Differences in Factors Associated With Initial Growth, CD4, and Viral Load Responses to ART in HIV-Infected Children in Kampala, Uganda, and the United Kingdom/Ireland

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Background: Few studies have directly compared response to antiretroviral therapy (ART) between children living in well-resourced and resource-limited settings. In resource-limited settings non-HIV contributors could reduce the beneficial effects of ART. We compare predictors of short-term immunological, virological, and growth response to ART in HIV-infected children in the United Kingdom/Ireland and Kampala.

Methods: We analyzed prospective cohort data from 54 UK/Irish hospitals (the Collaborative HIV Paediatric Study) and Mulago Hospital, Kampala, Uganda. Six- and 12-month responses are described among children initiating combination ART (≥3 drugs, ≥2 classes). Six months post-ART, predictors of viral load (VL) suppression <400 copies/mL, CD4% increases >10%, and height- and weight-for-age *z*-score increases ≥+0.5 were investigated using logistic regression.

Results: In all, 582 UK/Irish children (76% black African) were younger than 876 Kampala children at ART initiation (median 5.0 vs 7.6 years), with higher CD4% (14%, 8%), lower VL (172,491 and 346,809 copies/mL), and less stunting (−0.8, −2.8) and wasting (−0.6, −2.8). Post-ART, median 12-month changes in the United Kingdom/Ireland and Kampala in CD4% (+12%, +13%) and weight (+0.4, +0.5) were similar, but growth was less in Kampala (+0.20, +0.06, $P < 0.001$). Younger children in both cohorts had better immunological, weight, and growth responses (all $P < 0.001$). However, lower pre-ART CD4% predicted better immunological response in the United Kingdom/Ireland but poorer response in Kampala (heterogeneity $P = 0.004$). Although 70% children in both cohorts had suppressed <400 copies/mL at 6 months, adolescents starting ART in the United Kingdom/Ireland had somewhat poorer VL responses than those in Kampala ($P = 0.15$).

Conclusions: Overall immunological and virologic ART responses were similar in children in both cohorts. Poorer CD4 recovery in more immunosuppressed Kampala children and blunted growth responses likely reflect higher background malnutrition and infection rates in Uganda, suggesting the need for earlier HIV diagnosis, nutritional support, cotrimoxazole prophylaxis, and ART.

Key Words: ART, CD4, children, growth, HIV

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INTRODUCTION

Initiatives to rollout effective pediatric anti-HIV drugs in resource-limited settings have resulted in large numbers of children starting antiretroviral therapy (ART) in African countries in the last 2 years, although fewer than 5% of HIV-infected children needing ART are estimated to be receiving it.[1] The effectiveness of ART in African children may differ from children in well-resourced countries for a number of reasons, in particular, differences in nutritional status and current and past exposure to tuberculosis and other infections.[2,3] Although several studies have described immunological and virological responses to combination ART in children, these have been mainly from Europe and the United States,[4,5] although there are a few recent reports from Africa.[6–11] No pediatric studies have compared predictors of treatment response in children living in well-resourced and resource-limited settings. An important additional measure of ART effectiveness in children compared with adults is height and weight gain after ART initiation. Although growth failure is a feature of untreated HIV infection in well-resourced settings,[10,12,13] with children displaying early and sustained stunting and higher levels of wasting than uninfected children, in resource-limited settings there are additional non-HIV contributors to stunting and wasting, in particular high background rates of tuberculosis and other infections, food scarcity, and malnutrition. Previous studies from well-resourced countries have shown good short- and medium-term growth responses to combination ART.[12,14] However, it is unknown whether height and weight gain responses to ART

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are as good in resource-limited settings as they could be blunted by non–HIV-related factors.

Here we describe and compare short-term immunological, virological, and growth responses to ART in previously untreated HIV-infected children starting ART in the Collaborative HIV Paediatric Study (CHIPS)[15] in the United Kingdom and Ireland and at the Paediatric Infectious Diseases Clinic in the Mulago Hospital, Kampala, Uganda.

METHODS

CHIPS is a multicenter cohort of HIV-infected children under care in 54 hospitals in the United Kingdom and Ireland since 1996,[16] including approximately 83% of all children reported to the National Study of HIV in Pregnancy and Childhood and alive in 2006. CHIPS has been approved by the London Multicentre Research Ethics Committee. The Mulago cohort includes all children initiating combination ART at the PIDC, Mulago Hospital, Kampala, Uganda, since December 2002. It has ethics approval from the Makerere University Faculty of Medicine Research and Ethics Committee and the Uganda National Council for Science and Technology. Analyses are based on data reported to CHIPS to October 31, 2006, and to Mulago to February 28, 2007.

Eligible children were those initiating combination ART (according to Paediatric European Network for Treatment of AIDS[17] and WHO[18] guidelines, respectively), defined as regimens containing 3 or more drugs from 2 or more classes or triple nucleoside reverse transcriptase inhibitor regimens including tenofovir or abacavir, more than 6 months before the data cut-off, without previous exposure to ART, apart from drugs to reduce mother-to-child transmission. In addition, children had to have ≥1 viral load (VL), CD4, and weight or height measurement 6 months after ART initiation to be included.

Characteristics at ART initiation (baseline) and virological, immunological, height-for-age, and weight-for-age responses after 6 and 12 months were compared in the 2 cohorts using descriptive statistics, including Mann–Whitney rank sum, t tests for continuous variables, and χ^2 tests for proportions. Baseline parameters were the nearest measurement within 3 months before ART initiation, whereas 6- and 12-month parameters were the nearest measurement within a ±3-month window. Weight and height z-scores for both cohorts were based on UK growth charts,[19] as these can be used across the entire range of childhood/adolescence.

Multivariable predictors of virological, immunological, height-for-age, and weight-for-age responses 6 months after ART initiation were then explored using logistic regression. To ensure all important factors were included, cohort-specific models were first fitted separately using backward elimination (exit $P = 0.05$). Final results presented are from a single multivariable model adjusted for country, which includes all factors significant in the country-specific models and additional factors significant at the $P = 0.1$ level in the overall model. Interaction terms were fitted to compare responses between the 2 cohorts, and where significant interaction was observed (Wald heterogeneity $P \leq 0.1$), odds ratios are presented separately by cohort and heterogeneity P values given. Nonlinearity in the effects of major predictor variables were explored graphically using natural cubic splines with 3 knots at 10th, 50th, and 90th centiles.[20]

Responses were defined as follows: HIV-1 RNA suppression <400 copies/mL; CD4% increase of ≥10% from baseline; and increases of ≥0.5 in weight-for-age or height-for-age z-score. For the multivariable analysis, children with no baseline response variable measure were excluded, and a small number of missing values in other baseline predictors were imputed using chained estimation[21] with 10 imputations from multivariable models.[22] To explore a potential "learning effect" of ART prescribing and management, calendar time was classified into 3 periods: period 1 (1997/9), 2 (2000/2), and 3 (2003/6) for the United Kingdom/Ireland and period 1 (2003/4) and 2 (2005/7) in Kampala, with the reference category being the period of the earliest introduction of ART.

All analyses were conducting using STATA 9 (Stata Corp, College Station, TX).

RESULTS

Baseline Characteristics

A total of 654 children enrolled in CHIPS in the United Kingdom/Ireland between 1996 and 2006 had started ART naive at least 6 months previously, of whom 582 (89%) had ≥1 response variable (VL, CD4, weight, or height) measurements at 6 months and were included here. A further 19/654 (3%) were known to have died before 6 months, 30 (5%) were last seen <6 months after ART initiation, and 23 (4%) had ≥6 months follow-up but no measurements at 6 months. The 582 included children started ART between 1997 and 2006 with a median 3.6 years of subsequent follow-up and had similar baseline characteristics to all 654 children (data not shown). About 261/582 children (45%) had been born abroad, and 440 (76%) were black African.

Of 1604 children enrolled in Kampala to February 2007 and starting ART naive at least 6 months previously, 876 (55%) had ≥1 response measurement at 6 months and are included; 137 (9%) died within 6 months, 568 (35%) were last seen less than 6 months after ART initiation, and 23 (1%) had ≥6 months follow-up but no measurements recorded at 6 months. The 876 included children started ART between August 2003 and September 2006, and baseline characteristics were similar to the cohort as a whole. VL was only measured prospectively in a subset of these children based on period of enrollment [236 (27%) at baseline, 261 (30%) at 6 months, and 107 (12%) at 12 months].

About 46% of children in the United Kingdom/Ireland and 50% in Kampala were girls (Table 1). Children in the United Kingdom/Ireland started ART at a younger age (median 5.0 in the United Kingdom/Ireland vs 7.6 years in Kampala, 11% vs 24% 13 years or older, respectively), with less severe HIV disease: lower VL (median 172,491 vs 346,809 copies/mL); higher pre-ART CD4% (14% vs 8%); less stunting (median z-score −0.8 vs −2.8); and less wasting (median z-score −0.6 vs −2.8). Virtually all children in Kampala (98%) started nonnucleoside reverse transcriptase inhibitor–containing regimens, according to national

TABLE 1. Characteristics of Children at ART Initiation by Cohort

	UK/Ireland (n = 582)	Kampala (n = 876)	*P* Value*
Sex, female	269 (46)	440 (50)	0.12
Age, median (IQR)	5.0 (1.6–8.9)	7.6 (4.4–11.6)	<0.001
HIV-1 RNA (copies/mL)			<0.001
Measurements available	504 (87)	236 (27)	
Median (IQR)	172,491 (43,878–579,674)	346,809 (142,212–689,391)	
<500	6 (1)	0 (0)	
500 to <100,000	193 (38)	43 (18)	
100,000 to <750,000	209 (42)	142 (60)	
≥750,000	96 (19)	51 (22)	
CD4%			<0.001
Measurements available	553 (95)	876 (100)	
Median (IQR)	14 (8–21)	8 (3–12)	
<5	78 (14)	297 (34)	
5–14	209 (38)	475 (54)	
15–29	210 (38)	104 (12)	
≥30	56 (10)	0 (0)	
CD4 count, median (IQR)	350 (151–682)	234 (70–490)	<0.001
Height-for-age z-score			<0.001
Measurements available	383 (66)	830 (95)	
Median (IQR)	−0.82 (−1.60, +0.01)	−2.85 (−3.92, −1.74)	
<2.5th centile (z-score <−2)	63 (16)	582 (70)	
Weight-for-age z-score			<0.001
Measurements available	436 (75)	853 (97)	
Median (IQR)	−0.60 (−1.42, 0.18)	−2.80 (−4.20, −1.63)	
<2.5th centile (z-score <−2)	65 (15)	571 (67)	
CDC grade			<0.001
Measurements available	582 (100)	833 (95)	
A/WHO 1–2	253 (43)	316 (38)	
B/WHO 3	170 (29)	433 (52)	
C/WHO 4	159 (27)	84 (10)	
First-line ART regimen: NRTIs+			<0.001
Efavirenz	158 (27)	481 (55)	
Nevirapine	212 (36)	379 (43)	
Lopinavir/Ritonavir	45 (8)	16 (2)	
Nelfinavir	113 (19)	0 (0)	
Other protease inhibitor	9 (2)	0 (0)	
NRTI only	45 (8)	0 (0)	

Data are no. (%) unless otherwise indicated. IQR, interquartile range. Data are for children with ≥1 six-month response variable only. NRTI, nucleoside reverse transcriptase inhibitor.

*P values are for comparison of the United Kingdom/Ireland to Kampala, from Mann–Whitney rank sum tests for continuous variables and χ^2 tests for proportions.

guidelines, whereas 29% in the United Kingdom/Ireland started a protease inhibitor–containing regimen (Table 1). Only 4% children in the United Kingdom/Ireland had been exposed to ART in utero for prevention of mother-to-child transmission; these data were not available in Kampala.

Six- and 12-Month Response to ART

After the initiation of ART, overall in both cohorts there were comparable reductions in VL at 6 and 12 months and increases at 6 and 12 months in CD4% and weight *z*-scores (Table 2). However, there was wider variation in weight increase in Kampala (interquartile range for change in *z*-score at 6 months −0.30 to +0.91) than the United Kingdom/Ireland (−0.05 to +0.68) and median change in height-for-age *z*-score was greater at 6 and 12 months in the United Kingdom/Ireland (+0.08, +0.20, respectively) than in Kampala (−0.11, +0.06; $P < 0.001$, for 6 and 12 months). Of note, 16% of children in the United Kingdom/Ireland vs 70% in Kampala had height <2.5th centile (*z*-score <−2) at baseline (Table 1), and whereas this proportion reduced to 11% at 12 months in the United Kingdom/Ireland, it remained at 70% in Kampala. Twelve months after ART initiation, the median height *z*-score was −0.61 in the United Kingdom/Ireland compared with −2.76 in Kampala. While appreciating that 12 months is a relatively short time to observe catch-up growth, if these *z*-scores were maintained throughout childhood, the average 17-year-old boy (girl) would be 1.72 (1.60) m tall in the United Kingdom/Ireland, compared with the general UK population

TABLE 2. Changes in Virological, Immunological, Height, and Weight Responses 6 and 12 Months After ART Initiation by Cohort

Response Variable	6 Months			12 Months		
	United Kingdom/ Ireland (N = 582)	Kampala (N = 876)	*P* Value*	United Kingdom/ Ireland (N = 582)	Kampala (N = 876)	*P* Value*
HIV-1 RNA	n = 480	n = 214		n = 418	n = 70	
Mean (95% confidence interval) change in $\log_{10}$VL	−3.2 (−3.3 to −3.1)	−3.5 (−3.7 to −3.3)	0.08	−3.3 (−3.5 to −3.1)	−2.9 (−3.4 to −2.5)	0.11
N (%) <400 copies/mL	346 (72%)	159 (74%)	0.23	295 (71%)	47 (67%)	0.56
CD4	n = 532	n = 483		n = 454	n = 202	
Median (IQR) change in %	9 (4, 14)	9 (6, 14)	0.10	12 (7, 19)	13 (7, 18)	0.88
Median (IQR) change in count†	253 (92, 539)	235 (101, 422)	0.15	380 (139, 796)	316 (141, 543)	0.09
N (%) ≥10% increase	246 (46%)	212 (44%)	0.47	292 (64%)	131 (65%)	0.90
Height z-score	n = 340	n = 800		n = 297	n = 745	
Median (IQR) change	0.08 (−0.12, 0.29)	−0.11 (−0.35, 0.15)	<0.001	0.20 (−0.05, 0.56)	0.06 (−0.30, 0.49)	<0.001
N (%) ≥0.5 increase	52 (15%)	113 (14%)	0.62	84 (28%)	185 (25%)	0.25
N (%) <2.5th centile (z-score <−2)	41 (12%)	590 (74%)	<0.001	34 (11%)	518 (70%)	<0.001
Weight z-score	n = 399	n = 834		n = 351	n = 771	
Median (IQR) change	0.26 (−0.05, 0.68)	0.19 (−0.30, 0.91)	0.17	0.41 (0.04, 1.02)	0.49 (−0.03, 1.34)	0.34
N (%) ≥0.5 increase	133 (33%)	310 (37%)	0.18	160 (46%)	380 (49%)	0.25
N (%) <2.5th centile (z-score <−2)	24 (6%)	515 (62%)	<0.001	14 (4%)	404 (52%)	<0.001

*P values are for comparison of United Kingdom/Ireland to Kampala, from Mann–Whitney rank sum and t tests for continuous variables and χ^2 tests for proportions.
†Not all children had CD4 count measures available. These data are based on n = 523 measures at 6 months and n = 446 at 12 months for the United Kingdom/Ireland and n = 422 and n = 202 for Kampala, respectively.

average of 1.76 (1.64) m and only 1.53 (1.47) m in Kampala, a deficit of around 20 cm compared with HIV-infected counterparts in the United Kingdom/Ireland.

There was little association between changes in HIV-1 RNA, CD4%, weight, and height in both cohorts at 6 and 12 months (Spearman correlations <0.3). In particular, 8% of children in both the United Kingdom/Ireland and Kampala had an immunological but no virological response (as defined in Methods) at 6 months, vs 17% and 14% with neither, 40% and 37% with both, and 35% and 41% with virological but no immunological response.

Predictors of 6-Month Response to ART

Multivariable models suggested that, on average, children in the United Kingdom/Ireland and Kampala had a similar chance of achieving a virological, immunological, and height response at 6 months [adjusted odds ratio (aOR) = 1.35, 1.15, and 1.50, respectively, for Kampala vs the United Kingdom/Ireland, P = 0.16, 0.43, and 0.44, Table 3] but children in Kampala had poorer weight responses (aOR = 0.27 vs the United Kingdom/Ireland, $P < 0.001$). Older children in both cohorts were more likely to achieve virological suppression at 6 months (aOR = 1.04 per year older, P = 0.05), whereas younger children had an increased chance of CD4% increasing by ≥10% (aOR = 0.85 per year older, $P <$ 0.001). Girls had a higher chance of immunological response in both cohorts (aOR = 1.55, P = 0.001) and tended to also have a higher chance of a virological response (aOR = 1.30, P = 0.10). As expected, there was a trend toward children with higher VLs at baseline having a slightly lower chance of suppression at 6 months across both cohorts (aOR = 0.83 per $\log_{10}$ higher, P = 0.10).

Children starting ART in later calendar years were more likely to achieve better immunological, virological, and weight responses in both cohorts, with a less pronounced relationship for height response, particularly in Kampala (heterogeneity P = 0.20, Table 3). Younger children put on more weight after ART in both cohorts (aOR = 0.90, $P < 0.001$) and also grew more, although this height effect was more marked in UK/Irish children (aOR = 0.61 and 0.84 per year older in the United Kingdom/Ireland and Kampala, respectively; heterogeneity $P < 0.001$). Unsurprisingly, heavier and taller children at ART initiation in both cohorts had smaller gains in weight and height, respectively, suggesting that weight and height tended to normalize most in those with the greatest impairments at baseline.

The most marked difference between the 2 cohorts was that, after adjusting for other factors, children with lower baseline CD4% had "poorer" immune response at 6 months in Kampala (aOR = 1.26 per 5% increase, P = 0.01), whereas in the United Kingdom/Ireland, these children had "better" CD4% response (aOR = 0.69, $P < 0.001$; heterogeneity $P <$ 0.001) (Table 3). In fact, the relationship between CD4% at ART initiation and CD4 response was not linear (nonlinearity P = 0.02, Fig. 1); whereas children with baseline CD4% >15% had smaller gains in CD4% at 6 months in both cohorts, children in Kampala with low pre-ART CD4% had poorer immune responses compared with those in the United Kingdom/Ireland (heterogeneity P = 0.004).

The other major difference between predictors of 6 months response in the 2 cohorts was that low pre-ART

TABLE 3. Multivariable Predictors of Virological, Immunological, Height, and Weight Responses 6 Months After ART Initiation

Predictor (at ART initiation)	6-Month Response Variable*			
	HIV-1 RNA Response (<400 copies/mL)	Immunological Response (≥10% increase in CD4% over baseline)	Height z-Score Response (≥0.5 increase in z-score over baseline)	Weight z-Score Response (≥0.5 increase in z-score over baseline)
	aOR (95% CI), *P* value	aOR (95% CI), *P* value	aOR (95% CI), *P* value	aOR (95% CI), *P* value
Cohort: Kampala vs United Kingdom/Ireland†	1.35 (0.88–2.06), $P = 0.16$	1.15 (0.81–1.63), $P = 0.43$	1.50 (0.54–4.19), $P = 0.44$	0.27 (0.17–0.43), $P < 0.001$
Age (per year increase)				
United Kingdom/Ireland	}1.04 (1.00–1.08), $P = 0.05$	}0.85 (0.83–0.88), $P < 0.001$	0.61 (0.52–0.72), $P < 0.001$	}0.90 (0.87–0.93), $P < 0.001$
Kampala			0.84 (0.80, 0.90), $P < 0.001$	
			Heterogeneity $P < 0.001$	
Sex: girl vs boy	1.30 (0.95–1.79), $P = 0.10$	1.55 (1.19–2.04), $P = 0.001$	*P = 0.77*	*P = 0.34*
HIV-1 RNA (per 1 $\log_{10}$copies/mL increase)	0.83 (0.67–1.04), $P = 0.10$	*P = 0.94*	*P = 0.27*	*P = 0.26*
CD4% (per 5% increase)				
United Kingdom/Ireland		0.69 (0.62–0.76), $P < 0.001$		0.96 (0.85–1.09), $P = 0.53$
Kampala		1.26 (1.05–1.51), $P = 0.01$		0.78 (0.67–0.91), $P = 0.001$
	P = 0.76	Heterogeneity $P < 0.001$	*P = 0.89*	Heterogeneity $P = 0.03$
Height (per unit z-score increase)				
United Kingdom/Ireland			0.42 (0.30–0.59), $P < 0.001$	‡
Kampala			0.59 (0.52–0.68), $P < 0.001$	
	P = 0.74	*P = 0.38*	Heterogeneity $P = 0.06$	
Weight (per unit z-score increase)				
United Kingdom/Ireland			‡	0.47 (0.38–0.58), $P < 0.001$
Kampala				0.57 (0.52, 0.63), $P < 0.001$
	P = 0.14	*P = 0.50*		Heterogeneity $P = 0.10$
Calendar period, vs period 1 (1997/9 United Kingdom/ Ireland and 2003/5 Kampala)				
Period 2				
United Kingdom/Ireland (2000/2)	}1.93 (1.33–2.83), $P = 0.001$	}1.45 (1.06–1.99), $P = 0.02$	1.46 (0.57–3.72), $P = 0.43$	}2.09 (1.46–2.99) $P < 0.001$
Kampala (2005/7)			0.54 (0.30, 0.97), $P = 0.04$	
Period 3 (United Kingdom/ Ireland) (2003/6)	3.53 (2.26–5.52), $P < 0.001$	1.62 (1.07–2.44), $P = 0.02$	1.50 (0.62–3.62), $P = 0.36$	1.90 (1.13–3.19), $P = 0.02$
			Heterogeneity $P = 0.08$	

95% CI, 95% confidence interval.

*Multivariable models for each response variable are adjusted for country and all predictor variables significant ($P \leq 0.1$) in country-specific or overall models. Odds ratios are presented separately by country where significant interaction exists (Wald heterogeneity $P \leq 0.1$). *P* values in italics refer to predictor variables excluded from the model ($P > 0.10$), in which case odds ratios are not presented.

†Country effects are estimated for a boy aged 6 in the first calendar period with a CD4 of 10% and height and weight *z*-scores of −1.5 (see Figs. 1 and 2 for more details of country effects).

‡Weight- and height-for-age are strongly associated (Spearman correlation 0.83) and therefore are not presented in the same model together.

CD4% predicted better weight response in Kampala independently of baseline weight-for-age (aOR = 0.78, $P = 0.001$) but was not associated with weight response in the United Kingdom/Ireland (aOR = 0.96, $P = 0.53$; heterogeneity $P = 0.03$). Of note, the effects of baseline height and weight values on height and weight response were greater in the United Kingdom/Ireland (aOR = 0.42, $P < 0.001$, and aOR = 0.47, $P < 0.001$, respectively) than Kampala (aOR = 0.59, $P < 0.001$,

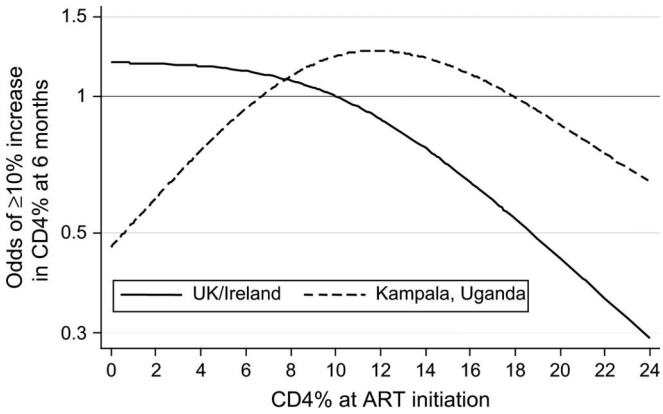

FIGURE 1. Effect of CD4% at ART initiation on the odds of immunological response (≥10% increase in CD4% over baseline) at 6 months by cohort. The model presented is adjusted for all multivariable predictors of immunological response in Table 3. The reference category is a child in the UK/Ireland with a CD4% of 10% at ART initiation.

and aOR = 0.57, $P < 0.001$, respectively; both heterogeneity $P < 0.001$).

Age at ART initiation and calendar period were the only factors significantly associated with all four 6-month responses. Figure 2 further explores the effect of age on these responses. The adjusted odds of immunological and height response decreased linearly (year by year) with increasing age (nonlinearity $P = 0.48$ and 0.96, respectively, Figs. 2B, C). In contrast, there was a nonlinear association between age and HIV-1 RNA suppression <400 copies/mL at 6 months (nonlinearity $P < 0.001$) with some evidence for a different association between cohorts (heterogeneity $P = 0.15$). In particular, the odds of suppression increased until the age of 7–8 in both cohorts and then decreased rapidly in adolescence in the United Kingdom/Ireland, whereas remaining approximately constant in adolescents in Kampala (Fig. 2A). There were smaller gains in weight with increasing age at ART initiation throughout childhood and adolescence in Kampala, whereas there was little variation in weight response after 7 years of age in the United Kingdom/Ireland (nonlinearity $P = 0.003$, heterogeneity $P = 0.03$, Fig. 2D).

DISCUSSION

Several pediatric studies have described immunological and virological responses to combination ART in well-resourced countries,[5,23–27] although some included children with prior exposure to suboptimal mono or dual therapy,[25–27] a subpopulation no longer relevant to children presenting today, and most studies have been small.[24,25] This analysis is one of the largest studies describing HIV and early growth responses to ART across childhood and also the first to directly compare initial responses to ART among children in 2 very different environments, the United Kingdom/Ireland and Kampala, Uganda. Although not all children in the 2 cohorts are included in this analysis, we believe that the results are generalizable as those excluded were similar in terms of baseline characteristics.

Early mortality after ART initiation has been reported to be approximately 7-fold higher in HIV-infected adults in Africa compared with adults in well-resourced settings,[28]

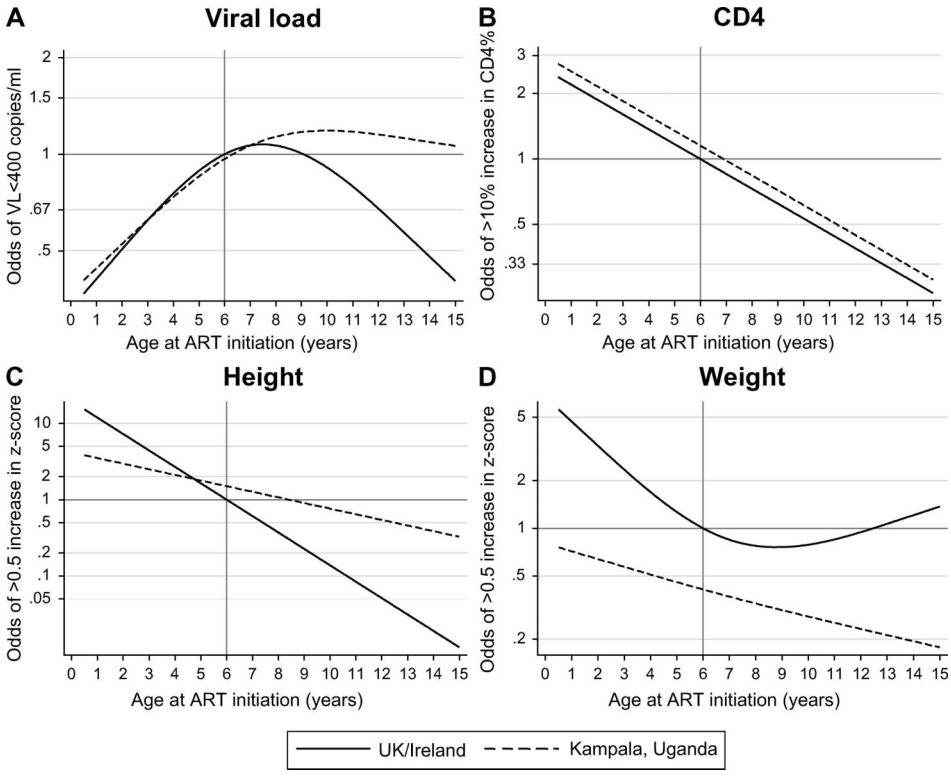

FIGURE 2. Effect of age at ART initiation on virological, immunological, height, and weight responses at 6 months. All models are adjusted for multivariable predictors of 6 month response in Table 3. The reference category is a child in the UK/Ireland aged 6 at ART initiation.

whereas in our study of children, the difference was around 3-fold. However, the UK/Irish cohort included children starting combination ART soon after its introduction in 1996 and children born in Africa and presenting in the United Kingdom with advanced disease, both of which would tend to increase mortality rates. Also, children in the Kampala cohort were older than those in the United Kingdom/Ireland; older "survivors" in Africa may have lower mortality rates.[6] We noted improvements in all outcomes over calendar time in both cohorts, likely reflecting a "learning curve" in improved management of ART and care of children, possibly more effective antiretrovirals in later years in the United Kingdom/Ireland, and children with more advanced disease being more likely to start ART in the earlier calendar years. Of note, the majority of children in both cohorts were of black African origin, so differences in responses are unlikely to reflect underlying racial differences, although UK/Irish children were from a variety of African countries and may have more diverse viral subtypes.

At ART initiation, important differences between the cohorts included younger age and less advanced HIV disease in the United Kingdom/Ireland and a much higher prevalence of wasting and stunting in Kampala, similar to other descriptions of African children with HIV infection.[6–8,29,30] After 6 and 12 months, overall viral suppression, CD4% increase and weight gain were similar in both cohorts. Of note, there was evidence for wider variation in weight gain in Kampala than in the United Kingdom/Ireland, perhaps reflecting variations in food availability in Uganda. Lower pre-ART CD4% predicted better weight response in Kampala independently of baseline weight-for-age, whereas in the United Kingdom/Ireland, ART contributed to weight gain independently of CD4%. This suggests that in Uganda, ART may have a larger effect on weight at lower rather than higher CD4% values, possibly with non-HIV factors contributing more to malnutrition at higher CD4% values. In contrast, in the United Kingdom/Ireland, ART contributed to weight gain irrespective of baseline CD4%, and baseline height and weight had a greater effect on 6-month height and weight responses than in Kampala, supporting a greater role of HIV in these impairments in the United Kingdom/Ireland than Uganda.

Height responses were blunted at 6 and 12 months in Kampala children, despite their greater potential for catch-up growth than UK/Irish children. They were also lower than results from a recent South African study, albeit of much younger children (median age 23 months).[9] It is plausible that the degree of long-term wasting and stunting before starting ART in the older Kampala children could compromise short-term height response, with weight gain needing to occur first. Longer term height responses from Kampala children were published recently and reported catch-up height starting to occur by 2 years, but lagging behind weight.[31] In well-resourced settings, the effect of ART on height deficit and body composition abnormalities has been shown to be mostly beneficial, but studies have mainly reported short-term outcomes, as in our analysis.[12,32,33] In a randomized trial of ART regimens in children in Europe, differences in height at 6 and 12 months paralleled VL outcome in each regimen,[33] raising the possibility of using height as a marker for ART response.[14,32,33] However, our findings suggest that growth may not be a useful surrogate for VL in the short term; longer term outcomes in both well-resourced and resource-limited settings are required with greater numbers of children. Many other factors may differentially impact on short-term growth responses in our 2 cohorts, including immune reconstitution syndrome and higher early morbidity and mortality in Uganda.

As in previous studies from well-resourced settings, in both our cohorts older children had a marginally higher chance of virological suppression but lower chance of immunological response after ART.[5,34] However, in the United Kingdom/Ireland, but not in Kampala, children with the lowest CD4% at ART initiation had the best immunological response to ART.[5,16] One possible explanation would be greater effects of nutrition and/or coinfections on immune recovery in Kampala. However, although malnutrition blunts the immune system, neither height- nor weight-for-age independently predicted CD4 recovery in either cohort and thus a direct effect of malnutrition seems unlikely. As with height, better immune recovery among the most immunocompromised children in the United Kingdom/Ireland may relate to their better nutritional status and/or other environmental factors such as a lower burden of coinfections, giving a greater ability to "bounce back" once virus is suppressed. One multicenter cohort of nearly 600 children starting ART across 14 resource-limited countries (10 in Africa) reported good immune responses even among those with CD4% $<5\%$ pre-ART, but all were less than 5 years of age at ART initiation.[8] The potential for poorer immune recovery in older children starting ART with low CD4 values in resource-limited settings is a major cause for concern and warrants further investigation.

Older children and adolescents in Kampala had a superior virological response to ART compared with those in United Kingdom/Ireland. Clinicians have already commented on the difficulties faced by newly HIV-diagnosed adolescents in the United Kingdom/Ireland and that adherence to medication is particularly poor in this group. Many have to cope with the diagnosis of HIV infection and also with the upheavals and social circumstances of having recently arrived in the United Kingdom or Ireland from another country. In contrast, the better virological response in Kampala adolescents may be attributed to particularly successful adolescent support programs at the Mulago Hospital in Kampala.

In conclusion, overall VL and CD4 responses were similar among HIV-infected children starting ART in Kampala and the United Kingdom/Ireland. However, there were important differences in weight and height responses between the cohorts, in particular, short-term height and immunological responses at very low CD4% were poorer in Kampala. Longer term follow-up and comparisons between the cohorts is planned. However, based on these short-term responses, this study can begin to inform the debate about timing of initiation of ART in resource-limited settings in both adults[35] and children.[36] Findings point toward the need for earlier HIV diagnosis, nutritional support, and cotrimoxazole prophylaxis for children in Kampala, although further insight into the timing of ART in both well-resourced and resource-limited settings is likely to require evaluation in a large clinical trial.

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