

# Toxicity of stavudine- and nevirapine-containing antiretroviral treatment regimens: incidence and risk factors after three years in a large cohort in Rwanda



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## Objectives

Although stavudine- and nevirapine-containing regimens are currently the pillar of many antiretroviral treatment (ART) programs in low-income countries, long-term toxicity of these regimens in such settings remains poorly described.

## Methods

Médecins Sans Frontières has been supporting the ART program in two health centers in Rwanda since 2003, where approximately 90% of the > 3000 patients started a regimen containing stavudine/nevirapine. Probabilities of "time to first-toxicity" related to nevirapine and stavudine were calculated, and a risk factor analysis was performed using multivariate logistic regression analysis.

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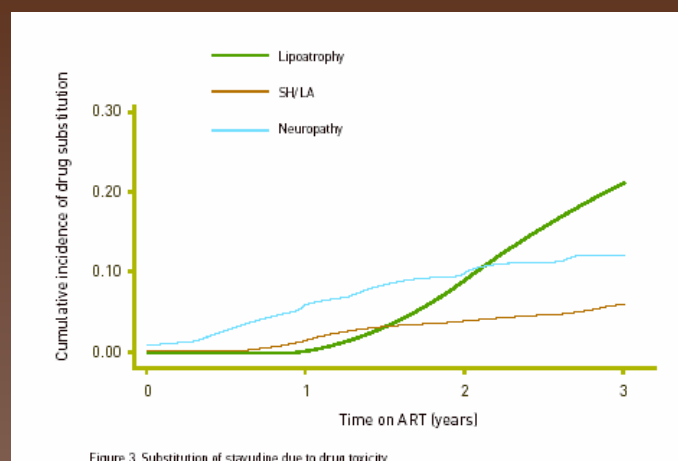
**Table 1: Incidence of occurrence of severe side-effects related with stavudine or nevirapine**

Drug related toxicity	Events (%)	Rate /1000 py	Patients with toxicity-related drug substitution (%) <sup>b</sup>			
			6 m	12 m	24 m	36 m
<b>NVP (n=2667)</b>						
Toxicity all	170 (6.4)	39	6.0	6.4	6.9	7.2
Skin toxicity	131 (4.9)	30	4.9	5.1	5.3	5.4
Liver toxicity	40 (1.5)	9	1.1	1.3	1.6	1.8
<b>D4T (n=2694)</b>						
Toxicity all	448 (16.6)	107	2.6	8.6	22.5	35.4
Neuropathy	206 (7.6)	49	2.3	6.0	9.8	12.1
SH/LA <sup>a</sup>	85 (3.2)	20	0.2	2.0	4.5	6.0
Lipoatrophy (La)	180 (6.7)	43	0.0	1.0	9.2	19.8
SH/LA and/or La	248 (9.2)	59	0.3	2.6	12.9	24.2

<sup>a</sup> Symptomatic Hyperlactatemia/Lactic Acidosis

<sup>b</sup> Kaplan-Meier estimates, time to first severe toxicity (ie requiring treatment change) at specified months on ART

**Figure 1. Timing of occurrence of toxicity related to stavudine**



**Figure 3. Substitution of stavudine due to drug toxicity**

## Results

A total of 2694 patients started a stavudine-containing regimen, of whom 448 patients (16.6%) changed stavudine for reasons of toxicity. The main early side effect was peripheral neuropathy. After six months on ART, cases of symptomatic hyperlactatemia became more apparent and after 1 year of ART, a growing incidence of lipoatrophy was reported. It was the most frequent complication by 3 years of treatment (19.8%), without signs of stabilization. Whereas older age, advanced clinical disease and low baseline CD4 counts were associated with the occurrence of neuropathy, female sex, and a high baseline body mass index (BMI) > 25 kg/m<sup>2</sup> increased the risk of symptomatic hyperlactatemia/lipoatrophy. Of the 2667 patients starting nevirapine-containing ART, 170 experienced nevirapine-related toxicity requiring drug substitution, with 4.9% manifesting skin toxicity and 1.5% hepatotoxicity respectively. Elevated baseline liver function tests and a baseline BMI < 20 kg/m<sup>2</sup> were identified as risk factors for hepatotoxicity. No association with baseline CD4 count or sex was seen.

## Conclusions

The currently used treatment regimens in low-income countries are associated with significant short and long-term toxicities. Lipoatrophy, in particular, is a major long-term side-effect. Alternative regimens are needed to prevent these toxicities. Meanwhile the identification of underlying risk factors could help target closer monitoring and earlier identification of patients at higher risk of drug toxicity.