Poster 584

Initial growth, CD4, and viral load responses to HAART in Ugandan compared to UK/Irish HIV-infected children

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Abstract

Background: Large numbers of HIV-infected children are now starting antiretroviral therapy (ART) in African countries. Responses to ART in Africa may differ from those among children in well-resourced settings due to increased prevalence of non-HIV related factors including pre-ART nutritional status, current and past exposure to infections and food availability.

Methods: We compared 6 and 12 month responses to ART in HIV-infected children from 54 hospitals in the UK and Ireland (Collaborative HIV Paediatric Study, CHIPS) and from the Mulago Hospital, Uganda. Predictors of viral load (VL) suppression <400 copies/ml, CD4% increases >10% and height-, weight-for-age z-score increases ≥+0.5, six months post-ART (starting ≥3 drugs, ≥2 classes) were investigated using logistic regression.

Results: 582 children in CHIPS started combination ART naive and had 1 or more outcomes at 6 months since 1997, and 876 in Mulago since 2003. At baseline, CHIPS children (76% black African) were younger than Mulago children (median age 5.0 vs 7.6 years), with higher pre-ART CD4% (14% vs 8%), lower VL (172,491 vs 346,810 copies/ml), less stunting (-0.8 vs -2.8) and wasting (-0.6 vs -2.8). Following ART initiation, there were similar changes in CD4% (median +12%, +14%) and weight (+0.5, +0.4) at 12-month in CHIPS and Mulago, but less change in height in Mulago (+0.06 vs +0.20, heterogeneity p<0.001). Controlling for other factors, younger children had better immunological, weight and growth responses in both cohorts (all p<0.001) but marginally poorer VL responses (p=0.08) and girls had a better immunological response than boys in both cohorts (OR=1.55, p=0.001). In contrast, lower pre-ART CD4 predicted better immunological response in CHIPS but poorer response in Mulago (heterogeneity p=0.005). Although 70% children in both cohorts had VL <400c/ml at 6 months, adolescents starting ART in UK/Ireland had poorer VL responses than those in Uganda.

Conclusions: Immunological and virological responses to ART were similar in children in resource-limited and well-resourced settings. Poorer CD4 recovery in more immunosuppressed children and more blunted growth responses in Uganda probably reflect higher malnutrition and co-infection rates in Africa, supporting the need for earlier HIV diagnosis, ART and nutritional support in resource-limited settings. Poorer virologic responses among UK/Irish adolescents may reflect poorer adherence levels and needs further investigation.

Rationale

- Initiatives to rollout paediatric anti-HIV drugs in resource-limited settings have led to large numbers of children starting ART in African countries in the last 2 years
- **No paediatric studies have compared predictors of treatment response in children living in well-resourced and resource-limited settings**
  - compared to adults, an important additional measure of ART effectiveness in children is growth and weight gain after ART initiation
- **The effectiveness of ART in African children may differ from children in well-resourced countries for various reasons:**
  - current and past exposure to infections, high background pathogen load
  - additional non-HIV contributors to stunting and wasting, such as differences in nutritional status, food scarcity and malnutrition
- **We therefore aimed to compare children initiating HAART naïve in resource-rich (UK/Ireland) and resource-limited (Uganda) settings in terms of:**
  - short-term (6 and 12 month) immunological, virological and growth responses to ART
  - predictors of response to ART

Characteristics at ART initiation

- 582 children in CHIPS initiating ART naïve in 1997-2006 were younger with less advanced HIV disease and growth impairment than 876 children from the Mulago cohort initiating ART naïve in 2003-7 (Table 1). 45% of children in CHIPS were born abroad and 76% were black African.

Table 1: Characteristics of children at ART initiation

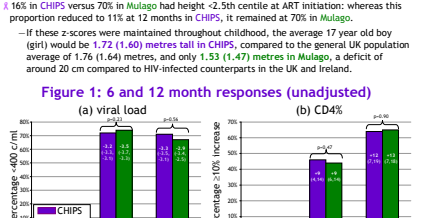
	UK and Ireland N=582		Uganda N=876		p-value
Sex: Number (%) girls	269	(46%)	440	(50%)	0.12
Age (median years, IQR)	5.0	(1.6-8.9)	7.6	(4.4-11.6)	<0.001
Viral load; baseline available (median, IQR)	504 (87%) 172,491 (43,878-579,674)		236 (27%) 346,810 (142,212-689,391)		
<500	6	(1%)	0	(0%)	<0.001
500-<100,000	193	(38%)	43	(18%)	
100,000-<750,000	209	(42%)	142	(60%)	
750,000+	96	(19%)	51	(22%)	
CD4%; baseline available (median, IQR)	553 (95%) 14% (8-21%)		876 (100%) 8% (3-12%)		<0.001
<5	78	(14%)	297	(34%)	
5-14	209	(38%)	475	(54%)	
15-29	210	(38%)	104	(12%)	
30+	56	(10%)	0	(0%)	
Height-for-age z-score; baseline available (median, IQR)	383 (66%) -0.82 (-1.60, +0.01)		830 (95%) -2.85 (-3.92, -1.74)		<0.001
N (%) < 2.5th centile (z-score<-2)	63	(16%)	582	(70%)	
Weight-for-age z-score; baseline available (median, IQR)	436 (75%) -0.60 (-1.42, 0.18)		853 (97%) -2.80 (-4.20, -1.63)		<0.001
N (%) < 2.5th centile (z-score<-2)	65	(15%)	571	(67%)	
CDC/WHO Stage; baseline available	582	(100%)	833	(95%)	
A / WHO 1-2	253	(43%)	316	(38%)	<0.001
B / WHO 3	170	(29%)	433	(52%)	
C / WHO 4	159	(27%)	84	(10%)	
First-line HAART regimen					
EFV containing (+NRTIs)	158	(27%)	481	(55%)	<0.001
NVP containing (+NRTIs)	212	(36%)	379	(43%)	
KAL containing (+NRTIs)	45	(8%)	16	(2%)	
NFV containing (+NRTIs)	113	(19%)	0	(0%)	
Other PI containing (+NRTIs)	9	(2%)	0	(0%)	
Triple NRTI	45	(8%)	0	(0%)	

Note: Restricted to children with at least one response variable at 6 months. p-values from chi-squared or ranksum. % not missing is percentage of total, % in italics represent percentage of those not missing for each factor.

6/12 month ART responses (unadjusted)

- After ART initiation, overall both cohorts had comparable reductions in viral load at 6 months (Fig 1) and increases at 6 and 12 months in CD4% and median weight z-scores. But
  - there was wider variation in weight increase in Mulago (IQR -0.3 to +0.9) than CHIPS (-0.1 to +0.7)
  - median change in height-for-age was greater at 6 and 12 months in CHIPS than Mulago
- 16% in CHIPS versus 70% in Mulago had height <2.5th centile at ART initiation: whereas this proportion reduced to 11% at 12 months in CHIPS, it remained at 70% in Mulago.
  - If these z-scores were maintained throughout childhood, the average 17 year old boy (girl) would be **1.72 (1.60) metres tall in CHIPS**, compared to the general UK population average of 1.76 (1.64) metres, and only **1.53 (1.47) metres in Mulago**, a deficit of around 20 cm compared to HIV-infected counterparts in the UK and Ireland.

Figure 1: 6 and 12 month responses (unadjusted)



Note: Numbers on graphs show the median (IQR) change from ART initiation in each cohort (mean change in $\log_{10}$ HIV RNA copies/ml using interval regression). P values are from χ^2 tests for the percentage with viral load and CD4% response, and ranksum tests for change in weight /height-for-age

Methods

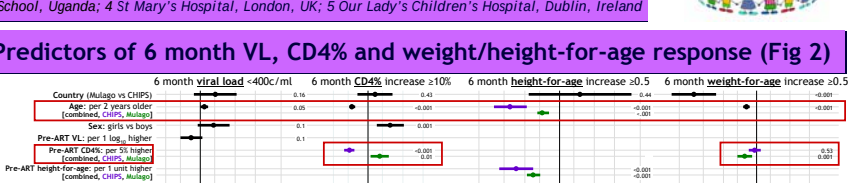
CHIPS is a multicentre cohort of HIV-infected children under care in 54 hospitals in the UK and Ireland since 1996. The Mulago cohort includes all children initiating combination ART at the Pediatric Infectious Disease Clinic, Mulago Hospital, Uganda since December 2002. Analyses are based on data reported to CHIPS to 31 October 2006 and to Mulago to 28 February 2007.

Eligible children were those who initiated combination ART more than 6 months before the cut-off date, defined as regimens containing ≥3 drugs from ≥2 or triple NRTI regimens including tenofovir or abacavir, without previous exposure to ART, apart from drugs to reduce mother-to-child transmission. We described changes 6 and 12 months after ART initiation in CD4%, height-for-age (z-score) and weight-for-age (z-score), taken to be the nearest measurement within +/- 3 months and HIV-1 RNA (to six months only, as few children in Mulago had 12 month viral load data).

We then investigated sex and age, CD4%, HIV-1 RNA, weight/height, and calendar year at ART initiation as predictors of 6 month virological, immunological, growth and weight response using logistic regression, and compared predictors between the two cohorts using interaction tests.

- For analysis of each response variable, children with no baseline for this variable were excluded and the small number of remaining missing pre-ART values in other baseline variables were imputed using chained estimation with 10 imputations from multivariable models
- To explore a potential 'learning effect' of ART prescribing and management, calendar time was classified into early (1997/9), medium (2000/2) and late (2003/6) periods in CHIPS and early (2003/4) and medium (2005/7) periods in Mulago, with reference category the earliest introduction of ART
- Final results presented are from a single multivariable model adjusted for country, including all factors significant in the country specific models and additional factors significant at the p<0.1 level in the joint model
- Odds ratios (OR) are presented separately for CHIPS and Mulago where significant heterogeneity exists (interaction p<0.10), and non-linearity in factor effects explored graphically using natural cubic splines with 3 knots at 10th, 50th and 90th centiles.

Predictors of 6 month VL, CD4% and weight/height-for-age response (Fig 2)

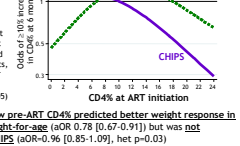


Notes: Estimates from multivariable logistic regression models: p values are the overall effect of this factor on response. Separate effects are given when the heterogeneity in factor effects between CHIPS and Mulago is significant at the 10% level (CHIPS effect in purple, Mulago effect in green). Where no significant heterogeneity exists, the combined effect estimate is given in black.

Using multivariable logistic regression models to predict 6 month responses and adjusting for baseline differences between the cohorts (Table 1), we found that

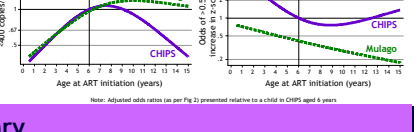
- CHIPS and Mulago children had a **similar chance of achieving a virological, immunological and height response at 6 months** (adjusted (a)OR=1.35, 1.15 and 1.50 for Mulago versus CHIPS, p=0.19, 0.43 and 0.44, Fig 2) but **children in Mulago had poorer weight responses** (aOR=0.27 versus CHIPS, p<0.001)
- The most marked difference was that children with **lower baseline CD4% had poorer immune response at 6 months in Mulago** (aOR=1.26 [1.05-1.51] per 5% higher) whereas **in CHIPS, these children had better CD4% response** (aOR=0.69 [0.62-0.76], p<0.000), Fig 2)
  - In fact the relationship between CD4% at ART initiation and CD4 response was not linear (Fig 3); those with CD4% >15% had poorer immune responses in both cohorts, but children in Mulago with low pre-ART CD4% had poorer immune responses in contrast to CHIPS (heterogeneity p=0.005)

Figure 3: Effect of CD4% at ART initiation on the odds of CD4% increase ≥10% at 6 months



- The other major difference was that **low pre-ART CD4% predicted better weight response in Mulago independently of baseline weight-for-age** (aOR 0.78 [0.67-0.91]) but was **not associated with weight response in CHIPS** (aOR=0.96 [0.85-1.09], het p=0.03)
  - this suggests that in Africa, ART contributes to greater improvements in wasting at low compared to high CD4%, possibly because non-HIV causes of malnutrition have more impact in those with higher CD4%; in UK/Ireland, ART contributes to weight gain irrespective of CD4%
  - the effects of baseline growth/weight on growth/weight response were greater in CHIPS than Mulago, also supporting a greater HIV-attributable role for these impairments in the UK/Ireland than Uganda
- **Younger children** in both cohorts were **marginally less likely to achieve VL suppression** at 6 months (adjusted (a)OR=1.04 per year older, p=0.08). In contrast, younger children in both cohorts had an **increased chance of achieving ≥10% increase in CD4%** (aOR=0.85 per year older, p<0.001). Younger children **put on more weight** following ART in both cohorts (aOR=0.90, het p=0.74), and also **grew more**, although this was more marked in UK/Irish children (aOR=0.61 and 0.84 per year older in CHIPS and Mulago respectively, het p<0.001).
- **Exploring the effect of age at ART initiation further showed that**
  - the adjusted odds of immunological and height response decreased linearly (year by year) with increasing age (non-linearity p=0.51 and 0.91)
  - in contrast, there was a non-linear association between age and VL <400 copies/ml at 6 months (non-linearity p<0.001) and a trend towards differences in this association between cohorts (het p=0.13), with **the odds of VL suppression increasing until 7-8 years, and then decreasing rapidly in adolescence in CHIPS, whilst remaining approximately constant in adolescents in Mulago (Fig 4(a)).**
  - there were smaller gains in weight with increasing age at ART initiation throughout childhood and adolescence in Mulago, whereas there was little variation after 7 years in CHIPS (non-linearity p=0.007, het p=0.03, **Fig 4(b)**).

Figure 4: Effect of age at ART initiation on 6 month responses



Note: Adjusted odds ratios (as per Fig 2) presented relative to a child in CHIPS aged 6 years

Summary

- **Overall viral suppression, CD4% increase and weight gain were similar in both cohorts at 6 and 12 months after ART initiation, but growth responses were blunted in Ugandan children, despite their greater potential for catch-up growth than in UK/Irish children**
- **Immunological responses at very low CD4% were also poorer in Ugandan than UK/Irish children**
  - may related to poorer nutritional status and/or other environmental factors such as a lower background burden of infectious disease
- **Poorer virologic responses among UK/Irish adolescents may reflect poorer adherence**
- **Our findings highlight the importance of monitoring growth as well as weight gain over longer periods on ART in resource-limited settings**
- **Investigations to evaluate the effects of nutritional support on growth in children initiating ART in resource-limited settings are urgently needed**
- **Finally, this study has relevance for questions currently being raised about the timing of initiation of ART in resource-limited settings in both adults and children. Earlier HIV diagnosis and nutritional support are clearly required for children in Africa, and initiating ART earlier in the course of the disease may well be beneficial**

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