Differences in body circumference, skin fold thickness and lipid profile measurements among HIV-infected children on and not on stavudine-based therapy in Uganda and Zambia in the CHAPAS-3 clinical trial

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BACKGROUND

- Lipodystrophy is a major side effect of antiretroviral therapy (ART) especially in adults, and although there have been some reports among HIV-infected children [1,2], paediatric data are limited
- Stavudine (d4T) has particularly been associated with lipodystrophy among HIV-infected adults owing to intracellular accumulation of the drug and its metabolites
- In HIV-infected children, d4T clearance is enhanced, potentially protecting them from these effects [3]. In addition, the relative d4T dose in paediatric fixed dose combination "baby" tablets is lower than used in adults, and is also lower compared to the 4mg/kg licensed dose for children [4]
- Features of lipodystrophy have been observed to reverse when children have been switched from d4T-containing regimens [5]; however, clinical lipodystrophy is more difficult to diagnose in growing children than in adults
- We compared body circumferences, skin-fold thickness (SFT) and lipid levels, as objective measures of lipodystrophy, among HIV-infected ART naïve vs experienced children at enrolment into the CHAPAS-3 trial, and in HIV-uninfected controls

METHODS

- HIV-infected children, either ART naïve or on stavudine (d4T) for ≥2 years without clinical evidence of lipodystrophy, were randomised to receive d4T, abacavir (ABC) or zidovudine (ZDV) with lamivudine and efavirenz (EFV) or nevirapine in fixed dose combination dual or triple dissolvable paediatric formulations (Cipla Ltd) in the CHAPAS-3 trial (ISRCTN69078957)
  - 478 children were randomised between Nov 2010 and Jan 2012 and will be followed for at least 96 weeks until Nov 2013. The primary endpoint is toxicity.
- At enrolment, mid-upper arm (MUAC) and calf (CC) circumferences, SFT (biceps, triceps, sub-scapular, supra-iliac) and fasting lipids (total cholesterol (TC), low density lipo-protein (LDL), high density lipoprotein (HDL), triglycerides (TRIG)) were measured
  - The same measurements were made for HIV-uninfected controls recruited from siblings, the community and outpatient clinics in JCRC, Kampala, and University Teaching Hospital, Lusaka, Zambia
- Age/sex adjusted z-scores for MUAC, CC, SFT and the sum of SFT (SSF) used Dutch reference data [6]. ART-naïve and -experienced children were compared using the likelihood ratio test from linear regression, using Stata v11.0.

Drugs used in CHAPAS-3

Arm A

STAVUDINE, LAMIVUDINE & NEVIRAPINE 6/30/50mg (Triomune Baby) and 12/60/100 (Triomune Junior)

Description: Oval shaped with layered colouring (½ white, ½ colour).

STAVUDINE, LAMIVUDINE 6/30 mg (Lamivir-S Baby) and 12/60 mg (Lamivir-S Junior)

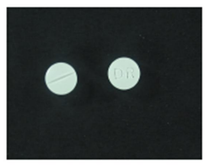
Description: Round, Lam-S Baby is blue and Lam-S Junior is pink

Arm B

ZIDOVUDINE, LAMIVUDINE & NEVIRAPINE TABLET 60/30/50mg (Duovir-N Baby)

Description: White to off white, circular, biconvex, uncoated tablets for oral suspension, deep score on one side and embossed "DN" on other side.

ZIDOVUDINE & LAMIVUDINE TABLET 60/30 mg (Duovir Baby)



Description: White, circular, biconvex uncoated tablets having score on one side & embossed "DR" on other side.

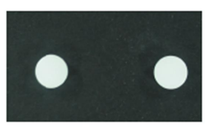
Arm C

ABACAVIR, LAMIVUDINE AND NEVIRAPINE TABLET 60/30/50 mg (Abamune-LN Baby)

Description: Capsule shaped, bilayered uncoated tablet for oral suspension with one layer orange in colour having deep score line and embossed "L" "N" and plain on other side having white colour.

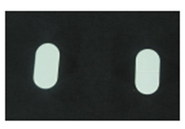
Nevirapine

NEVIRAPINE TABLET 50 mg (Nevimune Baby)



Description: White to off white coloured ,circular shaped ,biconvex, uncoated tablet for oral suspension, plain on both sides.

NEVIRAPINE TABLET 100 mg (Nevimune Junior)



Description: White colored capsule shaped biconvex film coated tablet plain on one side and central breakline on other side.

Efavirenz

EFAVIRENZ TABLET 600 MG (Efavir 600)

Description: Yellow coloured capsule shaped ,biconvex ,film coated tablet with deep score on one side& double deep score on other side.

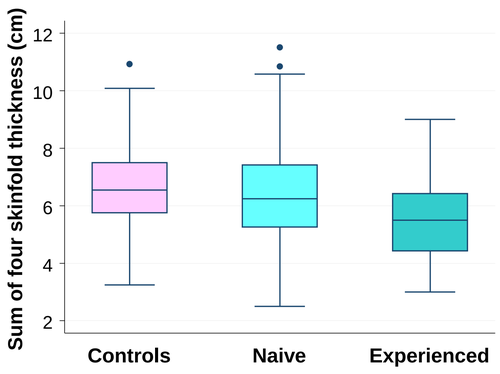
RESULTS

Table 1: Demographic characteristics

	Controls (n=88)	Naive (n=331)	Experienced (n=113)	All (n=532)	p-value
Gender:Male	39 (44%)	165 (50%)	59 (52%)	263 (49%)	0.52*
Female	49 (56%)	166 (50%)	54 (48%)	269 (51%)	
Age: Median [IQR]	2.2 [1.5,3.0]	2.5 [1.5, 4.0]	6.0 [5.5, 7.0]	3.0 [1.5,5.0]	<0.001**
Years on ART≠ Median[IQR]	-	-	3.5 [2.7, 4.2]	-	-

* Chi-square test ** One-way test of ANOVA ≠ All were on d4T; 4% were on EFV

Fig 1: Differences in sum of four skin-fold thicknesses between HIV infected naïve vs experienced children and HIV uninfected controls



- To date, 88 controls have been recruited at the JCRC Kampala site: control recruitment is ongoing
- Controls included are a similar (young) age to the HIV-infected ART-naïve children in CHAPAS-3, but are much younger than the HIV-infected ART-experienced children who had been on d4T-containing ART for a median of 3.5 years (Table 1)
- Table 2 compares the different objective measurements of lipodystrophy between groups

Table 2: Differences in z-scores for body circumferences/skin-fold thickness measurements and lipid levels between HIV infected naïve/experienced participants and HIV uninfected controls

	Mean (standard deviation) absolute z-score or lipid level			Mean Difference between naïve children and controls		Mean Difference between experienced children and controls		Mean Difference between experienced and naïve children	
Z-score / Lipid level	Controls	Naïve	Experienced	Mean difference (95%CI)	p-value**	Mean difference (95%CI)	p-value**	Mean difference (95%CI)	p-value**
MUAC	-0.65 (1.06)	-1.56 (1.25)	-1.24 (0.97)	-0.91 (-1.19,-0.63)	**<0.001**	-0.60 (-0.92,-0.27)	**<0.001**	0.31 (0.05,0.57)	**0.02**
Calf circumference	-0.80 (1.50)	-2.34 (1.49)	-1.80 (1.04)	-1.54 (-1.88,-1.21)	**<0.001**	-1.00 (-1.40,-0.61)	**<0.001**	0.54 (0.23,0.84)	**<0.001**
Biceps ¥	-0.21 (0.76)	-0.17 (0.89)	-0.43 (0.91)	0.05 (-0.16,0.26)	0.66	-0.21 (-0.46,0.30)	0.09	-0.26 (-0.46,0.07)	**0.009**
Triceps ¥	-0.29 (0.88)	-0.41 (0.97)	-1.02 (0.78)	-0.12 (-0.36,0.12)	0.32	-0.73 (-1.00,-0.46)	**<0.001**	-0.61 (-0.82,-0.41)	**<0.001**
Sub-scapular ¥	0.13 (1.04)	0.11 (1.23)	0.15 (1.15)	-0.02 (-0.32,0.29)	0.92	0.02 (0.32,0.38)	0.92	0.04 (0.23,0.32)	0.75
Supra-iliac ¥	-0.27 (0.85)	-0.25 (1.10)	-0.92 (0.92)	0.03 (-0.24, 0.29)	0.84	-0.64 (-0.95,-0.34)	**<0.001**	-0.67 (-0.91,-0.43)	**<0.001**
Sum of four¥	-0.35(1.02)	-0.72(1.70)	-0.94(1.28)	-0.37(-0.76, 0.02)	0.06	-0.59(-1.03,-0.14)	**0.009**	-0.22(-0.57,0.13)	**0.22**
WAZ*	-0.33 (1.15)	-1.51 (1.29)	-0.90 (0.88)	-1.17 (-1.46,-0.89)	**<0.001**	-0.56 (-0.91,-0.22)	**0.001**	0.61 (0.34,0.88)	**<0.001**
HAZ*	-1.02 (1.56)	-2.45 (1.63)	-1.48 (1.22)	-1.42 (-1.79,-1.06)	**<0.001**	-0.46 (-0.89,-0.03)	**0.04**	0.96 (0.63,1.30)	**<0.001**
TC #	141.6 (35.6)	126.1 (33.8)	154.4 (27.6)	-15.5 (-23.5, -7.5)	**<0.001**	12.1 (3.3, 22.3)	**0.008**	28.3 (21.1, 35.5) ≠	**<0.001**
LDL#	85.8 (31.1)	71.3 (29.4)	83.1 (21.2)	-14.4 (-21.4, -7.5)	**<0.001**	-2.7 (-11.03,5.7)	0.53	11.8 (5.3, 18.2) ≠	**<0.001**
HDL#	38.5 (11.9)	26.9 (11.6)	54.1 (16.1)	-11.6 (-14.6, -8.5)	**<0.001**	15.6 (11.9, 19.3)	**<0.001**	27.2 (24.2, 30.1) ≠	**<0.001**
Trig#	101.9 (49.3)	94.4 (70.3)	45.1 (38.6)	-7.5 (-22.7, 7.7)	0.33	-56.8 (-77.9, -38.7)	**<0.001**	-49.3 (-63.8, -34.7) ≠	**<0.001**

¥Skin-fold thickness * WHO 2007 reference #Mean serum levels (mg/dl) ≠Age/sex adjusted **likelihood ratio test from linear regression

CONCLUSIONS

- Malnutrition, as shown by the lower WAZ and HAZ, could explain the lower circumference values in HIV-infected ART-naïve children
- Among the HIV infected ART-experienced children, thinner skin-fold thicknesses and higher total cholesterol and LDL values could be ART (particularly d4T)-related
- The higher HDL among ART-experienced versus ART-naïve HIV-infected children is partly a reflection of normalisation on ART of the abnormal HDL levels associated with HIV infection [7].
- During trial follow-up, we will evaluate the effect of ABC, ZDV and d4T on development of lipodystrophy in naïve children and its reversibility over 96 weeks in ART (d4T) experienced children randomised to switch to ZDV or ABC

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