HIV Reports

Prevalence of Lipodystrophy and Metabolic Abnormalities in HIV-infected African Children after 3 Years on First-line Antiretroviral Therapy

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Background: Most pediatric lipodystrophy data come from high-income/middle-income countries, but most HIV-infected children live in sub-Saharan Africa, where lipodystrophy studies have predominantly investigated stavudine-based regimens.

Methods: Three years after antiretroviral therapy (ART) initiation, body circumferences and skinfold thicknesses were measured (n = 590), and fasted lipid profile assayed (n = 325), in children from 2 ARROW trial centres in Uganda/Zimbabwe. Analyses compared randomization to long-term versus short-term versus no zidovudine from ART initiation [unadjusted; latter 2 groups receiving abacavir+lamivudine+non-nucleoside-reverse-transcriptase-inhibitor (nNRTI) long-term], and nonrandomized (confounder-adjusted) receipt of nevirapine versus efavirenz.

Results: Body circumferences and skinfold thicknesses were similar regardless of zidovudine exposure ($P > 0.1$), except for subscapular and supra-iliac skinfolds-for-age which were greater with long-term zidovudine ($0.006 < P < 0.047$). Circumferences/skinfolds were also similar with efavirenz and nevirapine (adjusted $P > 0.09$; $0.02 < P < 0.03$ for waist/waist-hip-ratio). Total and high-density lipoprotein (HDL)-cholesterol, HDL/triglyceride-ratio ($P < 0.0001$) and triglycerides ($P = 0.01$) were lower with long-term zidovudine. Low-density lipoprotein (LDL)-cholesterol was higher with efavirenz than nevirapine ($P < 0.001$). Most lipids remained within normal ranges (75% cholesterol, 85% LDL and 100% triglycerides) but more on long-term zidovudine (3 NRTI) had abnormal HDL-cholesterol (88% vs. 40% short/no-zidovudine, $P < 0.0001$). Only 8/579(1.4%) children had clinical fat wasting (5 grade 1; 3 grade 2); 2(0.3%) had grade 1 fat accumulation.

Conclusions: Long-term zidovudine-based ART is associated with similar body circumferences and skinfold thicknesses to abacavir-based ART, with low rates of lipid abnormalities and clinical lipodystrophy, providing reassurance where national programs now recommend long-term zidovudine. Efavirenz and nevirapine were also similar; however, the higher LDL observed with efavirenz and lower HDL observed with zidovudine suggests that zidovudine+lamivudine+efavirenz should be investigated in future.

Key Words: HIV, Africa, children, antiretroviral therapy, lipodystrophy, lipids

(*Pediatr Infect Dis J* 2015;34:e23–e31)

The lipodystrophy syndrome, which includes central lipohypertrophy, lipoatrophy of extremities, face and buttocks, and metabolic abnormalities, has been reported among naive and experienced HIV-infected children on antiretroviral therapy (ART) in resource-rich and resource-limited settings.[1–14] Observed risk factors in children include: use of stavudine and protease inhibitors; advanced HIV disease, high viral loads and low CD4; duration of HIV infection/older age; puberty; female gender; white ethnicity; high body mass index (BMI); and rapid immunological recovery post-ART.[1,2,4,6,8,13–18]

Much lipodystrophy data in children come from middle-income/high-income countries, whereas >90% of HIV-infected children live in sub-Saharan Africa[19] where underlying malnutrition, micronutrient deficiencies, co-infections and advanced HIV disease are more prevalent. Lipodystrophy studies specifically among sub-Sarahan African children are thus needed. Two recent cross-sectional studies in Uganda and Tanzania reported clinically ascertained lipodystrophy in 27–34% children, although most cases were mild[13,14]; a third cross-sectional randomized comparison of nevirapine versus lopinavir-containing ART reported lipodystrophy in 8.4%.[20] Importantly, most[13,14] or all[20] children had substantial stavudine exposure, which was associated with lipodystrophy,[13,14] similar to a cross-sectional study of skinfolds/circumferences in Ugandan/Zambian children.[21]

Many African ART programs are moving away from stavudine-containing regimens in children, as in adults.[22–24] Children now predominantly receive zidovudine-containing regimens, as concerns remain about tenofovir's impact on bone metabolism and renal function,[25,26] and abacavir remains expensive.[27] Like stavudine, zidovudine is a thymidine-analog nucleoside reverse transcriptase inhibitor (NRTI) so could potentially lead to lipodystrophy, albeit at lower rates.[13,14,28] Non-nucleoside reverse transcriptase inhibitors (NNRTIs) have also been associated with lipodystrophy,[1] with, if anything, higher rates in those receiving nevirapine versus efavirenz.[29,30]

Here, we investigate the contribution of zidovudine and efavirenz/nevirapine to body circumferences, skinfold thicknesses, metabolic parameters and clinically determined lipodystrophy, in randomized (zidovudine) and nonrandomized (efavirenz/nevirapine) comparisons 3 years after ART initiation in the ARROW trial.[31]

METHODS

In ARROW (ISRCTN24791884), previously untreated Ugandan/Zimbabwean children/adolescents age 3 months to 17 years, eligible for ART using World Health Organization (WHO) 2006 criteria,[32] were randomized 1:1 to clinically driven monitoring versus laboratory plus clinical monitoring for toxicity (hematology/biochemistry) and efficacy (CD4). Children were also randomized 1:1:1 in a factorial design to open-label lamivudine+abacavir+NNRTI continuously (Arm-A, no zidovudine); induction-maintenance with 4-drug lamivudine+abacavir+NNRTI+zidovudine for 36 weeks, followed by lamivudine+abacavir+NNRTI (Arm-B; short-term zidovudine) or lamivudine+abacavir+zidovudine (Arm-C; long-term zidovudine). The NNRTI (nevirapine/efavirenz) was chosen by clinicians according to local availability (varying by country) and age. Caregivers gave written consent; older children (8–17 years) aware of their HIV status also gave assent or consent following national guidelines. ARROW was approved by Research Ethics Committees in Uganda, Zimbabwe and the UK. Children were recruited from 3 centers in Uganda [Joint Clinical Research Centre, Kampala; Baylor-Uganda, Mulago and MRC/UVRI Uganda Research Unit on AIDS, Entebbe], and 1 in Zimbabwe (University of Zimbabwe, Harare).

Two centers (Joint Clinical Research Centre and Harare) undertook a metabolic sub-study with a separate protocol (approved by Research Ethics Committees in both countries) and consent/assent as above. The primary sub-study cross-sectional objective was to compare children randomized to long-term zidovudine-containing ART with short-term zidovudine-containing or nonzidovudine-containing ART in terms of prevalence of the lipodystrophy syndrome 3 years after ART initiation. At the scheduled visit 3 years (156 weeks) after ART initiation, questionnaires were completed by the caregiver and physician (same for all visits); body circumferences (waist, hip, mid-thigh, mid-upper-arm) and skinfold thicknesses (triceps, subscapular, supra-iliac, mid-thigh) were measured by 1 nurse at each site; and blood taken (no intake other than water for 6 hours prior, wherever possible) for total cholesterol and triglycerides in real-time, and in batched retrospective analysis lipid fractions [directly assayed high-density lipoprotein (HDL) and low-density lipoprotein (LDL)], glucose, total protein and albumin (Harare only). For circumferences and skinfold thicknesses, procedures were standardized with prespecified positions for 3 repeated measurements to reduce interoperator and intervisit variability, following the Anthropometric Standardization Manual,[33] using T/W callipers (Holtain limited, Crymych, UK) for skin-fold thicknesses. Waist and hip circumferences were also collected every 4–6 weeks in all ARROW children.

Analysis

Analysis used the mean of the 3 measurements at the visit nearest to 3-years from ART initiation within ±24 weeks. As no African reference data were available, Z-scores were determined using Dutch reference values and analyses focused on differences between groups.[34,35] No reference data was available for mid-thigh skinfold thickness. Weight-for-age and height-for-age were calculated using UK reference ranges.[36] Total and LDL cholesterol, triglycerides, glucose and albumin were considered abnormal according to;[37] HDL was considered abnormal if <1.04 mmol/L.[38]

Randomized ART strategy groups were compared using χ^2 or exact tests for categorical factors and one-way analysis of variance for continuous values. Randomization means these unadjusted comparisons are unbiased in expectation; there was no evidence of chance imbalances in pre-ART factors across groups ($P > 0.3$). A nonrandomized comparison of nevirapine versus efavirenz was also undertaken in children ≥3 years at ART initiation (no efavirenz

dose for <3 years at the time), adjusted for potential confounders: age at 3-year measurement, sex, center, ART-strategy randomization, calendar year of ART initiation, pre-ART CD4% and any change in NNRTI from initiation. Absolute Z-scores for waist/hip circumferences measured in all children (n = 1206) were also compared using generalized estimating equations (normal distribution, independent working correlation, closest measurement to 12-week timepoints in equally spaced windows) (models for change from baseline in the subset enrolled from May 2008 when measurements started were similar, data not shown).

Predictors of the sum of the skinfolds were considered using normal linear regression with backward elimination (exit $P = 0.05$) on the factors above plus pre-ART WHO stage; monitoring randomization; and CD4%, height and BMI for age at ART initiation, 3-years and change during the first 6 months on ART. ART-strategy randomization was included regardless of significance. Weight-for-age was not considered as it was strongly associated with height-for-age (Spearman correlation ≥0.74). Only 56% children had HIV viral load assayed at 3 years, so this was not considered. Nonlinearity in effects of continuous predictors was explored using natural cubic splines (3 knots at 10th, 50th and 90th centiles). Children were grouped by body circumference/skinfold Z-scores (7 measurements/child) using complete-linkage cluster analysis. All analyses were performed using Stata 12.1 (StataCorp). All *P*-values are two-sided. No adjustment was made a priori for multiple testing.

RESULTS

Seven hundred and eighteen ARROW children were enrolled (March 2007–October 2008) at metabolic sub-study centers; 686 were alive in follow-up 3 years later (27 deaths and 5 lost). Five hundred and ninety-two (86.3%) had 3-year measurements (remainder had measurements outside the window, or did not consent/were not approached, for example, if older children were unaccompanied). Two previously pregnant participants were excluded, leaving 590 in analyses, age median 9 years (range, 3–19).

Children had initiated ART (23.9% aged <3) with advanced disease, but recovered well (Table 1). Children randomized to Arms A, B and C had spent 3.5%, 24.8% and 96.5% child-time on zidovudine-containing ART, respectively, by the 3-year measurement. Arm A/B children >3 years at ART initiation and on nevirapine/efavirenz at 3 years had spent 99.1% and 98.1% child-time on nevirapine or efavirenz, respectively. At ART initiation and 3 years subsequently, only 5 and 2 children had BMI-for-age Z-score >2 (maximum BMI 23 and 19), respectively.

Anthropometric Measurements

After 3 years on ART, few children had measurements ≤5th percentile of Dutch reference ranges for central measures [0/576 (0.0%) waist circumference; 34/578 (5.9%) hip; 33/577 (5.7%) subscapular and 16/578 (2.8%) supra-iliac skinfold thickness]. Substantial proportions were ≤5th percentile for extremities [402/576 (69.8%) mid-thigh and 190/579 (32.8%) mid-upper arm circumference; 144/578 (24.9%) triceps skinfold thickness]. However, proportions were similar in children receiving long-term zidovudine (71.2%, 32.8%, 22.1%, respectively) and not receiving long-term zidovudine (ie, receiving long-term abacavir; 69.1%, 32.8%, 26.3% respectively; $P > 0.3$); <1% measurements were ≥95th percentile on any measure.

There were no significant differences by randomized ART-strategy, or long-term zidovudine (Arm-C) versus no or short-term zidovudine-containing combined (Arms A/B), for any body circumference ($P>0.5$; Z-score $P > 0.6$), waist-hip ratio ($P > 0.14$; Z-score, $P > 0.6$), or waist-arm ratio ($P > 0.6$) (Table 1). There were also no significant differences in skinfold thicknesses or triceps skinfold Z-score

TABLE 1. Characteristics at ART Initiation and at 3-year Measurement

	Total N = 590	JCRC N = 265	Harare N = 325
Male	300 (50.8%)	129 (48.7%)	171 (52.6%)
At ART initiation			
Age <3 years	141 (23.9%)	77 (29.1%)	64 (19.7%)
CD4: median (IQR)	318 (168, 583)	362 (181, 636)	305 (160, 540)
CD4%: median (IQR)	12 (7, 16)	14 (8, 18)	11 (7, 15)
Weight-for-age Z-score: median (IQR)	−2.1 (−3.2, −1.2)	−1.7 (−2.8, −1.0)	−2.5 (−3.6, −1.5)
Height-for-age Z-score: median (IQR)	−2.4 (−3.3, −1.6)	−2.0 (−2.9, −1.1)	−2.8 (−3.5, −1.9)
BMI-for-age Z-score: median (IQR)	−0.8 (−1.6, 0.0)	−0.7 (−1.5, 0.0)	−0.8 (−1.8, 0.0)
WHO stage			
1/2	174 (29.5%)	135 (50.9%)	39 (12.0%)
3	347 (58.8%)	97 (36.6%)	250 (76.9%)
4	69 (11.7%)	33 (12.5%)	36 (11.1%)
Randomized treatment strategy			
Arm A (3TC/ABC/NNRTI throughout)	195 (33.1%)	89 (33.6%)	106 (32.6%)
Arm B (36 weeks ZDV)	201 (34.1%)	90 (34.0%)	111 (34.2%)
Arm C (long-term ZDV)	194 (32.9%)	86 (32.5%)	108 (33.2%)
Allocated monitoring strategy			
Laboratory and clinical monitoring (routine CD4 monitoring)	290 (49.2%)	130 (49.1%)	160 (49.2%)
Clinically driven monitoring (no CD4 monitoring)	300 (50.8%)	135 (50.9%)	165 (50.8%)
Three-year measurement			
Years on ART: median (IQR)	3.0 (3.0, 3.0)	3.0 (3.0, 3.0)	3.0 (2.8, 3.1)
Age: median (IQR)	9.7 (6.0, 12.6)	8.9 (5.6, 12.4)	10.6 (6.5, 12.7)
ART combination			
3TC+ABC+NVP	210 (35.6%)	56 (21.1%)	154 (47.4%)
3TC+ABC+EFV	177 (30.0%)	119 (44.9%)	58 (17.8%)
3TC+ABC+ZDV	190 (32.2%)	88 (33.2%)	102 (31.4%)
Other NVP-containing first-line	1 (0.2%)	0 (0.0%)	1 (0.3%)
None*	1 (0.2%)	1 (0.4%)	0 (0.0%)
2NRTI+ALV	10 (1.7%)	1 (0.4%)	9 (2.8%)
EFV+ALV	1 (0.2%)	0 (0.0%)	1 (0.3%)
Tanner stage			
1	109 (18.5%)	30 (11.3%)	79 (24.3%)
2	76 (12.9%)	32 (12.1%)	44 (13.5%)
3	49 (8.3%)	19 (7.2%)	30 (9.2%)
4-5	48 (8.1%)	29 (10.9%)	19 (5.8%)
>=10 years but not staged	2 (0.3%)	1 (0.4%)	1 (0.3%)
<10 years at 3-year measurement	306 (51.9%)	154 (58.1%)	152 (46.8%)
CD4: median (IQR)	780 (543, 1092)	850 (575, 1209)	750 (533, 1019)
CD4% >10% above pre-ART	525 (89.0%)	226 (85.3%)	299 (92.0%)
Weight-for-age Z-score: median (IQR)	−1.3 (−2.1, −0.6)	−1.2 (−1.9, −0.5)	−1.5 (−2.1, −0.8)
Height-for-age Z-score: median (IQR)	−1.7 (−2.3, −1.0)	−1.3 (−2.0, −0.6)	−1.9 (−2.5, −1.3)
BMI-for-age Z-score: median (IQR)	−0.5 (−1.1, 0.1)	−0.5 (−1.1, 0.0)	−0.5 (−1.1, 0.1)
HIV viral load			
No value available	240 (40.7%)	98 (37.0%)	142 (43.7%)
<80 (% of those with values)	267 (76.3%)	125 (74.9%)	142 (77.6%)
80–399 (% of those with values)	21 (6.0%)	11 (6.6%)	10 (5.5%)
400––- (% of those with values)	62 (17.7%)	31 (18.6%)	31 (16.9%)

*Voluntary decision since week 133

ABC indicates abacavir; 3TC, lamivudine; ZDV, zidovudine; NVP, nevirapine; EFV, efavirenz; ALV, lopinavir/ritonavir (Aluvia); ART, antiretroviral therapy; IQR, interquartile range.

($P > 0.1$), but subscapular and supra-iliac skinfold Z-scores were slightly but significantly higher in those receiving zidovudine long-term (Arm-A/B vs. C $P = 0.006$, $P = 0.02$, respectively).

There were also no significant differences in skinfold thickness, hip, mid-thigh and mid-upper arm body circumferences and their Z-scores, or waist-arm ratio, between efavirenz-containing and nevirapine-containing regimens (adjusted $P > 0.09$; Table 1), but waist circumference (and Z-score) and waist-hip ratio were slightly but significantly lower in those receiving efavirenz in the metabolic substudy ($P = 0.04$, 0.03 and 0.02, respectively; waist-hip ratio Z-score marginally lower, $P = 0.06$). In all 1206 children, there were no differences in waist and hip circumference Z-scores between children receiving efavirenz or nevirapine in the long-term (Figure 1). Hip circumference was slightly but significantly higher in those receiving efavirenz at ART initiation and then over the first 60 weeks on ART, leading to a significant difference overall

($P = 0.01$) (driven by greater nevirapine use in younger children). However, there was no evidence of difference overall in waist circumference or waist-hip ratio ($P = 0.13$ and 0.12, respectively), and no differences in waist/hip circumferences or their ratio by randomized ART-strategy ($P > 0.2$).

Cluster analysis identified 4 main groups of children: those relatively large-for-age on all measurements (relatively high Z-scores) but with higher body circumferences than skinfold thicknesses (ie, very lean, n = 103, 29.1% Arm-C); relatively large-for-age on all measurements but with higher skinfold thicknesses than body circumferences (plump; n = 70, 42.9% Arm-C); intermediate-for-age on all measurements (n = 337, 33.2% Arm-C) or low-for-age on all measurements, although typically with even lower body circumferences than skinfold thicknesses (n = 54, 25.9% Arm-C). Proportions in Arm-C did not differ significantly between the 4 groups (Arm-C vs. A/B $P = 0.17$).

At 3 years, the sum of the 4 skinfolds was significantly ($P < 0.05$) and independently higher in children receiving long-term zidovudine (Arm-C) versus no (Arm-A) or short-term (Arm-B) zidovudine [Arm-C vs. A/B adjusted difference +0.49 mm (95% confidence interval (CI), +0.02, +0.97); $P = 0.04$], girls, Ugandan children (vs. Zimbabwean) and those with higher current BMI-for-age (Table 2). In children with pre-ART height-for-age Z-score ≥3, sum-of-skinfolds 3 years after ART initiation increased significantly with higher pre-ART height-for-age ($P < 0.0001$); in children with height-for-age ≤3 pre-ART, there was no evidence of association ($P = 0.44$). Current height-for-age had no independent effect ($P = 0.29$) after adjustment for pre-ART height-for-age (Spearman correlation = 0.73). Under 10 years, there was only weak association between age and sum-of-skinfolds ($P = 0.07$); over 10 years, sum-of-skinfolds increased significantly with older age ($P < 0.0001$), likely reflecting pubertal effects.

Biochemistry

Biochemistry was available for 319 children, 256 (80.3%) known to have fasted for >6 hours (75.2% Arm-A, 78.0% Arm-B, 87.6% Arm-C; $P = 0.06$). Mean total and HDL cholesterol were significantly lower with long-term zidovudine (Arm-C, HDL 0.8 mmol/L) compared to no (Arm-A, 1.2 mmol/L) or short-term zidovudine (Arm-B, 1.2 mmol/L) (one-way analysis of variance $P < 0.0001$), with LDL similar across ART-strategy (Table 3). Mean triglycerides were 0.8 mmol/L, with no significant differences by ART-strategy; consequently the HDL/triglyceride ratio was significantly lower with long-term zidovudine (Arm-C, 1.4) than no (Arm-A, 2.1) or short-term zidovudine (Arm-B, 2.4) ($P < 0.0001$). Similarly, the total cholesterol/triglyceride ratio was significantly lower in Arm-C (5.6) than Arm-A (7.1) or Arm-B (7.5) ($P = 0.01$). Eighty-one children (25.4%) had elevated total cholesterol, fewer in Arm-C ($P = 0.008$; Table 4); 39/81 had a family history of hypertension and 13 of stroke. However, 174 (55.1%) children still had abnormally low HDL, more in Arm-C ($P < 0.0001$). Mean glucose, total protein and albumin were 4.74 mmol/L, 76.9 g/L and 40.2 g/L, respectively, with no significant differences between long-term, short-term or no zidovudine.

LDL cholesterol was significantly higher in those taking efavirenz-containing versus nevirapine-containing regimens [adjusted difference +0.44 mmol/L (95% CI, +0.18, +0.70); $P = 0.001$]; HDL was nonsignificantly lower [−0.12 mmol/L (95% CI, −0.27, +0.04)], as was albumin [−1.46 g/L (95% CI, −3.00, +0.08)]. There were no other significant biochemical differences between efavirenz-containing and nevirapine-containing groups.

Although there was weak correlation between total cholesterol and triglycerides (Spearman correlation = 0.30), pairwise correlations between lipid fractions, triglycerides and the other biochemical measurements were low (Spearman correlation <0.3). Biochemical and anthropometric measurements were uncorrelated (Spearman rho <0.2).

Physician Assessment of Changes in Body Shape Since ART Initiation
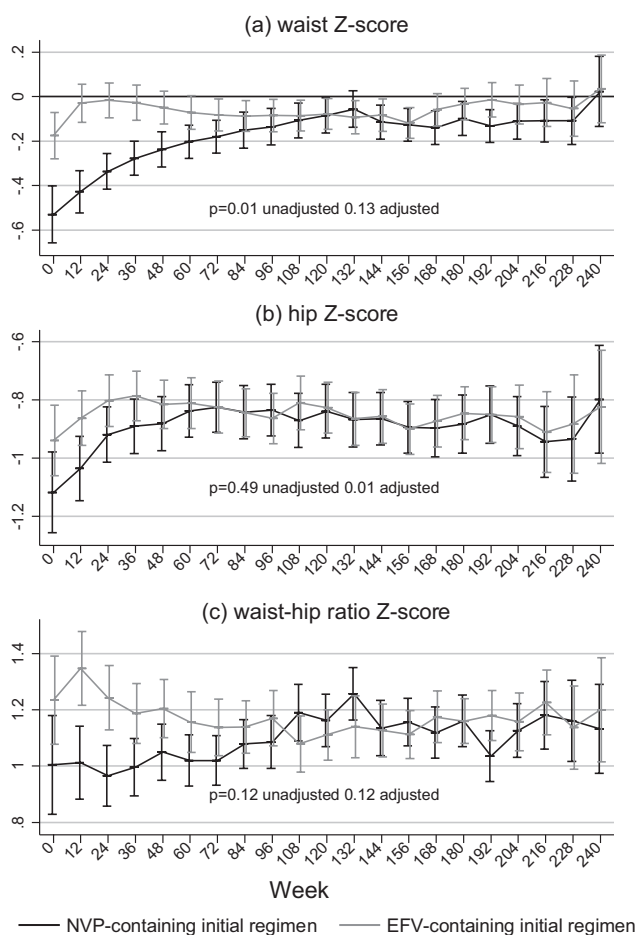
Any fat loss since ART initiation was reported in only 7/419 children (1.7%) (all mild-moderate), 4 also with more visible veins reported (not reported in any other children). Five of the 7 children reported to have any fat loss were also classified as having clinical signs/symptoms of abnormal fat wasting (all Ugandan); the other 2 children (Zimbabwean) were not. A further 3 children were also classified as having clinical signs/symptoms of abnormal fat wasting (changes in body shape data were missing). Hence in total 8/579 children (1.4%) had clinical signs/symptoms of fat wasting (Arm-A: 3/188; Arm-B: 3/198; Arm-C: 2/193), 5 grade 1 (2 Arm-A,1 Arm-B, 2 Arm-C) and the remainder grade 2. Of the 6 in Arm A/B (receiving abacavir long-term), 4 had received efavirenz, 1 nevirapine and 1 had substituted efavirenz with nevirapine for lipodystrophy.

Any fat gain since ART initiation was reported in 174/419 children (41.5%), only 1 severe (face and buttocks). Only 2 children had clinical signs/symptoms of abnormal fat accumulation reported by clinicians, both grade 1 (1 Arm-A, 1 Arm-C; both had received efavirenz, although only to week 36 in Arm-C).

Among all 1206 children/adolescents, there were only 8 ART-modifications for lipoatrophy/lipodystrophy (two <3 years on ART and 3 in the children above with clinical signs/symptoms of abnormal fat wasting). Efavirenz was substituted with nevirapine in 2 children for gynecomastia (1 Arm-A, 1 Arm-B) and 3 for lipodystrophy (1 Arm-A, 2 Arm-B). Two children substituted zidovudine with nevirapine for lipoatrophy in Arm-C; and another Arm-C child, already off zidovudine because of anemia, substituted stavudine with tenofovir.

(a) waist Z-score

p=0.01 unadjusted 0.13 adjusted

(b) hip Z-score

p=0.49 unadjusted 0.01 adjusted

(c) waist-hip ratio Z-score

p=0.12 unadjusted 0.12 adjusted

Week

——— NVP-containing initial regimen   ——— EFV-containing initial regimen

Note: NVP=nevirapine, EFV=efavirenz, ART=antiretroviral therapy

FIGURE 1 Long-term impact of efavirenz versus nevirapine-based ART on waist and hip circumferences in children initiating ART aged over 3 years

DISCUSSION

Detailed investigation of a large, nonblinded group of children randomized to first-line ART containing long-term, short-term or no zidovudine, found no increased risk of lipoatrophy/

TABLE 2. Independent Predictors of the Sum of 4 Skinfold Measurements 3 Years After ART Initiation

Factor	Estimate (mm) (95% CI)	P
Allocated treatment strategy, vs. Arm A (3TC/ABC/NNRTI)*		0.13
Arm B (36 weeks ZDV)	0.1 (−1.1, 1.2)	0.87
Arm C (long-term ZDV)	1.0 (−0.1, 2.1)	0.07
Male	−3.8 (−4.7, −2.9)	<0.0001
Height-for-age Z-score at ART initiation (per unit Z-score higher)		<0.0001
Z-score at ART initiation ≤ −3	−0.3 (−1.2, 0.5)	0.44
Z-score at ART initiation > −3	1.1 (0.6, 1.7)	<0.0001
BMI-for-age Z-score at 3-year measurement	2.6 (2.1, 3.1)	<0.0001
Age at 3-year measurement (per year increase)		<0.0001
<10 years	0.24 (−0.02, 0.50)	0.07
≥10 years	1.5 (1.3, 1.8)	<0.0001
Harare	−3.4 (−4.4, −2.4)	<0.0001
Reference category: Ugandan girl, aged 10, in Arm A (3TC/ABC/NNRTI); with height-for-age −2 at ART initiation and BMI-for-age −1 three years after ART initiation	28.6 (25.4, 31.8)	<0.0001

*Arm-C versus A/B combined P = 0.04 [adjusted difference +0.49 mm (95% CI, 0.02, 0.97)].

ABC indicates abacavir, 3TC, lamivudine; ZDV, zidovudine.

Factors considered that were not included in the final model were pre-ART WHO stage, CD4% and BMI-for-age; 3-year CD4% and height-for-age; change in CD4%, height-for-age and BMI-for-age during first 6 months on ART; monitoring randomization. ART strategy randomization was included regardless of statistical significance. Weight-for-age was strongly associated with height-for-age and therefore was not considered, nor was viral load as only 56% of children had a value available.

body shape changes with long-term zidovudine use using WHO weight-band ART doses through 3 years, and generally similar impact of zidovudine+lamivudine and abacavir+lamivudine NRTI backbones. Along with reassuring data on low incidence of excess anemia with zidovudine already reported,[31] these similar lipodystrophy rates provide important reassurance where first-line pediatric regimens have changed from stavudine to zidovudine, as there have been concerns that zidovudine (also a thymidine analogue) could still cause lipoatrophy/lipodystrophy, albeit at lower rates than stavudine. The substantially lower potential for lipoatrophy from zidovudine is supported by reversal of signs in Thai children switched from stavudine to zidovudine-containing regimens.[39] Efficacy is also important when considering the relative merits of different pediatric ART regimens. However, ARROW children receiving long-term zidovudine were all on triple NRTI maintenance regimens. While lipoatrophy/body shape changes on this regimen are plausibly generalizable to standard long-term zidovudine+lamivudine+NNRTI regimens, poorer virologic response with 3NRTI regimens over the longer-term[31] is unlikely to reflect responses on zidovudine+lamivudine+NNRTI. In children, abacavir+lamivudine was virologically superior to zidovudine+lamivudine in a randomized comparison over 5 years,[40,41] but inferior to stavudine+lamivudine in a South African cohort study.[42] In adults, a meta-analysis of 9 randomized trials (n = 2159) concluded there was no virologic difference between zidovudine-containing and stavudine-containing regimens.[43] The relative virologic efficacy of stavudine-containing, zidovudine-containing and abacavir-containing NRTI backbones in children is therefore currently unclear, but will be addressed by the CHAPAS-3 trial (www.chapas3trial.org).

Overall, lipodystrophy rates among ARROW children were low compared to previous studies in African ART-treated children,[13,14,20] possibly because stavudine (as a first-line substitution) and protease inhibitor (as second-line) use was minimal. Alternatively, observed rates may highlight challenges in applying subjective lipodystrophy definitions when children's body shapes are changing, given low clinical suspicion without stavudine/protease inhibitors. As lipodystrophy has rarely been assessed blinded to ART (nor did we do this), it is impossible to exclude the potential for ascertainment bias, although this is less likely with skinfold and body circumference measurements. Another study limitation is that we did not assess anthropometry or metabolic parameters pre-ART,

so we could only compare children cross-sectionally after 3 years on ART (albeit based on randomized groups), rather than comparing changes from ART initiation. The relatively low pre-ART weight-for-age, which would be expected to be associated with low cholesterol and raised triglycerides, might have shifted the balance between harmful and beneficial effects of ART on anthropometric/metabolic parameters toward benefit in the short-term to medium-term.[44]

We found children receiving long-term zidovudine had significantly lower HDL and total cholesterol (likely driven by lower HDL) than those receiving NNRTI-based ART long-term, leading to substantially lower HDL/triglyceride and total cholesterol/triglyceride ratios. Lower HDL could reflect a greater tendency to dyslipidemia with long-term zidovudine, or could be because children receiving long-term zidovudine were all on 3 NRTI maintenance regimens with no NNRTI. How potentially greater risk from low HDL balances against lower risk from reduced total cholesterol/triglyceride ratio is unclear, but an abnormal HDL/triglyceride ratio has been strongly associated with coronary disease in adults, suggesting atherogenic effects.[45] We also found significantly higher LDL, and a trend toward lower HDL cholesterol, in children receiving efavirenz versus nevirapine. Increases in nonfasting HDL cholesterol were lower among adults receiving efavirenz compared with nevirapine,[46] and in a large Tanzanian cohort.[44] Although these studies found no significant differences in calculated (not measured) LDL, 1 randomized trial reported significant decreases in LDL cholesterol following switch from efavirenz-containing to nevirapine-containing ART in adults with dyslipidemia.[47] No child in this substudy was receiving zidovudine+lamivudine+efavirenz (used very rarely in ARROW as a toxicity substitution), but, together, these results suggest that this combination could more likely lead to disturbed lipid profiles over the longer-term. As this regimen is commonly used globally, and is likely to become even more so given recent licensing of efavirenz in children <3 years[48] and suggestion of improved virologic suppression versus nevirapine,[49,50] this should be investigated in future studies. However, our findings show that such studies will need to directly measure HDL, and ideally also LDL.

Despite their statistical significance, most changes in lipids were still within the normal range. The only significant difference in graded toxicity was for total cholesterol, where 13.3% of those receiving long-term zidovudine had elevated values (all

TABLE 3. Impact of Long-term Zidovudine versus No Long-term Zidovudine (Randomized) and Efavirenz versus Nevirapine (Nonrandomized) on Body Circumferences, Skinfold Thicknesses and Lipid Parameters 3 Years After ART Initiation

Factor	Mean (SD) All	Mean (SD) no ZDV (Arm A)	Mean (SD) short-term ZDV (Arm B)	Mean (SD) long-term ZDV (Arm C)	Unadjusted p A vs. B vs. C (df = 2)	p A/B vs. C (df = 1)	Unadjusted difference C – A/B (95% CI)	p EFV vs.NVP	Adjusted difference EFV-containing - NVP-containing (Arm A/B)
Body circumferences									
Waist circumference (cm)	57.6 (6.91)	57.5 (6.57)	57.7 (6.91)	57.5 (7.26)	0.94	0.87	−0.10 (−1.3, 1.1)	**0.04**	−1.21 (−2.37, −.05)
Hip circumference (cm)	63.4 (10.2)	62.8 (9.92)	64.0 (10.51)	63.3 (10.28)	0.50	0.87	−0.15 (−1.93, 1.63)	0.88	−0.13 (−1.79, 1.53)
Mid–thigh circumference (cm)	33.6 (5.37)	33.5 (5.35)	33.8 (5.48)	33.6 (5.31)	0.83	0.92	−0.05 (−.98, 0.89)	0.31	−0.55 (−1.62, 0.52)
Mid–upper arm circumference (cm)	18.2 (2.83)	18.3 (2.87)	18.2 (2.84)	18.1 (2.77)	0.88	0.62	−0.12 (−.61, 0.37)	0.09	−0.48 (−1.03, 0.07)
Waist–arm ratio	3.2 (0.21)	3.2 (0.23)	3.2 (0.21)	3.2 (0.19)	0.77	0.62	0.01 (−.03, 0.05)	0.70	0.01 (−.05, 0.07)
Waist–hip ratio	0.9 (0.06)	0.9 (0.06)	0.9 (0.06)	0.9 (0.06)	0.15	0.84	0.00 (−.01, 0.01)	**0.02**	−0.02 (−.03, 0)
Waist circumference Z-score	−0.1 (0.62)	−0.1 (0.65)	−0.1 (0.59)	−0.1 (0.63)	0.38	0.79	0.01 (−.09, 0.12)	**0.03**	−0.17 (−.32, −.02)
Hip circumference Z-score	−0.7 (0.80)	−0.7 (0.83)	−0.8 (0.81)	−0.7 (0.77)	0.87	0.65	0.03 (−.11, 0.17)	0.80	−0.03 (−.23, 0.18)
Mid-thigh circumference Z-score	−2.4 (1.04)	−2.4 (1.17)	−2.5 (0.99)	−2.4 (0.97)	0.76	0.71	0.03 (−.15, 0.22)	0.21	−0.20 (−.5, 0.11)
Mid–upper arm circumference Z-score	−1.5 (1.03)	−1.4 (1.09)	−1.5 (0.99)	−1.5 (1.00)	0.37	0.61	−0.05 (−.22, 0.13)	0.10	−0.25 (−.54, 0.05)
Waist–hip ratio Z-score	1.0 (0.91)	1.0 (0.86)	0.9 (0.93)	0.9 (0.95)	0.66	0.90	−0.01 (−.17, 0.15)	0.06	−0.23 (−.46, 0.01)
Skinfold thicknesses									
Triceps skinfold thickness (mm)	5.7 (2.01)	5.7 (2.02)	5.7 (2.28)	5.8 (1.68)	0.84	0.56	0.10 (−.25, 0.45)	0.52	−0.20 (−.79, 0.4)
Subscapular skinfold thickness (mm)	5.3 (1.64)	5.2 (1.53)	5.2 (1.72)	5.4 (1.65)	0.27	0.11	0.23 (−.05, 0.52)	0.20	−0.27 (−.69, 0.15)
Supra-iliac skinfold thickness (mm)	4.6 (1.76)	4.5 (1.64)	4.6 (2.01)	4.7 (1.59)	0.69	0.53	0.10 (−.21, 0.4)	0.47	−0.18 (−.66, 0.3)
Mid–thigh skinfold thickness (mm)	7.2 (3.14)	7.1 (3.04)	7.2 (3.42)	7.4 (2.92)	0.55	0.28	0.30 (−.24, 0.85)	0.35	−0.41 (−1.26, 0.44)
Sum of the skin folds (mm)	22.8 (7.31)	22.5 (6.95)	22.7 (8.45)	23.3 (6.32)	0.53	0.26	0.73 (−.55, 2)	0.28	−1.07 (−3.01, 0.88)
Triceps skinfold thickness Z-score	−1.5 (0.75)	−1.5 (0.73)	−1.5 (0.80)	−1.4 (0.72)	0.26	0.11	0.11 (−.02, 0.24)	0.75	−0.03 (−.24, 0.17)
Subscapular skinfold thickness Z-score	−0.8 (0.88)	−0.8 (0.81)	−0.9 (0.83)	−0.6 (0.97)	**0.01**	**0.006**	0.21 (.06, 0.36)	0.24	−0.14 (−.38, 0.1)
Supra-iliac skinfold thickness Z-score	−1.2 (0.56)	−1.2 (0.53)	−1.3 (0.46)	−1.2 (0.68)	**0.047**	**0.02**	0.12 (.02, 0.21)	0.86	−0.01 (−.12, 0.1)
Biochemistry*									
Total cholesterol (mmol/L)	3.9 (0.98)	4.0 (0.94)	4.1 (0.97)	3.5 (0.92)	**≤0.0001**	**≤0.0001**	−0.57 (−.79, −.35)	0.15	0.25 (−1, 0.6)
HDL cholesterol (mmol/L)	1.1 (0.46)	1.2 (0.50)	1.2 (0.44)	0.8 (0.28)	**≤0.0001**	**≤0.0001**	−0.40 (−.5, −.3)	0.14	−0.12 (−.27, 0.04)
LDL cholesterol (mmol/L)	2.1 (0.73)	2.1 (0.71)	2.1 (0.70)	2.0 (0.77)	0.50	0.24	−0.10 (−.27, 0.07)	**0.001**	0.44 (.18, 0.7)
Triglycerides (mmol/L)	0.8 (0.47)	0.8 (0.50)	0.8 (0.52)	0.8 (0.40)	0.90	0.68	−0.02 (−.14, 0.09)	0.46	0.07 (−.12, 0.27)
Total cholesterol/triglyceride ratio	6.8 (5.18)	7.1 (5.27)	7.5 (5.99)	5.6 (3.81)	**0.01**	**0.004**	−1.76 (−2.97, −.55)	0.99	−0.01 (−2.11, 2.08)
HDL cholesterol/triglyceride ratio	2.0 (1.81)	2.1 (1.72)	2.4 (2.23)	1.4 (1.11)	**≤0.0001**	**≤0.0001**	−0.91 (−1.33, −.49)	0.40	−0.30 (−1.01, 0.4)
Glucose (mmol/L)	4.7 (0.61)	4.7 (0.72)	4.7 (0.59)	4.8 (0.49)	0.86	0.61	0.04 (−.11, 0.18)	0.17	0.17 (−.07, 0.41)
Total protein (g/L)	76.9 (6.21)	76.8 (5.91)	77.0 (6.50)	76.8 (6.24)	0.96	0.91	−0.09 (−1.55, 1.37)	0.46	0.88 (−1.47, 3.22)
Albumin (g/L)	40.2 (3.70)	40.1 (3.52)	40.8 (4.26)	39.8 (3.16)	0.13	0.12	−0.69 (−1.56, 0.17)	0.06	−1.46 (−3, 0.08)

* Measured in Harare only.

ABC indicates abacavir; 3TC, lamivudine; ZDV, zidovudine; NVP, nevirapine; EFV, efavirenz.

Not all measurements were available for all children, so denominators are slightly different for different measurements. Bold indicates *P* values <0.05. Comparisons of randomized groups are unadjusted; see Section on Methods for factors adjusted for when comparing nevirapine/efavirenz.

TABLE 4. Graded Toxicity in Cholesterol, Lipid Fractions, Triglycerides, Glucose and Albumin 3 Years After ART Initiation

	Arm A (no ZDV) N = 105	Arm B (36 weeks ZDV) N = 109	Arm C (long-term ZDV) N = 105	Total N = 319
Total cholesterol (mmol/L)				$P = 0.008$
Normal: <4.4	73 (69.5%)	74 (67.9%)	91 (86.7%)	238 (74.6%)
Grade 1: 4.40-5.15	15 (14.3%)	21 (19.3%)	8 (7.6%)	44 (13.8%)
Grade 2: 5.16-7.77	17 (16.2%)	13 (11.9%)	6 (5.7%)	36 (11.3%)
Grade 3: >7.77	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.3%)
HDL cholesterol (mmol/L)				$P < 0.0001$
Normal: ≥1.04	55 (52.9%)	73 (67.0%)	14 (13.6%)	142 (44.9%)
Abnormal: <1.04	49 (47.1%)	36 (33.0%)	89 (86.4%)	174 (55.1%)
Missing	1	0	2	3
LDL cholesterol (mmol/L)				$P = 0.20$
Normal: <2.85	84 (80.8%)	94 (86.2%)	92 (87.6%)	270 (84.9%)
Grade 1: 2.85-3.34	15 (14.4%)	7 (6.4%)	6 (5.7%)	28 (8.8%)
Grade 2: 3.35-4.90	5 (4.8%)	8 (7.3%)	7 (6.7%)	20 (6.3%)
Missing	1	0	0	1
Triglycerides (mmol/L)				$P = 1.00$
Normal: <5.65	105 (100.0%)	109 (100.0%)	103 (100.0%)	317 (100.0%)
Missing	0	0	2	2
Glucose (mmol/L)				$P = 0.18$
Low-grade 2: 2.22-3.06	1 (1.0%)	0 (0.0%)	0 (0.0%)	1 (0.3%)
Low-grade 1: 3.05-3.55	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Normal: 3.65-6.10	97 (93.2%)	107 (98.2%)	103 (99.0%)	307 (96.8%)
High-grade 1: 6.11-6.94	3 (2.9%)	2 (1.8%)	1 (1.0%)	6 (1.9%)
High-grade 2: 6.95-13.88	3 (2.9%)	0 (0.0%)	0 (0.0%)	3 (0.9%)
Missing	1	0	1	2
Albumin (g/L)				$P = 0.68$
Normal: ≥35	99 (95.2%)	102 (93.6%)	100 (95.2%)	301 (94.7%)
Grade 1: 30–<35	5 (4.8%)	5 (4.6%)	5 (4.8%)	15 (4.7%)
Grade 2: 20–29	0 (0.0%)	2 (1.8%)	0 (0.0%)	2 (0.6%)
Missing	1	0	0	1

ZDV indicates zidovudine.

Tests exclude missing observations. Total and LDL cholesterol, triglycerides, glucose and albumin were considered abnormal according to the Division of AIDS grading[37]; HDL was considered abnormal <1.04 mmol/L (40 mg/dL).[38] Children with elevated total cholesterol were receiving lamivudine+abacavir+nevirapine (44 children), lamivudine+abacavir+efavirenz (21), lamivudine+abacavir+zidovudine (12), lopinavir/ritonavir+zidovudine+didanosine (2), lopinavir/ritonavir+lamivudine+didanosine (1) and lopinavir/ritonavir+efavirenz (1).

receiving 3NRTI maintenance), compared with 31.3% receiving NNRTI without zidovudine long-term; and HDL cholesterol, where 86.4% and 39.9% had abnormally low values respectively. However, most abnormalities were low grade (1–2); with the abacavir+lamivudine+NNRTI/3 NRTI long-term regimens used, we found very few children had sufficiently severe lipid abnormalities after 3 years on ART to consider switching or using lipid-lowering therapy. The modest nature of the changes, their unclear clinical significance and uncertainty regarding the role of pharmacologic interventions, suggest there is little reason to regularly monitor for lipid toxicity, as for other biochemical toxicities,[31] particularly in low-income settings. However, the impact over timescales longer than 3 years is unknown, although previous data in children suggest that the most pronounced lipid changes occur during the first year on ART.[51]

The major limitation of our study is its cross-sectional design, a consequence of being setup after trial recruitment had ended. However, zidovudine comparisons are randomized, eliminating 1 potential source of bias. Furthermore, those receiving long-term zidovudine were on a 3NRTI regimen, which is only recommended in WHO guidelines during tuberculosis treatment. Although nevirapine and efavirenz were not randomized, both drugs were used in substantial numbers in each center, based mainly on age and individual recruiting clinician preference. Another limitation is the lack of country-specific reference values, necessitating the use of Dutch reference data,[34,35] also used in Black African children in the UK. This makes interpreting absolute Z-scores difficult. Interestingly, Ugandan/Zimbabwean children appeared relatively similar to Dutch children on central measures, but had substantially more muscular/leaner extremities. This could be because of nondrug-specific ART (or even HIV) effects in these children, or to higher values in uninfected normal Dutch than Ugandan/Zimbabwean children. The lack of evidence supporting associations between abacavir and lipoatrophy, the low rates of lipoatrophy reported by clinicians regardless of ART exposure, and the generally more active lifestyle of African children support the former explanation. However, differences in Z-scores between groups are likely far less affected than absolute values. We found little or no evidence of differences between groups of Ugandan/Zimbabwean children in unadjusted and adjusted analyses, so using different reference values would have been unlikely to alter this. Direct LDL and HDL measurement in mostly fasted children was 1 study advantage. However, metabolic assays were only performed in Zimbabwe, whereas most children with abnormal clinical signs/symptoms of lipodystrophy were Ugandan, making comparisons of metabolic parameters between those with and without lipodystrophy impossible. Finally, we investigated a large number of different parameters; some results (eg, higher subscapular and supra-iliac skinfolds with long-term zidovudine) could therefore be false-positives from multiple testing.

In summary, we found no evidence that long-term zidovudine was associated with greater rates of lipodystrophy, or more severe abnormalities in body circumferences/skinfold thicknesses, than abacavir+lamivudine-based regimens in a randomized comparison 3 years after ART initiation, with only relatively small differences in HDL and total cholesterol. These findings suggest that both zidovudine and abacavir are similarly safe NRTI options with respect to lipodystrophy/lipoatrophy/lipid measurements, which is

reassuring given the wholescale move toward these regimens across Africa and the necessity for these children to receive ART. We also found no, or relatively small, differences between efavirenz and nevirapine. While these are longer-term data than those published to date on zidovudine-based ART in resource-limited settings, they are still short-term in the context of lifelong ART; given the severe adverse consequences of lipodystrophy, particularly for adolescents, and its impact on adherence, longer-term studies will be important.

ACKNOWLEDGMENTS

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