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Incidence and risk factors for neuropsychiatric events among Ghanaian HIV patients on long-term non-nucleoside reverse transcriptase inhibitor-based therapy

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ABSTRACT

Background: Non-nucleoside reverse transcriptase inhibitor (NNRTI)-based antiretroviral therapy (ART) is associated with neuropsychiatric toxicity. Little is known about the risk of short- and long-term neuropsychiatric toxicity in sub-Saharan Africa, where NNRTIs are widely used in first-line combination ART. This observational study assessed the risk of neuropsychiatric toxicity in Ghanaian patients starting first-line ART between 2004 and 2010 at a single centre.

Methods: In this retrospective observational study, frequencies of documented neuropsychiatric toxicity events were assessed and time to events calculated using a Kaplan–Meier analysis. Associations of neuropsychiatric toxicity with specific NNRTIs and other explanatory variables were examined using Cox proportional hazards modelling.

Results: Of 3999 patients initiating NNRTI-based ART, who were followed for a median of 30 (0.25–90) months (11,237 person years), 218 (5.5%) reported symptoms of neuropsychiatric toxicity at a rate of 21.4 events per 1000 person-years (95% CI, 18.8–24.2/1000 py). Events were more common with efavirenz than nevirapine (7.6% versus 2.4%), were usually reported within the first 2 months of ART initiation and persisted up to 84 months in a few patients. The most commonly reported neuropsychiatric adverse drug reactions were insomnia (50%), headaches (8%), dizziness (7%) and abnormal dreams (6%). The factors independently associated with neuropsychiatric toxicity were BMI < 16 kg/m^2 (aHR of 1.44 [95% CI, 1.02–2.03]) and use of efavirenz (aHR 3.29 [95% CI, 2.32–4.69]). Substitution of NNRTI on account of toxicity was reported in up to 17% of patients experiencing neuropsychiatric events.

Conclusions: NNRTI-related neuropsychiatric toxicity, mainly due to efavirenz, was infrequently documented in this Ghanaian cohort under routine clinical care settings. Regimens with more favourable tolerability will be needed as first-line agents in sub-Saharan Africa in the coming years.

1. Background

The introduction of antiretroviral therapy (ART) for the management of HIV has led to significant reductions in morbidity and mortality. In sub-Saharan Africa where nearly 65% of the 34 million HIV-infected individuals reside, there has been a massive rollout of ART over the last decade. ART is administered through national programs and first-line therapy usually comprises a dual backbone of a nucleoside reverse transcriptase inhibitor (NRTI) and a first generation non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz or nevirapine [1]. First-line ART has been reported to be effective and durable in these settings, its durability determined predominantly by the efficacy and tolerability of the regimens chosen [2,3]. The virological efficacy of efavirenz-based ART has until recently been shown to be equivalent or superior to all comparators but for its frequent neuropsychiatric toxicity [4].

A WHO-led survey in 2008 revealed that most national programs in sub-Saharan Africa favoured nevirapine over efavirenz due to cost differentials and availability of fixed combinations of nevirapine [5]. However, a recent WHO-led recommendation gives preference to efavirenz over nevirapine due mainly to skin rash and hepatotoxicity from the latter [6]. Thus, it is expected that use of efavirenz will become more widespread across the continent. However, patients from sub-Saharan Africa frequently harbour single nucleotide polymorphisms predisposing them to higher plasma concentrations of efavirenz with the possibility of developing more frequent neuropsychiatric toxicity and subsequent discontinuation of therapy. We have recently shown in a large

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Ghanaian cohort that variants in the CYP2B6*516G > T and *983 T > C were frequent and were marginally associated with increased risk for central nervous system (CNS) toxicity, and importantly influenced the risk for immunological failure [7]. However, very few studies have assessed the risk of neuropsychiatric toxicity over long-term use in sub-Saharan Africa where the HIV burden is highest and ART use is exponentially increasing. The aim of this study was to determine the frequency and determinants of neuropsychiatric toxicity on NNRTI-based ART among Ghanaians.

2. Methods

Ethical permission for this study was provided by the Committee on Human Research Publications and Ethics of the Kwame Nkrumah University of Science and Technology and the Komfo Anokye Teaching Hospital (KATH), Kumasi, Ghana (ref: CHRPE/AP/073/13). Our institutional review board waived the need for a written informed consent since this was a retrospective, observational study and anonymised data were collected from patients' records. Since 2004, patients referred to the HIV clinic in KATH, Kumasi have been treated as part of the National AIDS Control Program. Patients were referred from a large area of central and northern Ghana and, after starting ART, were reviewed at weeks 2, 4, 6 and 8, then 2 monthly for the first year and then every 6 months subsequently. HIV viral load was not available routinely and testing for HIV-2 and hepatitis B (HBV) co-infection has been performed only in limited circumstances. The criteria for starting ART in Ghana followed the WHO guidelines [1], with a change of the CD4 threshold for initiation from 200 to 350 cells/mm^3 in 2008. First-line ART comprised lamivudine plus either zidovudine or stavudine, plus either nevirapine or efavirenz. The choice between the use of either zidovudine or stavudine was determined by availability but zidovudine was avoided in patients with haemoglobin below 10 g/dL. For NNRTIs, nevirapine tended to be used preferentially in women of child-bearing age. Data on patients' response to ART including adverse side effects are routinely sought for and documented in case notes at each clinic appointment.

Neuropsychiatric symptoms associated with use of NNRTI's were routinely recorded without any standardised assessment of severity. Individual neuropsychiatric symptoms recorded in patients' records for which the attending clinician attributed to NNRTI were noted. For statistical analysis, the primary outcome was time to occurrence of Neuropsychiatric toxicity on ART. The cumulative incidence of neuropsychiatric toxicity was calculated using the Kaplan–Meier methodology and the median time to occurrence of the first event calculated using the Mann–Whitney's *U*-test, when the median time could not be determined by Kaplan–Meier methodology. Patients were censored either at the date of first CNS toxicity, at the last visit for patients that died, were transferred out or were lost to follow-up and at December 31, 2011 for the remainder. Patients on NNRTIs who were switched to second-line ART regimens due to either clinical or immunological failure were censored at the date of switching and defined as having experienced no specific first-line drug-related toxicity event. A risk factor analysis was performed using multivariate Cox proportional hazards regression model. Collinearity between variables was assessed. A backward selection method was used, retaining those variables with *p*-values <0.10 in the final model. The level of significance was set at $p < 0.05$. All analyses were performed using SPSS version 17.

3. Results

Baseline characteristics and incidence of neuropsychiatric adverse drug reactions: A total of 3999 patients initiating ART were followed for a median (range) of 30 (0.25–90) months and provided 11,236.8 person years on ART. Prior to initiation of ART, patients who subsequently developed neuropsychiatric toxicity compared with those who did not were significantly older and likely to have started efavirenz compared with nevirapine (Table 1).

Two hundred and eighteen (218) patients experienced a total of 235 events of neuropsychiatric toxicity during follow-up, giving 21.4 events per 1000 person-years (95% CI, 18.8–24.2/1000 person years). A total of 203 patients had one event, 13 patients experienced 2 events and 2 patients experienced 3 episodes of neuropsychiatric events during follow-up. Thus, the frequency of reported neuropsychiatric toxicity was 5.5% ($n = 3999$) with 7.6% ($n = 2376$) of efavirenz recipients and 2.4% ($n = 1623$) of nevirapine recipients experiencing an event. The median (range) time to first report of neuropsychiatric toxicity was 2 months (2–84 months). Most neuropsychiatric toxicities were reported in the first year of therapy after which the incidence of events declined, as shown in Fig. 1.

A total of 195 events were reported among patients on efavirenz-based ART compared to 40 events among those on nevirapine-based ART, odds ratio of 3.54 (2.50–5.00), $p < 0.0001$. A total of 252 neuropsychiatric symptoms were reported, the most common being insomnia (126), headaches (19), dizziness (17), abnormal dreams (14) and drowsiness (13), as shown in Table 2. Insomnia, headaches, abnormal dreams and drowsiness were significantly more common among patients on efavirenz-based ART compared with nevirapine-based ART. Other notable but rarely reported NNRTI-related neuropsychiatric toxicities included cerebellar ataxia ($n = 2$), dysarthria ($n = 5$) and seizures ($n = 3$). Cranial computed tomography scans were performed in the 3 reported cases of seizures and 2 cases of cerebellar ataxia but all were found to be normal.

3.1. Risk factors for neuropsychiatric toxicity

Predictor variables included in univariate analysis of baseline risk factors for neuropsychiatric toxicity included gender, age, body mass index (BMI), CD4 count, WHO clinical stage, HBV sero-status and NNRTI on which the patient developed toxicity. As shown in Table 3, the factors associated with neuropsychiatric toxicity included age ≥ 35 years at initiation of therapy with a hazard ratio (HR) (95% CI) of 1.55 (1.16–2.00), $p = 0.003$, BMI < 16 kg/m^2 with HR of 1.45 (1.03–2.04), $p = 0.04$ and use of efavirenz with HR of 3.43 (2.16–3.72), $p < 0.0001$. Furthermore, on multivariate analysis, BMI < 16 kg/m^2 and use of efavirenz were significantly associated with the risk of developing neuropsychiatric toxicity on ART with HR of 1.44 (1.02–2.03), $p = 0.04$ and 3.29 (2.32–4.69), $p < 0.0001$, respectively. A total of 33 of 195 events (17%) among patients on efavirenz-based ART led to substitution of efavirenz by nevirapine while 6 of 40 (15%) events among patients on nevirapine-based ART led to substitution of nevirapine by efavirenz ($n = 5$) and nelfinavir ($n = 1$). The substitutions of nevirapine by efavirenz simultaneously with report of neuropsychiatric events were performed in 5 patients due to their being initiated on anti-tuberculous therapy at the time when those toxicities occurred. This was to avoid drug interactions between nevirapine and rifampicin, which is used as a component of the quadruple anti-tuberculous drug regimen. However, most neuropsychiatric symptoms resolved under continual therapy without having to alter NNRTI dosage on account of neuropsychiatric toxicity.

4. Discussion

This is the first longitudinal study to evaluate in a retrospective cohort the frequencies of neuropsychiatric toxicity among Ghanaians. Neuropsychiatric toxicity due to NNRTI use has predominantly been reported among efavirenz recipients with a frequency ranging from 25% to 70% in various studies [8–12]. In this cohort, the reported frequency of neuropsychiatric toxicity on efavirenz was 7.6% while that on nevirapine was 2.4%, low overall frequencies compared with other reports. However, a similar retrospective study conducted among 2920 patients who initiated Efavirenz-based ART in Jos, Nigeria in an ART treatment program between 2004 and 2011 reported a rate of neuropsychiatric events rate of 29.9 per 1000 person-years of treatment [13] comparable