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Authors

Davies, Claire

Vaida, Florin

Otwombe, Kennedy

et al.

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Longitudinal Comparison of Insulin Resistance and Dyslipidemia in Children with and without Perinatal HIV infection in South Africa

Claire Davies[1,§], **Florin Vaida**[2,*], **Kennedy Otwombe**[3,4,*], **Mark F Cotton**[5], **Sara Browne**[6,*], **Steve Innes**[5,7,*]

[1]Division of Epidemiology and Biostatistics, Faculty of Medicine and Health Sciences, Stellenbosch University, South Africa

[2]Division of Biostatistics and Bioinformatics, School of Public Health, University of California, San Diego, United States

[3]Perinatal HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[4]School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

[5]Family Center for Research with Ubuntu, Department of Paediatrics and Child Health, Stellenbosch University, South Africa

[6]School of Public Health, University of California, San Diego, United States

[7]Desmond Tutu HIV Centre, University of Cape Town, South Africa

Abstract

Introduction: HIV infection is associated with insulin resistance (IR) and dyslipidemia driven by HIV-associated immune dysregulation and antiretroviral therapy (ART). Children living with perinatally-acquired HIV (CHIV) face many decades of exposure to these factors. We evaluated the longitudinal trajectory of IR and dyslipidemia in CHIV and HIV exposed uninfected children (CHEU), compared to children HIV unexposed (CHU).

Methods: 485 children (141 CHIV, 169 CHEU, 175 CHU) aged 5–16 years previously part of CHER and P1060 trials were followed annually at Tygerberg Children's Hospital, South Africa. The primary outcome was Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). Secondary outcomes included LDL cholesterol, triglyceride-to-HDL ratio, android fat mass and

[§]Corresponding author: Claire Davies, Stellenbosch University, Cape Town, South Africa, daviesc@sun.ac.za, Telephone: +27 61 326 7974.

[*]These authors contributed equally to senior co-authorship.

Authors' Contributions

All authors meet criteria for authorship. CD, SI, FV, SB contributed to the conception and design. CD, FV and KO contributed to the statistical analysis. CD drafted the initial manuscript. SI, FV, KO, SB, MC provided substantive edits to the manuscript. All authors have read and approved the final manuscript.

Conflicts of interest and sources of funding

There are no conflicts of interest.

systolic blood pressure (SBP). Outcomes were evaluated using linear mixed effects models, adjusting for potential confounders.

Results: CHIV had 73% greater HOMA-IR than CHU in ages 6–8 years (95% CI 15.9% to 158.2%, p<0.001), and 24.7% greater HOMA-IR than CHU in ages 9–10 years (0.3% to 55.1%, p = 0.04). By 10–11 years the difference was not significant (p=0.161).

Longitudinally, triglyceride-to-HDL was 47.94% (34.50% to 62.73%, p<0.001) higher in CHIV vs CHU; LDL was 0.25 mmol/l (0.10 to 0.39, p=0.001) higher in CHIV vs CHU; Android fat mass was 11.57% (−21.11% to −0.87%, p=0.035) lower in CHIV than CHU. No significant difference in SBP was found. CHEU and CHU had similar outcomes.

Conclusions: Early-treated CHIV have elevated insulin resistance which resolves with time. Triglyceride-to-HDL ratio and LDL cholesterol were elevated into puberty. CHIV should be monitored for IR, dyslipidemia and subclinical cardiovascular disease.

Keywords

HIV; Children; antiretroviral therapy; ART; insulin resistance; dyslipidemia; HOMA-IR

Introduction

Mortality in children living with perinatally-acquired HIV (CHIV) is decreasing owing to the success of antiretroviral therapy (ART), however an increased risk of non-communicable diseases is anticipated (1,2). Insulin resistance (IR) and dyslipidemia increase the risk of heart disease, stroke and type II diabetes (3), through obesity, elevated triglycerides, low high-density lipoprotein (HDL), impaired fasting glucose and elevated systolic blood pressure. Elevated low-density lipoprotein (LDL) is independently associated with increased atherosclerotic heart disease (4). IR indicates an impaired insulin response of target organs such as the liver, muscles and adipose tissue (5). IR and dyslipidemia are important components of the metabolic syndrome. The metabolic consequences of IR include elevated inflammatory markers and endothelial dysfunction (5). HIV infection is associated with IR and dyslipidemia (6–10). Contributory factors include persistent HIV-induced immune activation (11), co-infections such as hepatitis C and specific antiretrovirals (ARV) such as protease inhibitors and nucleoside reverse transcriptase inhibitors (12,13). This is alongside the traditional risk factors for IR, such as family history, tobacco smoke exposure (14), diet and physical inactivity (15).

Multiple studies report cross-sectional metabolic abnormalities in CHIV (6,16–23). However, there are few longitudinal studies (13,24–27) and none with an appropriate comparison group. Only one cross sectional study has been conducted in sub-Saharan Africa (21), where 88% of CHIV reside (28).

Our longitudinal cohort includes the first children globally to start ARVs soon after birth with minimal HIV disease and preserved CD4 counts (CHER trial (29,30)). Early ARV therapy (ART) is now standard-of-care globally and longitudinal data collection from this unique cohort offers a rare window into the likely future of the world’s early-treated CHIV generation. Early-treated CHIV differ from their predecessors as they have largely been

spared cumulative organ damage due to repeated opportunistic and intercurrent infections. However, they face many decades of cumulative ART exposure and HIV-associated immune activation. Further, as IR and dyslipidemia likely vary in genetic susceptibility, pubertal timing and diet, this unique South African cohort allows study of IR and dyslipidemia in early-treated CHIV in Sub-Saharan Africa.

We include two participant groups from the same local communities:– HIV unexposed (CHU); HIV exposed uninfected children (CHEU) (through vertical transmission prevention programmes). CHEU experience intermediate morbidity (31) between CHIV and CHU, suggesting HIV-related immune dysfunction early in life. These groups allow us to undertake valid comparisons within a population with high background rates of obesity, cardiovascular disease and diabetes (32). Our primary comparison was between CHIV and CHU, with a secondary comparison between CHEU and CHU. We chose CHU as the control group in both comparisons as they are unaffected by HIV, therefore representing the most accurate reflection of the effect of HIV on IR and dyslipidemia in this population.

We examined the longitudinal trajectory of metabolic markers, represented by the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), LDL cholesterol, triglyceride-to-HDL ratio, android fat mass and systolic blood pressure (SBP).

Methods

Setting and design

This longitudinal study includes children followed at the Family Centre for Research with Ubuntu (FAMCRU) (Stellenbosch University and Tygerberg Children's Hospital) from March 2014 to March 2020. The study was approved by Stellenbosch University's Health Research Ethics Committee (Federal Wide Assurance Number: 00001372; Institutional Review Board Number: IRB0005239; Project approval number N12/11/076). Ongoing approval included annual data and participant safety review. Children had previously participated in the Children with HIV Early antiRetroviral (CHER) trial and P1060 clinical trial (29,30,33) along with CHEU and CHU controls from the same communities. The CHER trial compared early time limited ART to deferred ART in infants with perinatal HIV 6–12 weeks of age. First-line ART was lopinavir-ritonavir, zidovudine and lamivudine. The IMPAACT P1060 trial compared nevirapine to lopinavir-ritonavir as a third antiretroviral, with zidovudine and lamivudine in CHIV between 6 months and 3 years of age. Thus all CHIV initiated ART in early childhood and historical clinical data was available since birth.

Exposure and Outcomes

The following cardiometabolic metrics were measured annually: fasting insulin, glucose and lipogram; extensive anthropometry (34); manual blood pressure (average of 3 measurements after minimum 15 minute rest using a manual sphygmomanometer); and dual-energy X-ray absorptiometry, DXA (Discovery DXA: Hologic, Mississauga, Ontario). CHIV were seen 3-monthly for clinical care and had largely sustained viral suppression, preserved CD4 and minimal clinical HIV disease.

The primary comparison was between CHIV and CHU, with a secondary comparison between CHEU and CHU.

The primary outcome was HOMA-IR, calculated according to the formula: {fasting insulin (microU/L) x fasting glucose (mmol/L)}/22.5.

LDL cholesterol, triglyceride-to-HDL ratio, DXA android fat mass (a metric of abdominal trunk fat), and SBP, were assessed independently as secondary outcomes. Android fat mass was selected as the indicator of visceral adiposity given DXA's ability to quantitatively distinguish abdominal fat from other soft tissues, and is predictive of an impaired metabolic profile (35). Metrics that use a ratio of visceral to subcutaneous fat (waist-hip circumference ratio; android-gynoid fat ratio; trunk-limb fat ratio) were excluded given their potential distortion by lipoatrophy in CHIV due to cumulative ART drug toxicities. BMI was excluded given the lack of differentiation between fat and lean mass, and visceral and subcutaneous fat. We conducted separate sub-analyses of triglycerides and HDL-cholesterol to determine if the triglyceride-to-HDL ratio was driven by triglycerides or HDL cholesterol.

Inclusion and exclusion criteria

All children with laboratory measurements of metabolic indicators over the 6 year period were eligible for inclusion. Information on metabolic indicators was collected at routine annual clinic appointments. Due to resource limitations and missed clinic appointments this was not always possible, thus children have varying numbers of data and timepoints. We excluded children with insulin levels above 20mIU/L for children <8 years old and 25mIU/L for children >8 years old from the HOMA-IR analysis given that this was likely an undeclared non-fasting state (36).

Statistical Analysis

We compared baseline characteristics between groups using the Chi-squared test for categorical variables and the F-test for quantitative variables. Age, height and Tanner stage at entry are as at first HOMA-IR measurement, since HOMA-IR was typically measured at the first study visit. Descriptive analyses included graphs of the mean outcome by children's age and HIV group.

The primary outcome was HOMA-IR, log-transformed due to skewness. The results were back-transformed, reported as relative mean percentage differences between groups. Log-HOMA-IR was modelled as a function of group and child's age using linear mixed effects models with child-specific random effects. We considered three models: random intercept only; random intercept and random height slope; and random intercept and random continuous-age slope, and chose the model with minimum Akaike information criterion (AIC) (37). In the mean response model, age was treated as a categorical variable, accounting for the expected non-linear decline in HOMA towards the end of puberty (38). Significance was declared at level α=0.05.

Confounders were assessed using a conceptual causal model, represented by a directed acyclic graph (DAG, Supplementary Figure 1). Gender was included as an *a priori* confounder; pubertal progression reflected by Tanner stage (39,40), ethnicity, height

(continuous variable) and family history of cardiovascular disease and diabetes (binary) were potential confounders. Traditional IR and dyslipidemia risk factors such as diet, breastfeeding status and tobacco smoke exposure (41,42) were excluded as are strongly influenced by HIV status in our setting and may lie on the causal pathway. As Tanner staging was missing a number of measurements (29%), we applied the following rules to fill in missing measurements: children <8 years old were assigned Tanner stage 1 (43,44) with children spending a maximum of 2 years in any one stage (45). This reduced missingness to 16%. Ethnicity was defined as “Black” or “Mixed”. The mixed ancestry group includes Khoi, San, Malay, European and African ancestry, unique to the Western Cape (46). Interaction effects considered for inclusion were age by height, HIV group by age, and gender by HIV group.

The mean model included HIV group (3 levels), gender, and age, as variables of interest. Interaction effects were included if significant at 0.05 level. Potential confounders were included if significant at 0.20 level using the likelihood ratio test (LRT) in backward model selection. The final model was fitted using restricted maximum likelihood.

Since ethnicity distribution differed across HIV groups, we checked if inclusion of ethnicity changed the coefficient of interest by >10% in sensitivity analyses.

Similar models were built for all secondary outcomes. Triglyceride-to-HDL ratio and android fat mass were log-transformed prior to analysis and reported after back-transformation. LDL cholesterol and SBP did not require transformation, and adjusted mean differences between groups are reported. Given that gender has a strong impact on android fat mass during puberty, gender interactions with Tanner stage, age and HIV group were considered for this outcome. We also conducted a sensitivity analysis comparing CHIV to CHEU. Statistical analysis was performed using RStudio (47).

Results

Characteristics of children

The cohort comprised 485 children (141 CHIV, 169 CHEU, 175 CHU). Children had recorded metabolic indicator measurements between the ages of 4.6 and 16.3 years old.

At baseline (Table 1), CHIV had their first HOMA measurement at a younger age than CHEU and CHU, and were therefore shorter in height. The median (IQR) follow-up time was 4.0 (3.0, 5.0) years among CHIV, 2.0 (1.0, 2.9) years among CHEU and 2.9 (1.1, 3.0) years among CHU. CHU had more prevalent family history of cardiovascular disease than CHIV ($p=0.031$). The proportion of Mixed race vs. Black children differed across HIV groups ($p<0.001$).

The unadjusted progression of all outcomes (HOMA-IR, android fat mass, triglyceride-to-HDL ratio, LDL cholesterol and systolic BP) by age is shown in Supplementary Figure 2. Supplementary Figure 3 shows the proportion of CHIV with viral suppression over time.

HOMA-IR

Unadjusted HOMA-IR increased slightly with children's age (Supplementary Figure 2). In multivariable analysis (Table 2), in the comparison between CHIV and CHU, the interaction between group and age was significant (p<0.001), with CHIV having a significantly greater HOMA-IR in age groups 6–8 years (73%, 95% CI 15.9% to 158.2%, p<0.001) and 9–10 years (24.7%, 95% CI 0.3% - 55.1%, p = 0.04). By 10–11 years, the difference was not significant (p=0.161). Stratum specific estimates are adjusted using the Holm method. For CHEU versus CHU, there was no significant difference in HOMA-IR between groups in all age groups. Age stratum-specific results are presented for comparison purposes. Figure 1 shows the impact of age and HIV group on each outcome, derived from the linear mixed models.

Android Fat Mass

Unadjusted android fat mass increased with age (Supplementary Figure 2). After adjusting for gender, height, age group, ethnicity, Tanner stage and the interaction between Tanner stage and gender, the mean android fat mass was 11.57% lower in CHIV than CHU (95% CI –21.11% to −0.87%, p = 0.035, see Table 3). No significant difference was found between CHEU and CHU. Ethnicity was included in the model as sensitivity analysis showed that its inclusion changed the coefficient of interest by >10%.

Triglyceride-to-HDL ratio

Descriptive graphs (Supplementary Figure 2) revealed that triglyceride-to-HDL ratio remained relatively flat with increasing age. The mixed effects model (Table 4) revealed that, after adjusting for gender, height, age group and Tanner stage, the mean triglyceride-to-HDL ratio was 47.94% greater in CHIV than CHU (95% CI 34.50% to 62.73%, p<0.001). No significant difference was found between CHEU and CHU. Sub-analysis revealed that the higher triglyceride-to-HDL ratio in CHIV was driven by higher triglycerides alone (49.3% greater in CHIV vs CHU, 95% CI 39.2% to 60.2%, p<0.001). No significant different in HDL cholesterol was found between CHIV and CHU (p=0.478)

LDL Cholesterol

LDL cholesterol decreased slightly with increasing age in descriptive graphs (Supplementary Figure 2). After adjusting for age group, height, Tanner stage, ethnicity and gender, mean LDL cholesterol was 0.25 mmol/l greater in CHIV than CHU (95% CI 0.10 to 0.39, p=0.001, Table 4). No significant difference was found between CHEU and CHU.

Systolic Blood pressure

SBP increased with age in descriptive graphs. No significant differences in SBP were found between CHIV and CHEU versus CHU, after adjusting age group, height and gender (Supplementary Table 1).

Sensitivity analysis comparing CHIV directly to CHEU revealed similar results (Supplementary Table 2).

Discussion

Statement of principal findings

Despite early ART and after adjusting for potential confounders, longitudinal analysis demonstrated that Triglyceride-to-HDL ratio and LDL Cholesterol remained significantly elevated into puberty in CHIV compared to CHU, despite a lower android fat mass. Longitudinal comparison of HOMA-IR showed a significant increase in CHIV versus CHU between 6 and 10 years which resolved with time.

Public Health implications

Prior to 2007, WHO guidelines recommended delaying ART initiation in infants with perinatally-acquired HIV until necessitated by advancing HIV disease. The CHER trial changed this treatment approach (29,30), and since 2008/2009 all ART programs have instituted immediate ART for infants with perinatally-acquired HIV, irrespective of CD4 or clinical evidence of HIV disease. Previous generations of CHIV have grown up with extensive organ damage from opportunistic infections, with their outcomes distorted by survivor bias. The current generation of CHIV about to enter puberty display a very different chronic disease pattern since they have been spared this organ damage, but have accumulated extensive ART exposures. Being the oldest homogenous group of early-treated African CHIV, our cohort provides a unique window onto the future of the current African generation of early-treated CHIV. In addition, this study isolates the effects of HIV and cumulative ART exposure on IR and dyslipidemia, without the effects of opportunistic infections and unsuppressed HIV. Our data could therefore serve as a baseline for future investigation IR and dyslipidemia in early-treated CHIV. This is particularly significant given the impending change in ART to replace lopinavir-ritonavir and efavirenz with integrase inhibitors, principally dolutegravir (DTG) and to replace zidovudine with tenofovir alafenamide (TAF). Both DTG and TAF are associated with excessive weight gain in persons living with HIV and potentially IR and dyslipidemia (48–51). Our findings mandate close surveillance of metabolic indicators in children transitioning to DTG. Optimally, this early-treated African CHIV cohort should continue close follow-up as they transition to DTG containing regimens to better understand factors leading to weight gain and potentially IR and dyslipidemia in well controlled paediatric populations.

Comparison with other studies

This is the first longitudinal study comparing measures of IR and dyslipidemia in early-treated CHIV to uninfected children in sub-Saharan Africa, making this an important contribution to current understanding of CHIV.

Comparisons with our study depend on the age range of the children being studied. Our findings are in line with two cross-sectional Sub-Saharan studies: Dirajlal-Fargo *et al* (22) studied CHIV, CHEU and CHU aged 2–10 years in Uganda, and found higher HOMA-IR amongst CHIVs, and no difference in HOMA-IR between CHEU and CHU children. Similar to our findings, in older CHIV, Frigati *et al* (21) studied South African youth with a median age of 12.1 years (IQR aged 11–14 years) and found no difference in IR between CHIV and

age-matched HIV-uninfected youth after adjusting for age, sex, family history of diabetes, BMI z-score, Tanner stage and waist circumference.

Two previous studies have compared insulin resistance in CHIV at different time points/ age groups: Beregszaszi (24) examined HOMA-IR in CHIV aged 2–18 years (median age 10 years) and found 13.2% of children had IR. Prospective follow-up showed a doubling of children with IR after 2 years. They attributed this increase in insulin resistance to puberty, especially in children with a severe underlying HIV disease (CDC classification B or C). Reis et al (17) examined CHIV among children (<10 years), early adolescents (10–14 years) and late adolescents (15–19 years) in a cross-sectional analysis. They found a statistically higher proportion (p=0.034) of insulin-resistant children (33.3%) compared with adolescents (12.5%). They used different definitions of insulin resistance for children vs. adolescents, in line with literature (52).

Other cross-sectional studies also show evidence of metabolic disturbances in CHIV, however comparisons with our study are difficult where no control groups were used (53); the age-range encompasses a wide age range (6), or only ART-naïve children are included (19).

Our study also supports other studies showing that CHIV have a greater triglyceride-to-HDL ratio and LDL cholesterol (54). This may be a result of both the HIV (which may affect fatty acid metabolism (55)) and ART (56).

Abdominal adiposity is a known predictor of IR, dyslipidemia and cardiovascular disease, with the expectation that increased abdominal fat indicates greater metabolic risk. We found weak evidence of lower abdominal fat in CHIV compared to CHU. However, in people living with HIV, hepatic steatosis (Non-Alcoholic Fatty Liver Disease) occurs frequently in lean individuals (57). In our cohort hepatic steatosis prevalence is higher in lean CHIV (8%) than lean CHU (0%) (58) . Hepatic steatosis is more strongly associated with cardiovascular disease than general visceral fat (59). Therefore, we speculate that lower overall abdominal fat with elevated hepatic fat in people living with HIV may indicate higher rather than lower cardiovascular disease risk.

CHEU are believed to have increased morbidity and mortality than CHU (60,61). Our study showed no significant difference between CHEU and CHU across all metabolic indicators. This is in line with data from Dirajlal-Fargo et al. (22). However, small real differences between CHEU and CHU may not have been detectable with the available sample sizes.

Strengths and limitations of the study

Strengths include the prospective design and longitudinal nature, the regular follow-up of early-treated CHIV in care and a suitable comparison group. Glucose and insulin levels were assayed in a centralised laboratory to standardise measurements.

Several limitations should be considered. Firstly, there are large differences in the number of outcome measurements per child, indicating missingness in metabolic measures. This could result from travel in and out of the province with family (common in our context), and in CHU not attending clinic visits when feeling healthy. However, mixed effects models

address missing data well. In addition, CHIV had more visits than CHEU and CHU owing to standard of care. We also had a relatively short median period of follow-up, especially amongst CHEU and CHU (2.0 and 2.9 years respectively).

The hyperinsulinemic-euglycemic clamp technique is the gold standard for assessing insulin sensitivity (62), but requires intravenous infusions. This time-consuming, labour-intensive technique is unsuitable for children. Instead, HOMA-IR is a robust surrogate index that estimates insulin sensitivity and β-cell function from fasting plasma insulin and glucose concentrations and has been widely used in epidemiological studies, especially in children (62,63).

Our study included different proportions of Mixed race vs. Black children across HIV groups ($p<0.001$). However, ethnicity was only a significant confounder for LDL Cholesterol ($p = 0.016$). The mixed ancestry group has high rates of cardiovascular disease and diabetes (46), which are consistent with high levels of LDL cholesterol. Our study also indicated that CHU were more likely to have a family history of cardiovascular disease ($p = 0.031$), however this could be owing to historical shorter life expectancy in families with HIV. Our study also included children on either lopinavir-ritonavir (82%) or an NNRTI (Nevirapine/ Efavirenz) (20%). Therefore, our results are only generalisable to children on these regimens. Data on birthweight had significant missingness (CHIV: 37% missing; CHEU: 87%; CHU: 86%); thus we were unable to adjust for birthweight in the analysis. However, the CHER trial had strict entry criteria with the exclusion of any child with a birthweight <2kg (29), and median birthweight for CHIV in our cohort was 3.1kg.

Generalisability

These findings are generalisable to CHIV in sub-Saharan Africa, where 88% of the world's CHIV reside (28). Our data may not extrapolate to African immigrants living in developed countries, whose environment and exposures are very different. Also, as very early treatment close to birth is now the norm, new paediatric cohorts with even earlier ART initiation must be studied.

Our dataset contained children with study visits ranging between 5 and 16 years old and from Tanner Stage 1 to Stage 5. However, as the median age at last visit was 11.9 (IQR 10.7, 13.5) years, at the last measurement only 8% of children had reached Tanner Stages 4 or 5. Therefore, our findings are drawn primarily from the pre-pubertal and early pubertal period. Further research is necessary to evaluate insulin sensitivity at the end of puberty in this population. Nonetheless, multiple studies have shown that childhood IR and dyslipidemia predicts adult IR and dyslipidemia (64,65).

Conclusion

Early-treated CHIV have elevated insulin resistance in the 6–10 year ages compared to CHU, which resolve with time. Triglyceride-to-HDL ratio and LDL cholesterol were elevated into puberty, in comparison to CHU. Early-treated CHIV should be monitored for IR and dyslipidemia, and subclinical cardiovascular disease, especially with increasing DTG use amongst CHIV.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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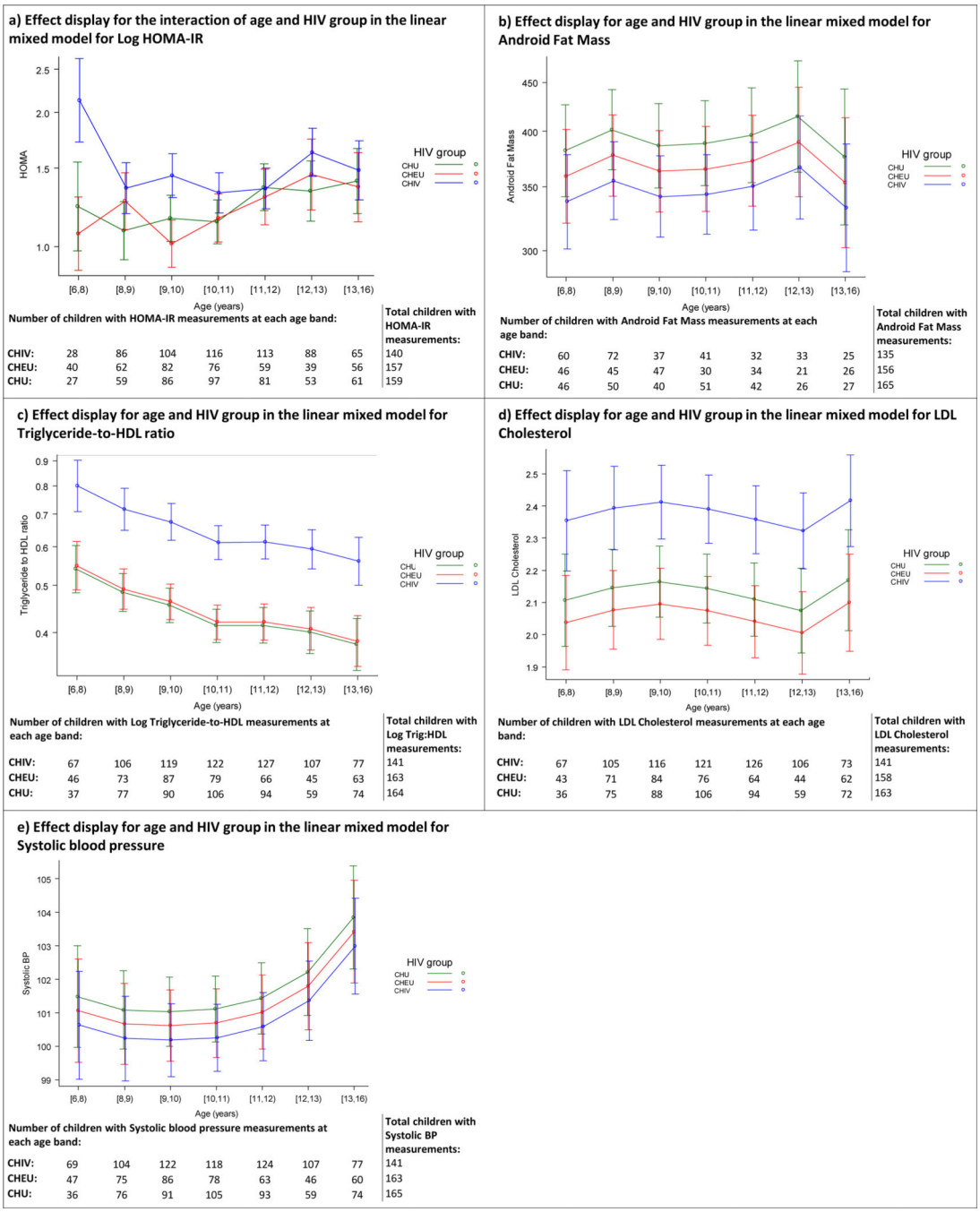

Figure 1:

Effect display of age and HIV group for each metabolic indicator from linear mixed models Each figure is a graphical depiction of the terms from the linear mixed models, after adjusting for gender, height, age group, and, where significant, Tanner stage and ethnicity. HOMA-IR, android fat mass, and triglyceride-to-HDL ratio were log-transformed prior to analysis and graphed with back-transformation. The figures have been constructed using the *Effects* package in R, and therefore the analysis only reflects the fixed effects of the model (not random effects), and assumes that other variables in the model are constant and take

on their average values. 95% Confidence intervals are shown, with standard errors computed from the covariance matrix of the fitted regression coefficients.

CHU: Children who are HIV unexposed; CHEU: Children who are HIV exposed uninfected; CHIV: Children living with perinatally-acquired HIV; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance

Table 1:

Baseline characteristics of the cohort, by HIV group. Age, height and Tanner stage at entry are as at first HOMA measurement. Median (IQR) and p-values (Chi-squared/ F-test) are reported.

	CHIV (n = 141)	CHEU (n = 169)	CHU (n = 175)	p-value
Age at entry (yr) – median (IQR)	8.67 (8.42, 9.52)	9.31 (8.15, 10.58)	9.41 (8.29, 10.32)	<0.001
Gender:				
Male, n (%)	64 (45%)	83 (49%)	98 (56%)	0.156
Female, n (%)	77 (55%)	86 (51%)	77 (44%)	
Height at entry (cm) – median (IQR)	127 (121, 130)	129 (124, 138)	131 (125, 138)	<0.001
Tanner stage at entry:				
Tanner stage 1/2, n (%)	125 (89%)	126 (80%)	108 (68%)	0.163
Tanner stage 3–5, n (%)	1 (1%)	6 (4%)	5 (3%)	
Tanner stage - missing at entry (%) †	14 (10%)	25 (16%)	46 (29%)	
Tanner stage - missing longitudinally (of all visits)	14%	14%	18%	
Ethnicity:				
Black, n (%)	128 (91%)	150 (89%)	91 (52%)	<0.001
Mixed, n (%)	13 (9%)	19 (11%)	84 (48%)	
Family history of cardiovascular disease				
Yes, n (%)	13 (9%)	18 (11%)	30 (17%)	0.031
No, n (%)	117 (83%)	121 (72%)	114 (65%)	
Missing, n (%) †	11 (8%)	30 (18%)	31 (18%)	
Family history of diabetes				
Yes, n (%)	34 (24%)	35 (21%)	42 (24%)	0.739
No, n (%)	96 (68%)	105 (62%)	103 (59%)	
Missing, n (%) †	11 (8%)	29 (17%)	30 (17%)	
Antiretroviral drugs				
Zidovudine, n (%)	141 (100%)	NA	NA	NA
Lamivudine, n (%)	141 (100%)	NA	NA	
Lopinavir/r, n (%)	116 (82%)	NA	NA	
Nevirapine, n (%)	27 (19%)	NA	NA	
Efavirenz, n (%)	2 (1%)	NA	NA	
Median age at ART initiation (months) – median (IQR)	4.0 (1.8, 7.9)			
ART regimen switch required	10 (7%)			

CHU: Children who are HIV unexposed; CHEU: Children who are HIV exposed uninfected; CHIV: Children living with perinatally-acquired HIV; NNRTI: Non-nucleoside reverse transcriptase inhibitors.

† Missing values are not included in the inferential analysis.

Table 2:

Association between HIV group and HOMA-IR using linear mixed effects model. Results show the mean percentage difference (with 95% CI) in HOMA-IR between the exposed group (CHIV/CHEU) and the unexposed group, CHU.

	CHIV vs. CHU		CHEU vs. CHU	
	Estimated mean percentage difference (95% CI)	**p-value**	**Estimated mean percentage difference (95% CI)**	**p-value**
6–8 years	73% (15.9% to 158.2%)	<0.001	−13% (−40.3% to 26.6%)	1
8–9 years	24.7% (−3.1% to 60.5%)	0.095	16.5% (−11.1% to 52.7%)	0.875
9–10 years	24.7% (0.3% to 55.1%)	0.040	−12.2% (−30.1% to 10.2%)	0.875
10–11 years	16.2% (−5.7% to 43.3%)	0.161	2% (−18.8% to 28.3%)	1
11–12 years	−0.6% (−19.8% to 23.4%)	1.000	−4.8% (−26% to 22.5%)	1
12–13 years	22.1% (−5.7% to 58.1%)	0.153	8.9% (−20.4% to 48.8%)	1
13–16 years	5.7% (−19.3% to 38.5%)	1.000	−3.1% (−27.5% to 29.5%)	1
Results of other confounders in the model				
	Mean % difference	**p-value**		
Sex: Male	−17.3% (−23.2% to −11.0%)	<0.001		
Height (per 1cm change)	2.1% (1.6% to 2.6%)	<0.001		

HOMA-IR was modelled on a logarithmic scale (base 10) given skewness, however parameter estimates and 95% CIs are back-transformed and represent the mean percentage difference in HOMA-IR compared to the stated reference. Results are after controlling for sex, height and age, and the interaction between age and HIV group. Results are Holm adjusted. Using the lowest AIC, the model with random intercept only had the lowest AIC. Models are derived in RStudio using the *nlme* package.

CHU: Children who are HIV unexposed; CHEU: Children who are HIV exposed uninfected; CHIV: Children living with perinatally-acquired HIV; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance

Table 3:

Association between HIV group and Android Fat Mass using linear mixed effects model. Results show the mean percentage difference (with 95% CI) in Android Fat Mass between the exposed group (CHIV/CHEU) and the unexposed group, CHU.

	Android Fat Mass		
	Estimated mean percentage difference (%)	***95% CI***	***p-value***
CHIV (vs. CHU)	−11.57	−21.11 to −0.87	0.035
CHEU (vs. CHU)	−6.00	−16.40 to 5.70	0.301
Height (per 1cm change)	2.79	2.22 to 3.37	<0.001
Age group: [6,8): reference	–	–	–
Age group [8,9)	5.14	−2.48 to 13.35	<0.001
Age group [9,10)	1.2	−8.46 to 11.87	
Age group [10,11)	1.77	−9.46 to 14.38	
Age group [11,12)	3.77	−10.25 to 19.97	
Age group [12,13)	8.6	−8.36 to 28.70	
Age group [13,16)	−1.52	−19.92 to 21.10	
Ethnicity - Black: reference	–	–	–
Ethnicity: Mixed	−6.38	−16.55 to 5.02	0.260
Sex: Male	−19.62	−26.59 to −11.99	<0.001
Tanner Stage I: reference	–	–	–
Tanner Stage II	−2.99	−13.28 to 8.52	0.059
Tanner Stage III	23.92	6.37 to 44.36	
Tanner Stage IV	73.55	29.59 to 132.42	
Interaction between gender and tanner stage:	–	–	–
Male : Tanner stage II	9.42	−3.76 to 24.40	<0.001
Male : Tanner stage III	−39.18	−47.72 to −29.26	
Male : Tanner stage IV	−58.31	−69.34 to −43.31	

Android fat mass was modelled on a logarithmic scale (base 10) given skewness, however parameter estimates and 95% CIs are back-transformed and represent the mean percentage difference in android fat mass compared to the stated reference. The model with random intercepts was optimal.

CHU: Children who are HIV unexposed; CHEU: Children who are HIV exposed uninfected; CHIV: Children living with perinatally-acquired HIV.

As no girls had a tanner stage of 5, we excluded all visit dates with a tanner stage of 5 (n=7), in order to include the interaction between gender and tanner stage.

Table 4:

Association between HIV group and Triglyceride-to-HDL ratio and LDL Cholesterol using linear mixed effects model. Results show the mean percentage difference (with 95% CI) in Triglyceride-to-HDL ratio between the exposed group (CHIV/CHEU) and the unexposed group, CHU, and the mean difference (mmol/l) (with 95% CI) in LDL Cholesterol between the exposed group (CHIV/CHEU) and the unexposed group, CHU.

	Triglyceride-to-HDL ratio		**LDL Cholesterol**	
	Estimated mean percentage difference (%) and 95% CI	***p-value***	***Estimated mean difference (mmol/l) and 95% CI***	***p-value***
CHIV (vs. CHU)	47.94 (34.50 to 62.73)	<0.001	0.25 (0.10 to 0.39)	0.001
CHEU (vs. CHU)	1.62 (−7.63 to 11.80)	0.740	−0.07 (−0.21 to 0.08)	0.347
Sex: Male	−6.85 (−13.84 to 0.70)	0.074	−0.11 (−0.22 to −0.00)	0.050
Height (per 1cm change)	1.29 (0.78 to 1.80)	<0.001	−0.002 (−0.009 to 0.004)	0.465
Age group: [6,8): reference	–	–	–	–
Age group [8,9)	−10.42 (−17.23 to −3.06)	0.025	0.04 (−0.04 to 0.12)	0.006
Age group [9,10)	−15.63 (−22.83 to −7.75)		0.06 (−0.04 to 0.16)	
Age group [10,11)	−23.4 (−31.14 to −14.79)		0.04 (−0.09 to 0.16)	
Age group [11,12)	−23.28 (−32.41 to −12.92)		0.00 (−0.14 to 0.15)	
Age group [12,13)	−25.75 (−36.13 to −13.68)		−0.03 (−0.21 to 0.15)	
Age group [13,16)	−29.92 (−41.29 to −16.35)		0.06 (−0.15 to 0.27)	
Tanner Stage 1: reference	–	–	–	–
Tanner Stage II	−3.46 (−9.76 to 3.29)	0.031	−0.06 (−0.13 to 0.01)	0.151
Tanner Stage III	−14.2 (−22.36 to −5.18)		−0.08 (−0.18 to 0.03)	
Tanner Stage IV	−16.02 (−28.31 to −1.61)		−0.24 (−0.41 to −0.06)	
Tanner Stage V	−10.48 (−36.24 to 25.70)		−0.22 (−0.58 to 0.14)	
Ethnicity			0.18 (0.03 to 0.32)	0.016

Triglyceride-to-HDL ratio was modelled on a logarithmic scale (base 10) given skewness, however parameter estimates and 95% CIs are back-transformed and represent the mean percentage difference in Triglyceride-to-HDL ratio compared to the stated reference. Using the lowest AIC, the Triglyceride-to-HDL model with random intercept only had the lowest AIC.

In the LDL Cholesterol model, the adjusted mean differences (in mmol/l) between HIV groups is shown. Using the lowest AIC, the model with random intercept and random slope with height had the lowest AIC.

CHU: Children who are HIV unexposed; CHEU: Children who are HIV exposed uninfected; CHIV: Children living with perinatally-acquired HIV