ 11 years	452 (58)	−8.1 (−12.3, −3.9)		−9.4 (−13.6, −5.2)		0.034 (−0.017, 0.0.84)	
Missing during first TI							
No	435 (56)	Ref		Ref		Ref	
Yes	344 (44)	3.3 (1.2, 5.5)	0.003	−5.2 (−7.5, −2.8)	< 0.001	−0.247 (−0.297, −0.197)	< 0.001
Length of TI							
1 to < 3 months	160 (21)	Ref		Ref		Ref	
≥ 3 to < 6 months	156 (20)	−0.2 (−3.6, 2.1)	0.293	−3.2 (−5.8, −0.5)	< 0.001	0.001 (−0.052, 0.054)	0.995
≥ 6 to < 24 months	283 (36)	−2.5 (−5.0, 0.0)		−1.6 (−4.0, 0.7)		−0.004 (−0.042, 0.034)	
≥ 24 months	180 (23)	−1.2 (−3.9, 1.5)		1.2 (−1.5, 3.8)		−0.004 (−0.046, 0.038)	
Year of first restart of ART							
< 2000	39 (5)	1.4 (−2.8, 5.6)		−3.3 (−7.3, 0.6)		−0.010 (−0.069, 0.049)	
2000–2004	248 (32)	Ref	0.033	Ref	0.014	Ref	0.990
2005–2009	336 (43)	−0.6 (−2.7, 1.5)		−0.4 (−2.4, 1.6)		−0.001 (−0.036, 0.033)	
≥ 2010	156 (20)	3.5 (1.0, 6.1)		2.3 (−0.2, 4.8)		−0.003 (−0.049, 0.044)	
Started new class at ART restart							
No	387 (50)	Ref		Ref		Ref	
Yes	392 (50)	−2.5 (−4.6, −0.7)	0.043	−0.1 (−1.8, 1.7)	0.652	0.001 (−0.022, 0.041)	0.556
Planned TI* (missing: *n* = 204)							
No	427 (74)	Ref		Ref		Ref	
Yes	148 (26)	1.6 (−0.7, 3.9)	0.158	2.6 (0.2, 5.0)	0.006	−0.014 (−0.052, 0.242)	0.479
Viral load							
At first TI (missing: *n* = 283)							
HIV RNA ≥ 400 copies/mL	363 (73)	Ref		Ref		Ref	
HIV RNA < 400 copies/mL	133 (27)	3.6 (1.2, 6.0)	0.003	4.7 (2.5, 6.9)	< 0.001	0.053 (0.002, 0.104)	0.043
Nadir CD4%							
Prior to ART initiation (missing: *n* = 205)							
< 15%	203 (35)	Ref		Ref		Ref	
≥ 15 to < 25%	171 (30)	4.8 (2.3, 7.3)	< 0.001	4.5 (2.2, 6.9)	< 0.001	0.014 (−0.035, 0.063)	0.323
≥ 25%	200 (35)	8.7 (6.3, 11.0)		7.9 (5.6, 10.2)		−0.023 (−0.065, 0.020)	
Prior to cART initiation (missing: *n* = 149)							
< 15%	306 (49)	Ref		Ref		Ref	
≥ 15 to < 25%	184 (29)	7.3 (5.2, 9.5)	< 0.001	5.6 (3.5, 7.7)	< 0.001	−0.003 (−0.045, 0.038)	0.969
≥ 25%	140 (22)	12.3 (9.9, 14.6)		9.4 (7.2, 11.7)		0.004 (−0.044, 0.052)	
During first TI (missing: *n* = 141)							
< 15%	288 (45)	Ref		Ref		Ref	

Table 2 (*Continued*)

		Intercept (CD4% at restart)		Asymptote (long-term CD4%)		*C* (speed of recovery)	
	n (%)	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value
≥ 15 to < 25%	232 (36)	10.8 (9.3, 12.4)	< 0.001	6.8 (4.9, 8.7)	< 0.001	−0.006 (−0.039, 0.027)	0.021
≥ 25%	118 (19)	21.0 (18.8, 23.2)		12.4 (10.3, 14.7)		0.138 (0.038, 0.267)	
CD4%							
At start of first TI (missing: *n* = 386)							
< 15%	53 (14)	Ref		Ref		Ref	
≥ 15 to < 25%	105 (27)	9.5 (5.9, 13.1)	< 0.001	5.5 (2.1, 8.9)	< 0.001	−0.059 (−0.114, −0.004)	0.084
≥ 25%	235 (60)	17.9 (14.6, 21.2)		13.5 (10.5, 16.5)		−0.046 (−0.094, 0.002)	
During first TI (mean) (missing: *n* = 141)							
< 15%	173 (27)	Ref		Ref		Ref	
≥ 15 to < 25%	277 (43)	9.5 (7.7, 11.3)	< 0.001	6.5 (4.5, 8.6)	< 0.001	0.000 (−0.032, 0.033)	0.995
≥ 25%	188 (30)	20.3 (18.4, 22.3)		14.6 (12.4, 16.8)		−0.002 (−0.043, 0.040)	

Parameters estimated using multilevel asymptotic regression models. The intercept represents the CD4% at restart of ART, with β representing the difference in mean CD4% in patients with specific characteristics and the reference group. Similarly, the asymptote represents the longer term CD4% (up to 24 months after restart) and β represents longer term differences in mean CD4%. *C* is a rate parameter; negative values indicate a slower increase in CD4% and positive values indicate a faster increase. Time to half the total CD4% recovery can be estimated as ln(2)/*c*.
cART, combination antiretroviral therapy; CI, confidence interval.
*Planned TI is defined as stopping ART because of physician's decision or side effects/toxicity.

with TIs. For example, in this study and the French cohort, the risk of TI was highest in those initiating ART before 2000, with 51% of the French cohort starting cART in this period [14] compared to only 27% of EPPICC. Further, in the French cohort the median age at TI was 5.8 years in those interrupting treatment from 1996 to 1999, rising to 13.6 years in 2005–2010 [14], suggesting that newer ART regimens are more tolerable and consequently TIs are occurring later and less often. However, the main message is that TIs are relatively common, occur mainly in the pre-adolescent or adolescent age group, and can last for a long period, often 1 year or more.

In our study, the most frequent reason for a TI (in about half of the cases known) was the patient's decision/noncompliance, and this is consistent with the occurrence of most TIs in the pre-adolescent and adolescent age range. In the subgroup who had more than one TI, the second, third and fourth TIs, respectively, occurred at 13.8, 14.8 and 15.8 years of age, reflecting the instability of ART adherence during adolescence. Only a quarter of TIs were attributable to treatment failure, 17% depended on the physician's decision and 9% were because of toxicity and side effects. Type of regimen, in particular PI-based versus NNRTI-based, was not associated with the reason for the TI. This suggests that treatment type was not a main reason for stopping treatment. Nevertheless, children on NNRTI-based regimens at TI were much more likely to switch to a new class of drug at restart compared with those on PI-based regimens (71% versus 41%, respectively). Switch to a different type of regimen was associated with higher CD4% at restart, but switching had no long-term effect.

At the first TI, children had relatively good immunological status (mean CD4% value 27.3%), although most lacked virological control [27% had a suppressed viral load (< 400 copies/mL)]. This is in line with the main reasons for TIs, confirming that the children and adolescents represent a group of patients who have low/irregular adherence, recent ART-related side effects/toxicity or treatment failure. At the end of the TI, the mean CD4% had fallen to 19%, rising to 27% by 2 years after the end of the TI and therefore slowly returning to pre-TI values. This may be reassuring in terms of the safety of TIs in children, as also suggested by planned interruption studies such as the extension study in the PENTA 11 trial [10] and the latest results from the CHER trial, which showed that long-term CD4-for-age recovery was equivalent to children's pre-interruption steady state [9]. Results from both trials are potential indicators that in childhood TIs could be a safe option with regular CD4 monitoring, even if not routinely recommendable. Moreover, authors from the CHER trial suggested that in children a preserved CD4 set-point exists which depends on thymic output and naïve CD4 T-cell dynamics. However, our results from a real-world setting suggest caution as several factors were found in multivariable analysis to influence long-term recovery after TI.

Age at TI was found to be associated with level of CD4% recovery, with the highest CD4% at restart and in the long term seen in the younger children aged < 3 years at the first TI. Furthermore, when we adjusted for CD4% during TI, CD4% recovery was highest in the youngest children, suggesting less ability to reconstitute CD4 cells with increasing age. This finding reinforces a

Table 3 Multivariable associations between characteristics and CD4 percentage (CD4%) at antiretroviral therapy (ART) restart (intercept) and in the 24 months after ART restart (asymptote) and speed of recovery (*C*) following the first treatment interruption (TI)

	Intercept (CD4% at restart)		Asymptote (long-term CD4%)		*C* (speed of recovery)	
	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value
Model 1: excluding laboratory data (n = 799)						
Constant	22.6 (19.5, 25.8)	< 0.001	33.19 (30.0, 36.4)	< 0.001	0.117 (0.103, 0.132)	< 0.001
Sex						
Male	Ref	< 0.001	Ref	< 0.001		
Female	3.7 (2.0, 5.4)		4.0 (2.5, 5.5)			
Age at first TI						
0 to < 3 years	Ref	< 0.001	Ref	< 0.001		
3 to < 6 years	−2.7 (−6.4, 1.0)		−3.4 (−6.0, −0.1)			
6 to < 11 years	−5.2 (−8.4, −2.0)		−5.7 (−8.5, −2.8)			
≥11 years	−7.3 (−10.5, −4.1)		−10.7 (−13.6, −7.8)			
Length of TI						
1 to < 3 months			Ref	0.027		
≥ 3 to < 6 months			−2.7 (−4.9, −0.4)			
≥ 6 to < 24 months			−1.3 (−3.3, 0.7)			
≥ 24 months			−0.7 (−3.0, 1.7)			
Year of first restart of ART						
2000–2004			−5.8 (−9.3, −2.4)	< 0.001		
< 2000			Ref			
2005–2009			0.3 (−1.5, 2.0)			
≥ 2010			0.7 (−1.5, 2.8)			
Model 2: including laboratory data (n = 365)						
Constant	10.6 (7.2, 14.0)	< 0.001	25.9 (21.0, 30.8)	< 0.001	0.127 (0.097, 0.157)	< 0.001
Sex						
Male	Ref		Ref			
Female	−0.7 (−2.3, 0.9)	0.393	0.3 (−1.6, 2.2)	0.739		
Age at first TI						
0 to < 3 years	Ref	0.428	Ref	< 0.001		
3 to < 6 years	1.5 (−2.0, −5.0)		−0.6 (−4.6, 3.5)			
6 to < 11 years	0.7 (−2.4, −3.9)		−2.5 (−6.2, 1.2)			
≥ 11 years	0.1 (−3.1, 3.3)		−5.8 (−9.5, −2.0)			
Length of TI						
1 to < 3 months			Ref	0.047		
≥ 3 to < 6 months			−3.5 (−7.0, −0.1)			
≥ 6 to < 24 months			−1.3 (−4.3, 1.6)			
≥ 24 months			1.6 (−1.8, 4.9)			
Year of first restart of ART						
< 2000			−6.9 (−12.1, −1.8)			
2000–2004			Ref	0.010		
2005–2009			−2.2 (−4.5, 0.1)			
≥ 2010			−2.6 (−5.4, 0.2)			
VL at first TI						
HIV RNA ≥ 400 copies/mL	Ref	0.903	Ref	0.007	Ref	0.008
HIV RNA < 400 copies/mL	−0.1 (−2.1 to 1.9)		4.7 (1.3, 8.1)		0.076 (0.020, 0.131)	
Nadir CD4% prior to cART initiation						
< 15%	Ref	0.002	Ref	0.747	Ref	0.900
≥ 15 to < 25%	3.8 (1.7, 5.8)		1.7 (−0.7, 4.0)		0.002 (−0.052, 0.057)	
≥ 25%	3.9 (1.5, 6.3)		1.5 (−1.2, 4.1)		−0.019 (−0.074, 0.036)	
Nadir CD4% during first TI						
< 15%	Ref	< 0.001	Ref	< 0.001	Ref	0.004
≥ 15 to < 25%	9.2 (7.3, 11.1)		7.3 (4.7, 9.8)		−0.005 (−0.054, 0.044)	
≥ 25%	17.8 (14.7, 21.0)		13.5 (10.0, 17.0)		0.338 (0.137, 0.539)	
Interaction: VL at start of TI × CD4% nadir during TI						
VL < 400 copies/mL and nadir CD4% ≥ 15 to < 25%			−3.2 (−7.9, 1.4)	0.038		
VL < 400 copies/mL and nadir CD4% ≥ 25%			−5.3 (−10.6, −0.1)			

Parameters were estimated using multilevel asymptotic regression models. The intercept represents the CD4% at restart of ART, with β representing the difference in mean CD4% in patients with specific characteristics and the reference group. Similarly, the asymptote represents the longer term CD4% (up to 24 months after restart) and β represents longer term differences in mean CD4%. *C* is a rate parameter; negative values indicate a slower increase in CD4% and positive values indicate a faster increase. The intercept, asymptote and *C* constants represent the mean CD4% at restart and in the long term and the rate parameter for patients in the reference groups. Time to half the total CD4% recovery can be estimated as ln(2)/*c*.
CI, confidence interval; VL, viral load.

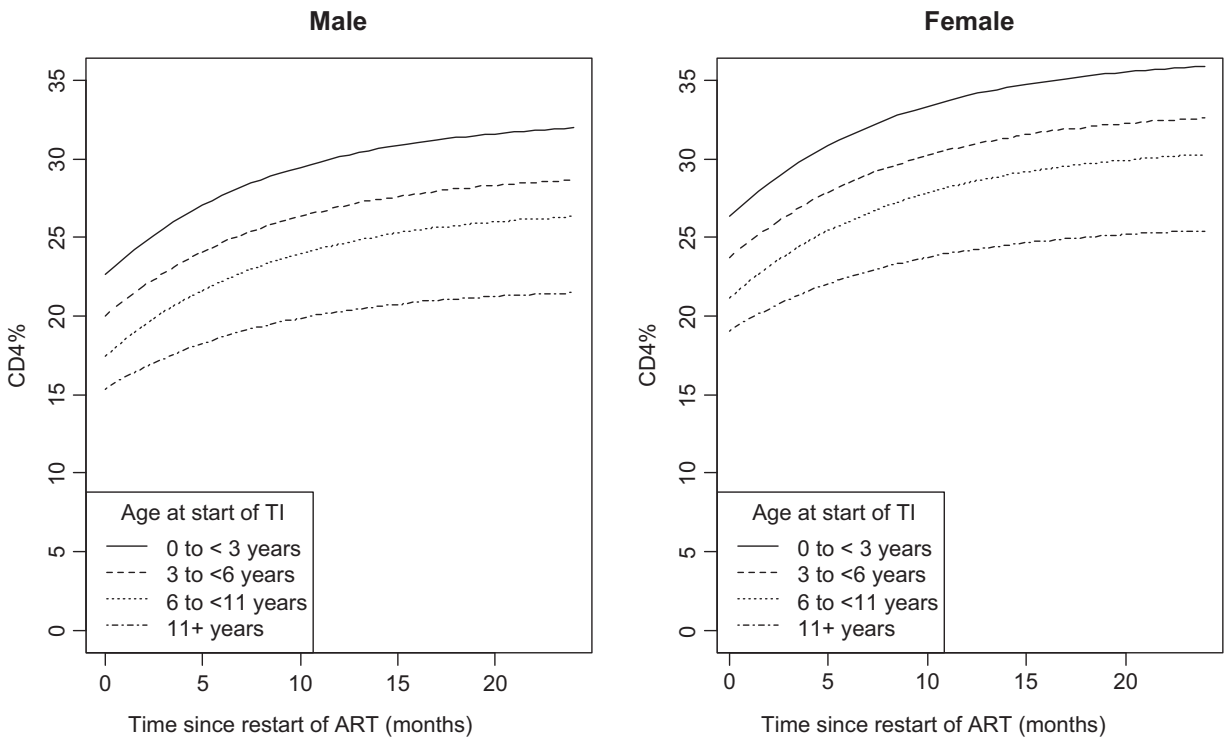

Fig. 2 Estimated mean CD4 percentage (CD4%) after restart of antiretroviral therapy (ART) following first treatment interruption (TI) by sex and age at start of first TI. Fitted values represent mean CD4% for a child restarting ART in 2010 or later following a TI of 6 to < 24 months without adjustment for prior CD4% or viral load.

general belief that children have major immunological advantages as compared to adults after starting ART. Indeed, younger children have been shown to produce a stronger recovery and more naïve CD4 T cells when the virus is suppressed as a consequence of persistence of high levels of thymic activity [13]. Adolescents have reduced thymic activity as compared with younger children and therefore a worse immunological response when resuming ART after TIs.

A very important issue is the safety of a TI in the first years of life in children who have commenced ART at an early age [21,22]. Findings from the CHER trial suggest the feasibility of this strategy [9]. Our results also suggest that good immunological recovery is possible in younger children interrupting treatment, particularly before 3 years of age.

In our study, we found that female patients had a CD4% on average 4% higher than that of male patients of the same age, both at restart of ART and in the long term. This is consistent with a study of pre-pubertal perinatally HIV-infected children which found lower HIV RNA and high CD4 levels in girls, with girls having a CD4% on average 3% higher than that of boys [23]. However, when we adjusted our model for CD4% nadir during the TI and prior to ART, the gender differences disappeared. This suggests that, while female individuals have a higher CD4% than male individuals on average, in male and female individuals with similar CD4% during the TI (and therefore at restart), CD4% recovery occurs at a similar rate.

We observed a high variability in the length of the TI, with about half of children interrupting ART for > 1 year. A mean 0.66% monthly decrease in CD4% during TIs among children has been reported [24] and, as a consequence, lower CD4% levels have been found in children with longer TIs. However, we found some differences in long-term CD4% by length of TI, but no difference in CD4% at restart. This may suggest that the children, in clinical practice, were advised to restart at similar CD4% levels, independently of the length of the TI. Surprisingly, we found that children who had a TI of 3 to < 6 months had the lowest long-term CD4% level. This could suggest that those children who restarted ART were the rapid progressors, who had a rapid CD4 decline following TI, when compared to those who were able to remain off treatment for longer periods. Early start of ART may have masked the 'individual' immunological progression profiles [25] observed as different patterns of progression (rapid progressors, low progressors and nonprogressors) in the

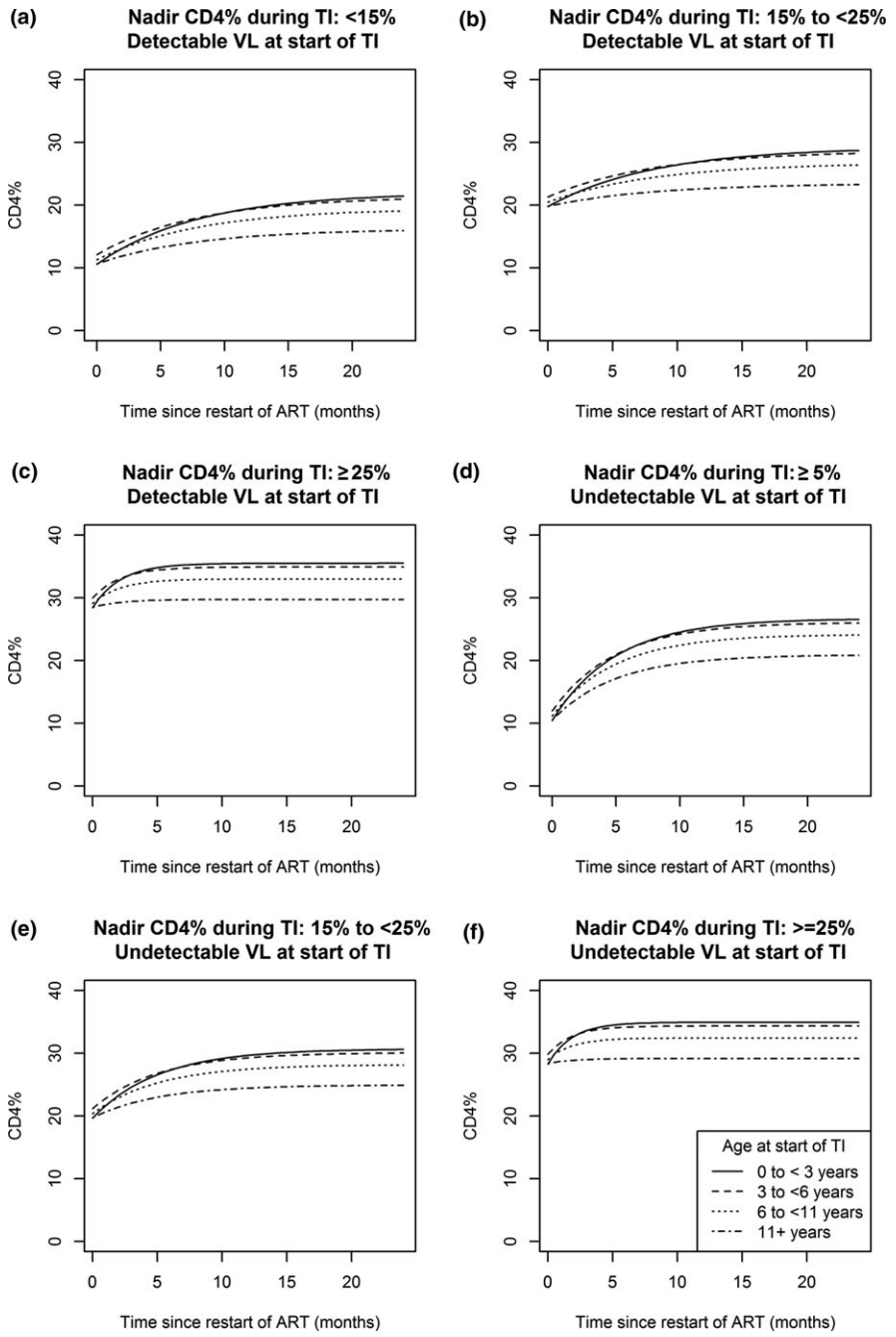

Fig. 3 Estimated mean CD4 percentage (CD4%) after restart of antiretroviral therapy (ART) following first treatment interruption (TI) by age, viral load (VL) at start of TI, and CD4% nadir during TI. Fitted values represent mean CD4% for a male patient restarting ART in 2010 or later following a TI of 6 to < 24 months who had a nadir CD4% of 15 to < 25% prior to initiation of first combination ART (cART).

natural history of paediatric HIV infection [26]. During the Tis, the 'individual' patterns of progression may re-emerge.

To explore the possible role of an individual 'immunological profile' in the CD4% slope during TI and after ART restart, we included CD4% nadir prior to cART and during TI in the analysis. We found a small effect of CD4% nadir prior to cART on CD4% at restart but this disappeared in the longer term in multivariable models. However, nadir during TI was a significant predictor of CD4% both at restart and in the longer term, with the biggest gains in CD4% seen in those with the lowest values during TI, and

in particular in those who were virologically suppressed prior to TI. In this subgroup of children with undetectable viral load at the beginning of TI, the beneficial effect of restarting ART could be much stronger in those children who experienced more immunological deterioration during TI, as children whose CD4% level drops the most have the largest gain to make [26].

Our collaborative study has several limitations, partly as a consequence of the multi-cohort, retrospective source of our data set. Firstly, we had no data on patients' adherence to ART before and after TIs. Secondly, we lacked data on functional aspects of immunological deterioration, such as inflammatory biomarkers or response to immunizations. Thirdly, data on clinical features of HIV infection were available from few cohorts and therefore were not included in the analysis. We also lacked detailed information on reason for TI. Reasons for stopping treatment reported to the participating cohorts by clinics include treatment failure, toxicity and noncompliance, as well as physician or patient decision. Physician's decision is used only if it was a decision based on a reason other than those listed above. We considered interruptions resulting from reasons reported as physician's decision as planned interruptions, but as no further details are available these could not be confirmed. Finally, cohorts included in the study range from having national coverage to being hospital based and so results may not be generalizable to children treated outside these sites. However, there are also several strengths in the collaborative nature of the study, which provided a large cohort of children and adolescents followed for many years after starting ART, with regular CD4 monitoring. The modelling made use of longitudinal CD4 measurements, with results providing insight into outcomes associated with TIs in a real-life setting. In this model, we used CD4% as it was hypothesized that age would be a strong predictor of CD4 recovery. While the majority of children were > 6 years old when restarting ART, 15% were aged < 6 years. The youngest children showed the strongest CD4% response on restarting ART and the use of CD4% rather than CD4 count allowed us to explore age effects which could potentially have been masked by natural decline had CD4 counts been used instead.

In conclusion, perinatally infected children are faced with the prospect of lifelong ART, with a high probability of accumulating side effects, metabolic toxicity, poor compliance, attrition and increasing numbers of mutations associated with ART resistance. Therefore, paediatric HIV experts world-wide should continue their efforts to determine whether the burden of ART can be reduced during childhood and adolescence. Our real-world data demonstrate that TIs continue to occur, particularly in adolescents, and mainly as a result of their decision. Our findings suggest that immunological recovery following a TI is less efficient at older ages and in those children/adolescents with low CD4% values during the TI. While young children did show good potential for recovery, it is important to monitor CD4 during any TI to ensure that treatment is restarted prior to large declines in CD4 cell count.

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Appendix 1: Collaborating cohorts

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Flow chart of participants included in the study.
Figure S2. Observed CD4% prior to first treatment interruption against predicted CD4% after 24 months on ART.

Table S1. Multivariable models for CD4% in the 24 months after restart of ART following first treatment interruption in children who initiated ART on cART.

Table S2. Multivariable associations between characteristics and CD4% after restart of ART following first ever 30-day and first ever 3-month treatment interruption (excluding laboratory data).

Table S3. Multivariable associations between characteristics and CD4% after restart of ART following first ever 30-day and first ever 90-day TI (including laboratory data).