Clinical Infectious Diseases

MAJOR ARTICLE

Evolution of CD4 T-Cell count with age in a cohort of young people growing up with perinatally acquired HIV

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Background: Recent studies have shown a decrease in CD4 count during adolescence in young people with perinatally acquired HIV (PHIV). We examine changes and predictors of CD4 over time in PHIV in the UK and compare to published CD4 data in the general population.

Methods*:* PHIV followed in the Collaborative HIV Paediatric Study who started antiretroviral therapy (ART) from 2000 onwards were included. Follow-up data from the UK Collaborative HIV Cohort Study were also used. Changes in CD4 count over time from age 10 to 20 years

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were analysed using mixed effects models. Potential predictors included demographics, age at ART start, nadir CD4 z-score (age-adjusted) in childhood and time-updated viral load.

***Results**:* Of 1,258 PHIV included, 669 (53%) were female, median [IQR] age at ART initiation was 8.3 years [3.5, 12.1] and nadir CD4 z-score was -4.0 [-5.9, -2.5]. In multivariable analysis, mean CD4 count was higher in PHIV who started ART before age 10 and had a nadir CD4 z-score ≥-4 in childhood; these PHIV had a decline in CD4 count after age 10 which was comparable to the general population. Mean CD4 count was lower in PHIV who had started ART before age 10 and had a nadir CD4 z-score <-4 in childhood; for this group the decline in CD4 count after age 10 was steeper over time.

***Conclusions**:* In children, as well as starting ART at an early age, optimising ART to maintain a higher CD4 z-score during childhood may be important to maximize immune reconstitution later in life.

Key words: CD4 T-Cell, perinatal, HIV, child, adult, UK

Key points: Young people with HIV who started ART before age 10 had a decline in CD4 count after age 10 either comparable to, if nadir CD4 z-score ≥-4, or steeper than, if nadir CD4 z-score <-4, the general population.

INTRODUCTION

In 2021, there were an estimated 1.7 million adolescents with HIV worldwide [1]. Due to the availability of effective antiretroviral therapy (ART), children with perinatally acquired HIV (PHIV) are surviving into adulthood [2]. However, some studies have shown poor health outcomes for young people with PHIV compared to younger children and adults with HIV, including lower levels of virological suppression, worse immunological status, poor growth and lower retention in care [3-7].

Current guidelines state that ART should be initiated immediately for all individuals with HIV [8], and initial CD4 recovery following the start of ART in children has been well described [9]. The few studies which have examined long-term CD4 evolution have shown a decrease in CD4 count during adolescence [7, 10-11], but the reasons for this decline remain unclear, including how much is part of the natural decline in CD4 count seen after infancy in the general population [12]. Previous studies have predicted that children starting ART at an early age are likely to follow a trajectory of CD4 expected in the general population [13-14], and higher CD4 counts before/at ART initiation have been associated with higher long-term CD4 [13-16] and a better CD4 response after treatment interruptions [17].

The aim of this analysis was to examine changes in, and predictors of, CD4 over time in young people with PHIV in the UK, and to compare the changes to published data on CD4 in young

people in the general population. A previous analysis specifically explored CD4 changes before and after transition to adult care in young people who had been followed in the Collaborative HIV Paediatric Study (CHIPS) and subsequently transitioned to adult clinics in the UK Collaborative HIV Cohort (UK CHIC) Study [10] and did not compare the results to the general population. Here we included all young people followed in CHIPS and linked updated datasets from the two studies, resulting in a larger cohort of young people with PHIV and with longer follow-up through paediatric and adult HIV care than previously.

METHODS

CHIPS is a national observational cohort of children with HIV in the UK and Ireland [18]. In brief, all infants born to women with HIV and all children <16 years at HIV diagnosis in the UK and Ireland, are reported to the Integrated Screening Outcomes Surveillance Service (ISOSS) (formerly the National Study of HIV in Pregnancy and Childhood). Children diagnosed with HIV were reported to CHIPS and followed from first presentation in paediatric care until the child transitioned to adult care. Follow-up data were collected annually until March 2021. The UK CHIC Study was a multi-centre study of adults with HIV aged ≥16 years, attending one of 21 collaborating adult outpatient clinics across the UK [19]. Routinely collected clinical information was submitted annually (until September 2019) from participating clinics to the study database. Both studies had National Health Service (NHS) Research Ethics approval.

In this analysis young people followed in CHIPS with documented perinatally acquired HIV, who started ART during or after the year 2000, with at least 1 CD4 measurement at age 10 years or older, were included. They were linked to the UK CHIC database, using their date of birth and sex, and either Soundex (an indexing system which encodes surnames), clinic name/clinic number or the young person's initials. Data used for the linkage were stored in a secure location with restricted access. Young people were grouped by age at the start of ART and nadir CD4 z-score (age-adjusted using CD4 counts) in childhood [20], to create 6 groups (A: started ART age ≤5 years and nadir CD4 z-score <-4, B: started ART age ≤5 years and nadir CD4 z-score ≥-4, C: started ART age >5 to <10 years and nadir CD4 z-score <-4, D: started ART age >5 to <10 years and nadir CD4 z-score ≥-4, E: started ART age ≥10 years and nadir CD4 z-score <-4, F: started ART age ≥10 years and nadir CD4 z-score ≥-4). Nadir CD4 z-score in childhood was defined as either the lowest CD4 z-score before age 10 years, or for young people without CD4 measurements before age 10, it was defined as the CD4 z-score at the start of ART (closest measurement within six months of starting ART).

Data were analysed using STATA version 17.0 (Stata Corp, College Station, Texas, USA). Characteristics of the young people included in the analysis with non-missing values were summarised using proportions, medians and interquartile range (IQR). Data were missing for <10% of young people for each variable unless specified. Immunodeficiency was categorised

based on the World Health Organization definition for children over 5 years using CD4 count [21].

Changes in CD4 count over time were analysed using mixed effects models, allowing for multiple CD4 measurements per young person. All available CD4 measurements from CHIPS and UK CHIC were analysed from age 10 to age 20 years. Time since age 10 was modelled using both linear and quadratic variables, which were included in all models. Person-level random effects were included for intercept and slopes (unstructured covariance matrix). The effect of predictors of changes in CD4 over time was explored and included the following variables: sex, ethnicity, country of birth, year of birth, age at ART start and nadir CD4 z-score groups, transitioned to adolescent/adult care and suppressed viral load <400 copies/ml within 6 months of the CD4 measurement (time-updated); ART regimen was not included as a predictor. Variables were included in the multivariable model using backwards elimination, and a p value <0.05 was considered statistically significant. Interactions between time/time squared since age 10 and each variable were added to the multivariable model if the interaction p value was <0.05. The statistical significance of predictors in the multivariate model are reported in the results section as p values adjusted for the presence of the other variables in the final model. Due to changes in the frequency of CD4 measurements over time, a variable for time since previous CD4 measurement (≤4months versus >4 months) was included in a sensitivity analysis. Additional sensitivity analyses included fitting the multivariable model separately to young people linked and not linked to UK CHIC.

Published data on CD4 counts in young people aged 10 to 20 years in the general population were identified using PubMed. Relevant search terms included lymphocyte, subset/subpopulation, reference/control value/range, child/childhood and adolescent. Reference and cited by lists from all papers found to be relevant were also searched.

RESULTS

Of 1,258 young people with PHIV included in the analysis, 53% were female and 84% were of black ethnicity (Table 1). The median age at ART initiation was 8.3 years and the median nadir CD4 z-score in childhood was -4.0. Most young people had no or mild immunodeficiency at age 10 (88%). Only 66% (612 of 932) of young people with available data had a suppressed viral load <400 copies/ml at age 10 (592 of 693 (85%) for those who started ART before age 10). At last follow-up 797 (63%) had transitioned to adolescent/adult care and 464 (37%) were linked to UK CHIC. Of those not linked, 389 (49%) were still being followed in CHIPS, 355 (45%) had transitioned to an adult clinic not participating in UK CHIC, 40 (5%) were lost to follow-up and 10 (1%) had died. 24% (304) had ever had an AIDS defining diagnosis (304, 24%), of which 75 had their first AIDS event after age 10, 59 of whom had started ART aged 10 years or older. 16 (1%) had died at a median age of 19 years (2 within a year of diagnosis), with 13 starting ART aged 10 years or older.

26,270 CD4 measurements from 1996 to 2020 were available for analysis. Young people had a median [IQR] of 2.8 [2.1, 3.3] CD4 measurements per year (only 24 (2%) had only 1 CD4 measurement) and the median age at the last CD4 measurement was 17.8 [16.0, 19.3] years. Of the 258 young people who were immunosuppressed (<500 cells/mm^3) at age 10, 42 of 63 (67%) with a CD4 measurement at age 20 (within +/- 6 months) were still immunosuppressed at age 20. In multivariable analysis, mean CD4 count at age 10 differed by age at the start of ART and nadir CD4 z-score, with young people who had started ART at a younger age and had a higher nadir CD4 z-score in childhood, having higher CD4 counts at age 10 ($p<0.001$) (Table 2). Young people who were female ($p<0.001$), of non-black ethnicity ($p=0.002$), born in later calendar years ($p<0.001$) and virally suppressed ($p<0.001$) also had higher mean CD4 counts at age 10.

In multivariable analysis, CD4 counts over time also differed by age at the start of ART and nadir CD4 z-score, and by sex ($p<0.001$ for all time variables, Table 2). Figure 1 shows the predicted association between CD4 over time (age 10 to 20 years) and age at the start of ART/nadir CD4 z-score groups for modelled females (Figure 1a) and males (Figure 1b) of black ethnicity, born in 2000 with suppressed viral load <400 copies/ml (time-updated). At age 10, mean CD4 count was highest in young people who had started ART before age 10 and had a higher nadir CD4 z-score, with a decline in CD4 count after age 10 which slowed over time in females (Figure 1a, groups B and D; Supplementary Table 1a) and was more linear in males (Figure 1b, groups B and D; Supplementary Table 1b). Mean CD4 count at age 10 was lower in young people who had started ART before age 10 and had a lower nadir CD4 z-score (Figures 1a/b, groups A and C; Supplementary Tables 1a/b) and the decline in CD4 over time was steeper than those who had a higher nadir CD4 z-score (groups B and D).

At age 10, young people who had started ART aged 10 years or older and had a higher nadir CD4 z-score (group F) had a similar mean CD4 count to group C; however, CD4 count remained stable in group F over time with a predicted average of 650 cells/mm^3 for both males and females (Figures 1/b; Supplementary Tables 1a/b). At age 10, mean CD4 count was lowest in young people who had started ART at age 10 or older and had a lower nadir CD4 z-score (group E). In this group, CD4 increased over time until approximately age 16, plateaued and then decreased, with a similar trend in males and females.

There was no evidence that mean CD4 counts differed over time by ethnicity or year of birth. On average, being virally unsuppressed was associated with having greater decreases or smaller increases in CD4 over time than being suppressed ($p<0.001$). There was no evidence of an effect of time since last CD4 measurement on CD4 trends over time ($p=0.168$) and fitting separate multivariable models to young people linked and not linked to UK CHIC found comparable results to the overall multivariable model (data not shown).

Published data from nine studies (seven in Europe or USA) of CD4 counts in the general population were identified [22-30] (Table 3). All studies were in young people without any known medical conditions except for one study which included young people admitted to

hospital for pre-surgery screenings for malformations, trauma or benign diseases [24] and one which included young people with bleeding disorders but no lymphocyte abnormalities [25].

Figure 2 shows published data from 4 studies which included young people aged 10 to 20 years and had three or more age groups in that range [22,23,29,30]. At age 10, the predicted mean CD4 count in young people in our study who started ART before age 10 and had a higher nadir CD4 z-score (groups B and D) was similar to CD4 counts in young people in the Netherlands (Comans-Bitter et al [22]) and German (Huenecke et al [23]) studies, with the predicted decline in CD4 over time in groups B and D comparable to the Comans-Bitter study but faster than the Huenecke study. By age 20 years, young people who had a lower nadir CD4 z-score, regardless of what age they started ART (groups A, C and E), had a predicted mean CD4 count lower than that observed in all 4 studies of young people in the general population.

DISCUSSION

Our study found that changes in CD4 count over time in a cohort of young people with PHIV varied by age at ART start and nadir CD4 z-score in childhood. For young people who started ART before the age of 10, CD4 count decreased from age 10. For those with a higher nadir CD4 z-score, the predicted decline in some subgroups was comparable to published data of CD4 counts in young people in the general population. However, for those who had a lower nadir CD4 z-score, the decline was steeper, and results from our model, assuming, on average, viral suppression <400 copies/ml over time, predicted average CD4 counts to approach mild immunodeficiency (350-500 cells/mm^3) by age 20 in some subgroups with characteristics associated with lower mean CD4 counts.

In our previous study we found a decline in CD4 count over time in 271 young people in the period before transition at adult care, which continued after transition in some groups, but we were unable to assess the trends by age at ART start and nadir CD4 due to limited sample size [10]. This current analysis builds upon our previous work and highlights the long-term impact of these factors and how the CD4 trajectory compares to the general population in Europe.

Rodriguez et al [11] found that in 132 young people who started ART at a median age of 5.7 years in Peru, CD4 count (unadjusted for viral load) decreased from age 5 to 18 years, and the decline was faster after age 13. A global cohort collaboration [7] also found that CD4 count (unadjusted for viral load) decreased from age 10 to 17 years in 19,557 PHIV who started ART at a median age of 6.9 years in 46 countries worldwide, with similar trends by sex and geographical region.

The decline in CD4 count observed in our study in young people who started ART before the age of 5 and had a higher nadir CD4 z-score in childhood appears to mirror the decline in CD4 observed at least one study in young people in the general population, although due to the small

sample size there is large variation in the median estimate. Mean CD4 counts also followed a similar trajectory over time for young people who started ART between 5 and 10 years of age and had a higher nadir CD4 z-score, and at age 20 were predicted to be higher than those who had a lower nadir CD4 z-score and started ART at any age.

For young people who started ART before age 10 and had a lower nadir CD4 z-score in childhood, the decline in CD4 was steeper. Children with HIV have a profound capacity for immune recovery following ART as thymic output is high in infancy [31]. However, our study implies that immune reconstitution may not only rely on early age of ART initiation, but also on the ability of the immune system to maintain a normal level of CD4 T cell numbers during childhood. Previous studies have suggested the importance of a high thymic output and diverse T cell receptor repertoire in maintaining viral suppression as well as contributing to high CD4 later in life [32-33]. Reassuringly there were few AIDS events or deaths in young people who started ART before age 10 in our study, however future research is needed to determine whether the steeper decline in CD4 seen in young people with a lower nadir CD4 during childhood results in different clinical outcomes during adulthood compared to the general population.

Our study found that changes in CD4 over time differed by sex, with females having higher mean CD4 counts than males in early and late adolescence. Previous studies in children [34-35] and adults [36-37] have suggested that females have a better immunological response than males after ART initiation, and Rudy et al [28] found that females in the general population without HIV infection had higher CD4 counts than males.

One limitation of our study is that we were unable to examine the effects of adherence to ART on CD4 evolution, as adherence information was not available. However, we adjusted our analysis for time-updated viral load as a surrogate. Another limitation is that we did not adjust for ART regimen, and young people who started ART in earlier calendar years and on older regimens may have contributed more CD4 data over time than those on newer regimens. However, we only included young people who started ART from 2000 onwards, when effective ART was available for children. Also, findings from young people in our study who started ART at older ages may not be relevant to infants starting ART today. Lastly, young people lost to follow-up or who died before age 10 would not have contributed to the analysis, and some young people in CHIPS transitioned to non-UK CHIC clinics and would not have contributed CD4 data after transition. Young people participating in CHIPS had high retention in paediatric care and low mortality rates [3], and sensitivity analyses fitting the model to young people linked and not linked to UK CHIC found comparable results.

In our study we have shown that for young people with PHIV and who started ART before age 10, having a lower nadir CD4 z-score in childhood was associated with a decline in CD4 count over time. This suggests that in children, as well as starting ART at an early age, optimising ART to maintain good levels of immune function may be important to maximize immune reconstitution later in life. Young people who start ART before age 10 with a higher nadir CD4

z-score during childhood, are likely to achieve CD4 levels during adolescence and early adulthood comparable to young people in the general population.

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Table 1: Characteristics of the 1,258 young people included in the analysis

	Total (n=1,258)	Linked to UK CHIC (n=464)
	n (%) or median [IQR]	
Female sex	669 (53)	245 (53)
Black ethnicity	1047 (84)	396 (86)
Born outside UK/Ireland	775 (62)	312 (67)
Year of birth		
Up to 1996	381 (30)	233 (50)
1997 to 2000	429 (34)	208 (45)
2001 onwards	448 (36)	23 (5)
Year of starting ART		
2000 to 2004	442 (35)	210 (45)
2005 to 2009	468 (37)	165 (36)
2010 onwards	348 (28)	89 (19)
Age started ART (years)	8.3 [3.5, 12.1]	10.3 [6.5, 13.2]
≤ 5 years	406 (32)	83 (18)
> 5 and < 10 years	352 (28)	140 (30)
≥ 10 years	500 (40)	241 (52)
Nadir CD4 z-score[a]	-4.0 [-5.9, -2.5]	-4.3 [-6.8, -2.8]
< -4	588 (49)	237 (54)

≥ -4	602 (51)	202 (46)
Age started ART (years) and nadir CD4 z-score[a]		
A: Started ART ≤ 5 years of age/nadir CD4 z-score <-4	138 (12)	34 (8)
B: Started ART ≤ 5 years of age/nadir CD4 z-score ≥-4	259 (22)	46 (10)
C: Started ART >5 to <10 years of age/nadir CD4 z-score <-4	211 (18)	89 (20)
D: Started ART >5 to <10 years of age/nadir CD4 z-score ≥-4	115 (10)	44 (10)
E: Started ART ≥ 10 years of age/nadir CD4 z-score <-4	239 (20)	114 (26)
F: Started ART ≥ 10 years of age/nadir CD4 z-score ≥-4	228 (19)	112 (26)
Median [IQR] age (years) started ART within age started ART and nadir CD4 z-score groups[a]		
A: Started ART ≤ 5 years of age/nadir CD4 z-score <-4	2.5 [0.7, 3.8]	3.4 [2.4, 4.0]
B: Started ART ≤ 5 years of age/nadir CD4 z-score ≥-4	1.2 [0.3, 2.8]	2.4 [1.6, 3.4]
C: Started ART >5 to <10 years of age/nadir CD4 z-score <-4	7.9 [6.8, 8.9]	8.2 [7.3, 9.1]
D: Started ART >5 to <10 years of age/nadir CD4 z-score ≥-4	6.9 [5.8, 8.0]	6.9 [5.9, 7.8]
E: Started ART ≥ 10 years of age/nadir CD4 z-score <-4	12.6 [11.3, 14.2]	12.5 [11.2, 14.2]
F: Started ART ≥ 10 years of age/nadir CD4 z-score ≥-4	13.1 [11.6, 14.8]	13.7 [12.0, 15.6]
CD4 count at age 10 years (cells/mm^3, within +/- 6 months)[b]	724 [480, 998]	621 [405, 910]
Immunodeficiency at age 10 years (within +/- 6 months)[b]		
None or not significant (≥ 500 cells/mm^3)	685 (73)	207 (63)
Mild (≥350 to <500 cells/mm^3)	144 (15)	65 (20)
Advanced (≥200 to <350 cells/mm^3)	86 (9)	39 (12)

Severe (<200 cells/mm^3)	28 (3)	17 (5)
CD4 z-score at age 10 years (within +/- 6 months)[b]	-1.3 [-2.9, -0.2]	-1.9 [-3.6, -0.5]
Viral load <400 copies/ml at age 10 years (within +/-6 months)[c]	612 (66)	174 (54)
Known to have transitioned to adolescent/adult care	797 (63)	442 (95)
Ever CDC Class C (AIDS) diagnosis	304 (24)	115 (25)
Ever CDC Class C (AIDS) at age 10 years	228 (18)	70 (15)
First CDC Class C (AIDS) event after age 10 years[d]	75 (6)	44 (9)
A: Started ART ≤ 5 years of age/nadir CD4 z-score <-4	2 (0.2)	1 (0.2)
B: Started ART ≤ 5 years of age/nadir CD4 z-score ≥-4	1 (0.1)	1 (0.2)
C: Started ART >5 to <10 years of age/nadir CD4 z-score <-4	2 (0.2)	1 (0.2)
D: Started ART >5 to <10 years of age/nadir CD4 z-score ≥-4	3 (0.3)	3 (0.7)
E: Started ART ≥ 10 years of age/nadir CD4 z-score <-4	38 (3)	21 (5)
F: Started ART ≥ 10 years of age/nadir CD4 z-score ≥-4	21 (2)	13 (3)
Age at first CDC Class C (AIDS) event (years)	3.4 [0.6, 10.0]	7.8 [2.7, 12.4]
Died[e]	16 (1)	6 (1)
C: Started ART >5 to <10 years of age/nadir CD4 z-score <-4	1 (0.1)	-
D: Started ART >5 to <10 years of age/nadir CD4 z-score ≥-4	1(0.1)	-
E: Started ART ≥ 10 years of age/nadir CD4 z-score <-4	8 (0.7)	4 (0.9)
F: Started ART ≥ 10 years of age/nadir CD4 z-score ≥-4	5 (0.4)	2 (0.4)
Age when died (years)	18.8 [15.2, 22.7]	22.7 [20.3, 25.2]
Years since diagnosis when died (years)	10.6 [6.0, 14.8]	11.7 [10.0, 14.8]

Abbreviations: n, number of young people; IQR, interquartile range; ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention.

[a] Nadir CD4 z-score was defined as either the lowest CD4 z-score before age 10 (n=945), or for young people without CD4 measurements before age 10, it was defined as CD4 z-score at start of ART (within 6 months) (n=245). Unknown for 68 young people.

[b] Unknown for 315 young people.

[c] Unknown for 326 young people.

[d] Nadir CD4 z-score unknown for 8 young people with first CDC Class C (AIDS) event after age 10 years

[e] All died after the age of 10 years. Nadir CD4 z-score unknown for 1 young person who died.

Table 2: Univariate and multivariable predictors of CD4 over time from age 10 to age 20 years.

	Univariable[a]			Multivariable (n=1,181)		
Predictor	Coefficient	95% CI	p value	Coefficient	95% CI	p value
Constant				664.1	588.2, 739.9	
Main effects:						
Time since age 10 (per 1 year increase after age 10)	-13.1	-16.3, -9.9	<0.001	1.4	-10.8, 13.6	0.824
Time since age 10 squared (per year squared increase after age 10)	-1.7	-2.1, -1.4	<0.001	-3.4	-4.6, -2.2	<0.001
Female (versus male)	21.6	-7.9, 51.1	0.151	67.9	31.2, 104.5	<0.001
Non-black ethnicity (versus black ethnicity)	96.5	56.5, 136.6	<0.001	52.3	18.8, 85.8	0.002
Born abroad (versus born in UK/Ireland)	-54.1	-84.6, -23.6	0.001	-	-	-
Year of birth (per 1 year increase since 1985)	23.5	20.4, 26.6	<0.001	6.7	3.4, 10.0	<0.001
Age started ART (years) and nadir CD4 z-score			<0.001			<0.001
A: Started ART ≤ 5 years of age and nadir CD4 z-score <-4	0.0			0.0		
B: Started ART ≤ 5 years of age and nadir CD4 z-score ≥-4	165.6	117.5, 213.8		197.3	132.5, 262.0	
C: Started ART >5 to <10 years of age and nadir CD4	-94.0	-143.1, -44.8		-97.7	-165.0, -30.4	

z-score <-4						
D: Started ART >5 to <10 years of age and nadir CD4 z-score ≥-4	44.2	-13.3, 101.7		132.4	54.9, 209.9	
E: Started ART ≥ 10 years of age and nadir CD4 z-score <-4	-264.8	-312.7, -216.9		-533.6	-604.8, -462.4	
F: Started ART ≥ 10 years of age and nadir CD4 z-score ≥-4	-95.4	-143.7, -47.1		-137.6	-206.8, -68.4	
Known to have transitioned to adolescent/adult care (versus not known to have transitioned)	-129.6	-160.6, -98.7	<0.001	-	-	-
Viral suppression (time updated, within +/- 6 months of CD4 count)			<0.001			<0.001
Suppressed, <400 copies/ml	0.0			0.0		
Not suppressed, ≥400 copies/ml	-149.8	-156.1, -143.6		-78.6	-96.5, -60.7	
Interactions with time/time squared since age 10:						
Sex (time)						<0.001
Male				0.0		
Female				-21.6	-29.9, -13.4	
Sex (time squared)						<0.001

Male				0.0		
Female				1.9	1.2, 2.7	
Age started ART (years) and nadir CD4 z-score (time)						<0.001
A: Started ART ≤ 5 years of age and nadir CD4 z-score <-4				0.0		
B: Started ART ≤ 5 years of age and nadir CD4 z-score ≥-4				-33.5	-48.8, -18.3	
C: Started ART >5 to <10 years of age and nadir CD4 z-score <-4				3.8	-10.8, 18.3	
D: Started ART >5 to <10 years of age and nadir CD4 z-score ≥-4				-35.7	-53.0, -18.3	
E: Started ART ≥ 10 years of age and nadir CD4 z-score <-4				102.8	86.9, 118.7	
F: Started ART ≥ 10 years of age and nadir CD4 z-score ≥-4				18.0	2.5, 33.5	
Age started ART (years) and nadir CD4 z-score (time squared)						<0.001
A: Started ART ≤ 5 years of age and nadir CD4 z-score <-4				0.0		

B: Started ART ≤ 5 years of age and nadir CD4 z-score ≥-4				3.5	2.0, 5.1	
C: Started ART >5 to <10 years of age and nadir CD4 z-score <-4				0.9	-0.5, 2.3	
D: Started ART >5 to <10 years of age and nadir CD4 z-score ≥-4				3.5	1.8, 5.1	
E: Started ART ≥ 10 years of age and nadir CD4 z-score <-4				-4.7	-6.1, -3.2	
F: Started ART ≥ 10 years of age and nadir CD4 z-score ≥-4				1.4	0.0, 2.9	
Viral suppression (time updated, within +/- 6 months of CD4 count) (time)						<0.001
Suppressed, <400 copies/ml				0.0		
Not suppressed, ≥400 copies/ml				-26.5	-34.4, -18.6	
Viral suppression (time updated, within +/- 6 months of CD4 count) (time squared)						<0.001
Suppressed, <400				0.0		

copies/ml						
Not suppressed, ≥400 copies/ml				2.1	1.3, 2.9	

Abbreviations: n, number of young people; CI, confidence interval; ART, antiretroviral therapy

[a] Number of young people in the univariable models, n=1,258 except for ethnicity n=1,249, country of birth n=1,256, years on ART at age 10 and nadir CD4 z-score n=1,190, and viral suppression n=1,257.

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Table 3: Published data on CD4 count in young people in the general population

Study	Country	Age range	Ethnicity	Gender	Average[a] CD4 count (cells/mm^3) at age (years):					
					10	12	14	16	18	20
Comans-Bitter et al. [22], 1997	Netherlands	0 to adults 5-10 years; n=35 10-16 years; n=23 adults; n=51	NG	NG	1000 (300-2000)[b]	800 (400-2100)[b]			700 (300-1400)[b]	
Huenecke et al. [23], 2008	Germany	2 months to 40 years 4-10 years; n=31 10-18 years; n=10 adults; n=20	NG	35% female	986[c] (499-1588)	954[c] (483-1537)	939[c] (475-1512)	931[c] (471-1500)	928[c] (469-1494)	926[c] (468-1491)
Tosato et al. [24], 2015	Italy	0 to 18 years 6-12 years; n=56 12-18 years; n=20	85% White	42% female	1030 (646-1515)		887 (610-1446)			-
Bofill et al. [25], 1992	UK	1 to 79 years 9-10 years; n*=25 11-79 years; n*=600	NG	NG	980[d] (243)	830[d] (288)				
Valiathian et al. [26], 2014	USA	12 to 67 years 12-18 years; n=50	NG	61% female	-	920 (467-1563)[e]				-
Shearer et al. [27], 2003	USA	0 to 18 years 6-12 years; n=90 12-18 years; n=90	53% African American	48% female	980 (650-1500)		840 (530-1300)			-
Rudy et al. [28], 2002	USA	14 to 20 years 14 yrs;	63% African	77% female	-	-	m: 833[d] (143)	m: 632[d]	m: 753[d] (207)	m: 712[d]

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		n*=3(m),5(f) 16 yrs; n*=13(m),55(f) 18 yrs; n*=36(m),108(f) 20 yrs; n*=11(m),35(f)	American				f: 779[d] (243)	(107) f: 866[d] (287)	f: 817[d] (273)	(192) f: 881[d] (319)
Mandala et al. [29], 2010	Malawi	0 to 92 years 5-10 years; n=52 10-15 years; n=49 15-20 years; n=51	African	53% female	1200 (800-2100)	1100 (800-1700)		900 (600-1200)		
de Moraes-Pinot et al. [30], 2014	Brazil	0 to 49 years 6-12 years; n=50 12-18 years; n=50 19-48 years; n=51	NG	43% female	858 (566-1298)		847 (640-1279)			813 (487 - 1141)

Abbreviations: n, number of subjects (except for * where n is number of tests (number of subjects was not given)); NG, not given; yrs, years; m, male; f, female

[a] Median and 10th and 90th percentiles in parenthesis, unless otherwise stated.

[b] 5th and 95th percentiles.

[C] Predicted values from exponential model and 90% lower and upper bounds in parenthesis.

[d] Mean and standard deviation in parenthesis.

[e] Range

FIGURE LEGENDS:

Figure 1: Predicted mean CD4 counts over time for young people with perinatal HIV, of black ethnicity, born in 2000 with suppressed viral load (time updated), by age at the start of antiretroviral therapy/nadir CD4 z-score groups.

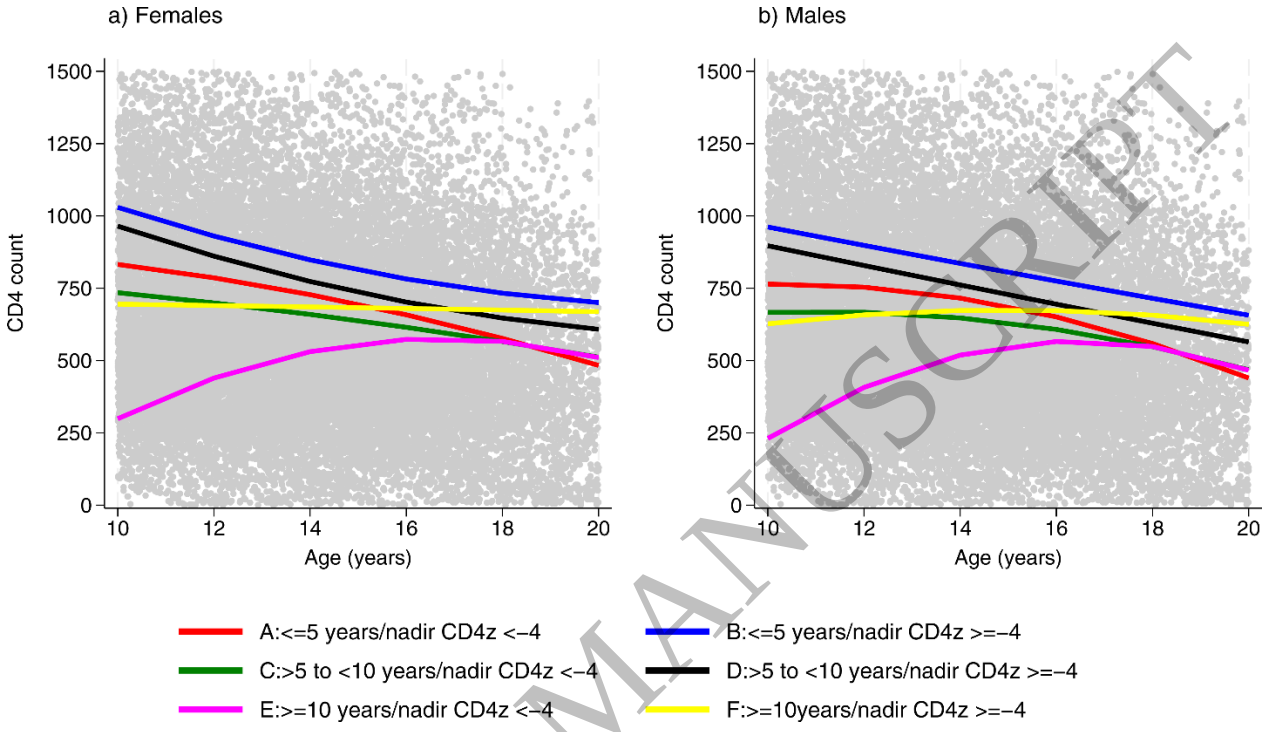

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Figure 2: Predicted mean CD4 counts over time for young people with perinatal HIV, of black ethnicity, born in 2000 with suppressed viral load (time-updated), by age at the start of antiretroviral therapy/nadir CD4 z-score groups, compared with published data on CD4 count in young people in the general population.