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HIV suppression with stavudine 30mg versus 40mg in adults over 60kg on antiretroviral therapy in South Africa

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Background

Combination antiretroviral therapy (cART) including stavudine, lamivudine, and nevirapine is the most widely used regimen in Africa [1]. This regimen achieves good virologic response but troubling long-term complications (usually starting after >6 months cART) [2-5]. In response to the high rates of adverse events, in 2007, the World Health Organization (WHO) recommended using stavudine 30mg twice daily for all adults, replacing the 40mg dose for adults over 60kg [6]. This was based on results of short-term dose ranging studies [7-9] and retrospective cohort analyses. A recent meta-analysis [10] also suggested similar performance of 30mg and 40mg stavudine. However, evaluation of outcomes of ART naïve patients weighing >60kg initiated on stavudine 30mg is lacking from Africa. In our community-based ART programmes we changed from use of 40mg to 30mg for individuals weighing >60kg in mid-2007. We compared virologic suppression and CD4 response at 6 months among individuals weighing >60kg who received a stable dose of either 30 or 40mg of stavudine.

Methods

Patients in this study were enrolled in community HIV care programmes, followed six months from cART initiation, and fulfilled the following criteria: 1) initiated cART including stavudine of either 40mg or 30mg between January 1, 2006 and January 1, 2008; 2) received a stable dose of stavudine; 3) weighed >60kg at cART initiation and during observation; 4) received a non-nucleoside reverse transcriptase inhibitor (NNRTI); 5) were cART naïve and had a known date of cART initiation, 6) had at least 150 days follow-up after cART initiation, and 7) were ≥18 years old. Patients within these HIV clinics received care through a standard algorithm that included HIV RNA monitoring (Amplicor HIV-1 Monitor, Roche Diagnostics) at six weeks and six months after cART initiation. CART eligibility was based on WHO criteria

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using a CD4 count <200 cells/mm^3 or WHO stage 4 condition. Starting in June 2007, clinics switched to use of 30mg stavudine, twice daily, for all patients.

Baseline factors were compared between subjects receiving 30mg and 40mg stavudine using chi-square and Wilcoxon rank sum tests, as appropriate. HIV RNA response was based on the lowest HIV RNA obtained within six months of cART initiation. If no HIV RNA test result was available, the subject was considered to have an HIV RNA >400 copies/mL to avoid excluding subjects without HIV RNA results because of discontinuation due to intolerance. We assessed the impact of classifying these subjects as treatment failures in a sensitivity analysis. The chi-square test was used to compare the proportion achieving HIV RNA <400 c/mL or <50 c/mL by stavudine group. Logistic regression was used to assess associations between covariates and HIV RNA suppression and to adjust for confounding; a multivariate model was built by including covariates with $p \leq 0.1$. CD4 change from cART initiation to six months was compared, by stavudine group, using the Wilcoxon rank sum test. Ethical approval was obtained from the University of KwaZulu-Natal and the London School of Hygiene and Tropical Medicine.

Results

691 patients were evaluated for analysis, 618 were included, 73 were excluded because of a change in stavudine dose or because stavudine dose was not recorded at a visit. Sex, age, and HIV RNA<400 c/mL at six months were similar between included and excluded patients. Of the included cART naïve subjects (all weighed >60kg at baseline and initiated cART between January 2006 and January 2008 at 51 community ART clinic sites), 110 received 30mg and 508 received 40mg stavudine. The two stavudine dose groups were different with respect to WHO stage, proportion receiving efavirenz, weight, and median $\log_{10}$ HIV RNA and CD4 count at cART initiation (Table). 9 (8.1%) in the 30mg group and 46 (9.1%) in the 40mg group had no HIV RNA measurement during the observation period and were counted as treatment failures.

We observed similar virologic suppression using <400 c/mL and <50 c/mL at 6 months by stavudine group: suppression to <400 c/mL for 30mg was 87/110 (79%, 95% confidence interval (CI): 71-87%) and for 40mg was 413/508 (81%, 95% CI: 78-85%) (p=0.6); <50 c/mL for 30mg was 66/110, (60%, 95% CI: 51-69%) and for 40mg was 297/508, (58%, 95% CI: 54-63%) (p=0.8). Completing sensitivity analysis excluding subjects without follow-up HIV RNA testing, we found 86% (95% CI: 0.79-0.93) and 89% (95% CI: 0.86-0.92) were suppressed with stavudine 30mg or 40mg groups, respectively (p=0.3). Using logistic regression we found no association between HIV RNA suppression and sex, weight, or WHO stage at cART initiation (Table). On univariate analysis, $\log_{10}$ HIV RNA at cART initiation, NNRTI agent, and weight all had p-values<0.1 for odds of achieving an HIV RNA <400 c/mL. On multivariate analysis adjusting for NNRTI agent, weight, and HIV RNA at cART initiation, stavudine dose remained unassociated with suppression (Table). CD4 change from cART initiation to 6 months on cART increased with a median of 126 cells/mm^3 (IQR 87-206) for the 30mg group and 110 cells/mm^3 (IQR 50-170) for the 40mg group (p=0.02).

Discussion

In an African operational cohort we found HIV RNA suppression at six months was similar between the two stavudine doses in patients weighing >60kg. Although the recipients were not randomized to dose, the dose decisions were made based on a change in guidelines and not as a result of individualization of patient management, reducing the chance of selection bias. However, our two stavudine groups did differ in some characteristics: the group receiving 30mg of stavudine had a lower CD4 count and higher WHO clinical stage at HAART initiation

and was more likely to receive nevirapine. These are factors sometimes associated with poorer HAART response [11-13], yet our outcomes were similar. Based on virologic outcomes at six months, our results provide additional support for the WHO recommendations for use of 30mg stavudine among individuals weighing >60kg. Long-term (>18 months) evaluation of side effects is essential to compare tolerance of stavudine 30mg versus 40mg.

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Table

Baseline characteristics and univariate and multivariate associations between stavudine dose and HIV RNA <400 c/mL at 6 months.

	stavudine 30mg (%, or IQR)	stavudine 40mg (%, or IQR)	p	Univariate Odds Ratio (95% CI)	Multivariate Odds Ratio (95% CI)
Stavudine dose					
30mg	110			Ref, p=0.7	Ref, p=0.9
40mg		508		1.1 (0.69-1.9)	1.0 (0.61-1.8)
Sex					
Male	38 (34)	212 (42)		Ref, p=0.9	
Female	72 (65)	296 (58)	0.2*	0.97 (0.64-1.4)	
NNRTI					
Efavirenz	56 (51)	307 (60)		Ref, p=0.1	Ref, p=0.2
Nevirapine	54 (49)	201 (40)	0.07*	1.4 (0.92-2.1)	1.4 (0.89-2.1)
WHO Stage					
I	2/81 (2)	43/349 (12)		Ref, p=0.6**	
II	11/81 (14)	84/349 (24)		1.2 (0.52-2.8)	
II	35/81 (44)	127/349 (36)		1.3 (0.58-2.8)	
IV	32/81 (40)	95/349 (27)	0.005*	1.2 (0.56-2.8)	
Age, years (median, IQR)	35 (31 -43)	36 (31-42)	0.5†		
Weight, kg					
60-64	48 (44)	117 (23)		Ref, p=0.06**	Ref, p=0.1**
65-69	35 (32)	125 (25)		1.1 (0.6-1.8)	1.1 (0.62-1.8)
70-74	14 (13)	94 (18)		0.73 (0.42-1.3)	0.74 (0.40-1.3)
≥75	13 (12)	172 (34)	0.001*	2.0 (1.1-3.6)	1.9 (1.0-3.4)
Baseline CD4 (median, IQR), cells/mm^3 (regression: per 10 cell increase)	91 (28-130)	115 (55-172)	0.001†	0.99 (0.96-1.0), p=0.3	
Baseline $\log_{10}$ HIV RNA (median, IQR), c/mL (regression: per $\log_{10}$/increase)	4.9 (4.5-5.3)	4.8 (4.3-5.2)	0.04†	0.75 (0.54-1.0), p=0.08	0.78 (0.55-1.1), p=0.1

*chi-square test,

†Wilcoxon rank sum test; NNRTI, non-nucleoside reverse transcriptase inhibitor,

**p for trend; Ref, reference value for regression of categorical variables