

Eight out of ten adults on stavudine-based antiretroviral treatment develop treatment-limiting lipodystrophy by six years of treatment in Cambodia

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Objectives

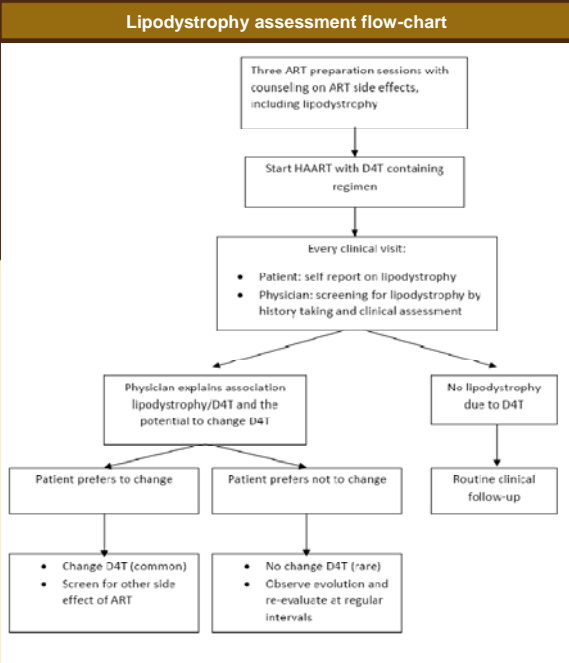
Although the majority of patients on antiretroviral treatment (ART) programs in low-income countries still take stavudine (d4T)-containing regimens, long-term toxicity of these regimens in such settings remains poorly described. This cohort study was conducted to report on the incidence, timing and risk factors for d4T-related severe drug toxicity (requiring substitution) under program conditions in Phnom Penh, Cambodia.

Methods

ART program data from Sihanouk Hospital-Center-of-Hope, Phnom Penh, Cambodia, launched March 2003. Side effects were evaluated at each follow-up visit in line with WHO guidelines. Reasons for d4T substitution could include: severe neuropathy (WHO grade III/IV), lactic acidosis/symptomatic hyperlactatemia (clinical, diagnosis of exclusion) and lipodystrophy (see flow-chart). Probabilities of "time to first treatment-limiting toxicity" related to d4T were calculated using Kaplan-Meier methods. A risk factor analysis was performed using multivariate Cox regression modeling, using a backward selection method retaining those variables with P<0.05.

Conclusions

Stavudine-based treatment regimens in low-income countries are associated with significant long-term toxicities. Lipodystrophy, in particular, is a major long-term side-effect. Phasing out of stavudine should be urgently implemented.



Results

In total, 2463 adult patients initiating d4T-based ART were included in the analysis, with a median age of 35 years (interquartile range (IQR) 30-40) and with 1272 (52%) females. The median baseline CD4 count was 76 cells/μL (IQR 23-191), the majority with WHO stage III (42%) or IV (40%) at treatment initiation. The median time of follow-up with exposure to d4T was 1.2 years (IQR 0.6-1.9). Out of 2463 adults initiating a d4T-containing regimen, d4T was replaced in 230 (9.3%) patients for neuropathy, 14 (0.6%) for lactic acidosis and 790 (32.1%) for lipodystrophy. The main early side effect was peripheral neuropathy (7.0% by 1 year). After the first year, lipodystrophy become predominant, with a cumulative incidence of 58.8% and 78.4% by 3 and 6 years respectively. Whereas older age (HR 1.53/10 years; 95%CI: 1.33-1.76) was associated with the occurrence of neuropathy, higher baseline CD4 counts (HR 0.82/100 cells/μL; 95%CI: 0.70-0.95), higher baseline body weight (HR 0.82; 95%CI: 0.70-0.95) and more weight increase in the first six months (HR 0.73/5 kg; 95%CI: 0.54-0.98) was protective. Being on TB treatment at ART initiation (HR 5.39; 95%CI: 1.66-17.49) and a higher baseline body mass index (HR 1.18/kg/m²; 95%CI: 1.06-1.32) increased the likelihood of lactic acidosis. Lipodystrophy was positively associated with female gender (HR 2.54; 95%CI: 2.18-2.95), ART initiation with efavirenz (HR 1.32; 95%CI: 1.12-1.57) and older age (HR 1.14/10 years; 95%CI: 1.04-1.21).

Table 1: Incidence of occurrence of severe side-effects related with stavudine

	Drug-related toxicity Stavudine n=2463	Events (%)	Rate /1000 py	Patients with toxicity-related drug substitution (%) – Kaplan-Meier			
				6 m	12 m	36 m	60 m
Neuropathy		230 (9.3)	65.2	2.3	7.0	16.4	19.5
Lactic acidosis		14 (0.6)	4.0	0.1	0.6	0.9	1.3
Lipodystrophy		790 (32.1)	224.0	0.8	6.9	58.8	78.4

Table 2: Risk factor for severe side-effects related with stavudine

RISK FACTOR	Adjusted hazard ratio	P-value
Neuropathy		
Age (per 10 year increase)	1.53 (1.33-1.76)	< 0.001
Baseline CD4 count (/100 cells/μl increase)	0.82 (0.70-0.95)	0.01
Baseline body weight (/10 kg increase)	0.82 (0.70-0.95)	0.007
Weight increase during first 6 months (/5 kg increase)	0.73 (0.54-0.98)	0.04
Lipodystrophy		
Sex		
Male	1	
Female	2.54 (2.18-2.95)	< 0.001
Age (per 10 year increase)	1.14 (1.04-1.21)	0.001
NNRTI at start		
NVP	1	
EFV	1.32 (1.12-1.57)	0.003
Lactic acidosis		
On TB treatment at ART initiation	5.39 (1.66-17.49)	0.005
Baseline BMI (per increase in kg/m ²)	1.18 (1.06-1.32)	0.003