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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Background Although stavudine- and nevirapine-containing regimens are currently the pillar of many antiretroviral treatment (ART) programmes in low-income countries, long-term toxicity of these regimens in such settings remains poorly described. With this study we aimed to document the incidence, timing and risk factors for nevirapine- and stavudine-related toxicity.

Methods MSF has been supporting ART programmes in two health centres in Rwanda since 2003, where approximately 90% of the >3,000 patients have started a regimen containing stavudine/nevirapine. Side effects were defined according to the WHO guidelines. Probabilities of ‘time to first severe toxicity’ requiring treatment change related to nevirapine and stavudine were calculated at 6, 12, 24, and 36 months using Kaplan-Meier analysis, and a retrospective risk factor analysis was performed using Cox proportional hazards modelling.

Results A total of 2,694 patients started a stavudine-containing regimen, with a median baseline CD4 count of 164 cells/µL (IQR 94–236) and a median duration of ART of 1.5 years (IQR 0.8–2.2). 448 patients (16.6%) changed regimens, mainly to zidovudine for reasons of toxicity. Within the first 6 months of ART, the main side effect was peripheral neuropathy (2.3%). After 6 months on ART, cases of symptomatic hyperlactatemia became more apparent (3.2%) and after 1 year of ART, a growing incidence of lipoatrophy was reported (6.7%). By 3 years of treatment, it was the most frequent complication (19.8%) without signs of stabilisation. Older age (>35 years) (adjusted HR 2.13 (1.53–2.98)) and advanced clinical disease (adjusted HR 1.57 (1.23–2.01)) were strongly associated with the occurrence of neuropathy, and there was a suggested association of CD4 counts <100 cells/µL (adjusted HR 0.71 (0.49–1.01)) with this toxicity. Female sex (adjusted HR 3.46 (1.55–7.70)/ 9.67 (3.92–23.87)), and a high baseline body mass index (>25 kg/m²) (adjusted HR 2.89 (1.75–4.76)/ 1.99 (1.34–2.96)) increased the risk of symptomatic hyperlactatemia/lipoatrophy. Of the 2,667 patients starting nevirapine-containing ART, 170 (6.4%) experienced nevirapine-related toxicity requiring drug substitution with efavirenz. 4.9% manifested skin rash and 1.5% hepatotoxicity. 90% of these toxicities occurred within the first 6 months of ART, with limited long-term toxicity documented. Elevated baseline liver function tests (adjusted HR 5.37 (2.04–14.14)) and a baseline BMI <20 kg/m2 (adjusted HR 2.94 (1.26–6.66)) were identified as risk factors for hepatotoxicity. No association with baseline CD4 count or sex was seen.

Conclusion 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. These data provide additional evidence of ART programmes’ urgent need for increased access to and availability of alternatives, such as tenofovir (TDF) or abacavir (ABV), which are at present prohibitively expensive. The identification of underlying risk factors could help with earlier identification of patients at higher risk of drug toxicity who need to be closely monitored to detect and manage toxicities early, and possibly changed to alternative first-line regimens.