Severe Neurotoxicity Associated with supra-therapeutic Efavirenz concentrations: a retrospective cohort study

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Declaration

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Dr P Arnab

2022/10/28

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Abstract

Introduction

Efavirenz, still used for first line antiretroviral therapy, is associated with neuropsychiatric symptoms, often occurring early in therapy. Severe neurotoxicity has been reported but the clinical phenotype and risk factors are poorly defined.

Methods

We retrospectively identified adults with supratherapeutic efavirenz concentrations (> 4 mg/L) obtained as part of routine clinical care at five hospitals in Cape Town, South Africa. Clinical and laboratory data at the time of efavirenz quantification were extracted from medical records. Logistic regression was performed to identify associations with neuropsychiatric symptoms, and with severe neurotoxicity (defined as Division of Allergy and Infectious Diseases altered mental status or ataxia ≥ Grade 3).

Results and Discussion

81 patients were included; 28 (34.6%) were male and 49 (60.5%) had concomitant isoniazid exposure. Median efavirenz concentration was 12.1 mg/L (interquartile range (IQR) 6.6-20.0). The most frequent neuropsychiatric manifestations were ataxia in 20 patients and psychomotor slowing in 24. The presence of any neuropsychiatric symptoms were associated with: longer duration, per 180 days, of efavirenz therapy (aOR 1.3; 95% CI, 1.0-1.7); increasing efavirenz concentrations per 1 mg/L increase (aOR 1.2; 95% CI, 1.1-1.4); higher efavirenz concentrations per 1 mg/L increase (aOR 1.2; 95% CI, 1.0-1.4); and isoniazid exposure (aOR 8.2; 95% CI, 2.5-26.7). Severe neuropsychiatric symptoms occurred in 47 (75%) patients at a median of 5.9 months (IQR 2.1-40.8) after efavirenz initiation. Odds of having severe symptoms compared with mild symptoms were 1.2-fold higher (95% CI, 1.1-1.4) for every 1 mg/L increase in efavirenz concentration. Among patients with severe neurotoxicity, symptoms resolved completely within 1 month in the 29 (94%) who discontinued efavirenz.

Conclusion

We describe a distinct clinical phenotype and factors. There were duration- and concentration-dependent effects, and higher risk with concomitant INH exposure and those with lower CD4 count. Despite most patients with severe neurotoxicity having symptom resolution within 1 month after stopping EFV, the overall 3-month mortality was high in this population.

Key words

Efavirenz, isoniazid, risk factors, neurotoxicity, cerebellar, Cape Town

Introduction

Efavirenz (EFV), a non-nucleotide reverse transcription inhibitor, has been a backbone of antiretroviral therapy (ART) for the last 15 years. Daily dosing, inclusion in fixed drug combinations, and lack of significant drug-drug interaction with rifampicin have made it a widely used first line drug in combination with two nucleoside reverse transcriptase inhibitors (NRTIs) (1), especially in resource-limited countries with high TB burdens (2) .

Efavirenz is metabolised in the liver by cytochrome P450 isoenzyme 2B6 (*CYP2B6*). Single nucleotide polymorphisms (SNPs) in *CYP2B6*, present in up to 20% of Sub-Saharan African populations (3,4,5), infer 'slow metaboliser' genotypes and lead to a risk of increased EFV concentrations, particularly in patients on concomitant TB treatment (6), as alternate pathways of EFV metabolism are also inhibited by isoniazid (INH).

Two major adverse effects of EFV include hepatotoxicity, secondary to an immunoallergic pathway (7), and central nervous system (CNS) toxicity possibly due to direct glial toxicity (6,8). Clinical features of CNS EFV toxicity range from sleep and mood disturbances in milder forms (9) through to psychosis, cerebellar ataxia, encephalopathy (10), and rarely, death (11); long term toxicity may promote the development of HIV associated neurocognitive disorder (HAND) (12). Apart from host genetics, clinical risk factors for efavirenz neurotoxicity have not been established. Previous cohort studies have not separated severe from milder symptoms and only small case series have documented severe EFV neuropsychiatric sequelae (10,11,13,14).

High rates of HIV-associated TB place patients in South Africa at particular risk of EFV neurotoxicity, especially given relatively high background prevalence of 'slow metaboliser' genotypes and ongoing use of EFV for ART by some clinicians despite dolutegravir availability. However, the diagnosis may be missed due to overlap with other common neurological syndromes, and pharmacogenetic risk stratification may not be feasible in resource-limited settings. We performed a retrospective cohort study to describe the clinical phenotype of severe EFV-induced neurotoxicity and explore risk factors for its development.

Methods

Study population

EFV concentrations are measured in routine care if there is a clinical suspicion of toxicity or as part of therapeutic drug monitoring. We searched the University of Cape Town Clinical Pharmacology laboratory database for EFV concentrations performed at five public sector Cape Town hospitals between February 2008 (when the database was started) and July 2017. Medical records of patients with elevated concentrations > 4 mg/L (normal range 1-4 mg/L) were retrieved and reviewed. We included data from all patients over the age of 18 years with available records.

Clinical data

The following data were extracted from medical records, national laboratory services and picture archiving and communications system: biometrics including age, weight, and gender; treatment history relating to ART, TB therapy and isoniazid preventive therapy (IPT); and clinical manifestations at the time of, and subsequent to, EFV toxicity. Results of blood, cerebrospinal fluid (CSF), and radiological investigations were recorded to exclude other causes of neuropsychiatric syndromes including: neurosyphilis; bacterial, TB or, fungal meningitis; neurological TB immune reconstitution inflammatory syndrome (IRIS); stroke; and metabolic abnormalities. Data was captured using unique participant identifiers onto paper case report forms and entered into an electronic database (REDCap).

EFV-associated neurotoxicity was defined by the presence of known neuropsychiatric manifestations of EFV toxicity, without an alternative clinical or radiological explanation. Indicative clinical features included ataxia or cerebellar signs, psychomotor slowing (including slowed speech, decreased movement, impaired cognitive function and catatonia), mood disorders, psychosis, sleep disorders and confusion (9,12,13,15). Severe EFV-associated neurotoxicity was defined as a Division of Allergy and Infectious Diseases (DAIDS) altered mental status Grade 3 or more ("Confusion, memory impairment, lethargy and somnolence causing inability to perform usual social and functional activities; or delirium, obtundation or coma") (16), and/or ataxia of DAIDS Grade 3 or more. Clinical records and additional databases were reviewed and the identified features of EFV toxicity recorded by the treating clinicians

were noted and then classified according to the DAIDS criteria. Clinical judgement was used to assess the severity of the patient if the records were unclear. Patients who had been identified as having an elevated EFV concentration but no neuropsychiatric effects were included as “non-neuropsychiatric” cases.

Analysis

Descriptive statistics were used to summarise the demographic and clinical characteristics of the study population. Univariable logistic regression was performed to determine associations between pre-specified variables and the primary outcome of severe EFV-associated neurotoxicity. Independent variables included age, weight, EFV concentration, duration of EFV therapy, isoniazid exposure (either as TB therapy or IPT), and sex. Data completeness was used to determine a candidate set of variables for inclusion in a multivariable model with only variables with <20% missing data included. This set was reduced by a backward step-wise model elimination using the Akaike Information Criterion (AIC) as the optimising criteria. We also used logistic regression to explore factors associated with the presence of neuropsychiatric symptoms of any severity, using cases with hepatitis (and no neurological manifestations) as a comparator. We checked for multicollinearity by testing correlation between clinically linked variables and quantifying effects on model parameters - predictors that resulted in increased variance greater than or equal to 10% without an impact on coefficient size were dropped from the final model to avoid collinearity. The Hosmer-Lemeshow statistic was used to assess the calibration of the final model; discriminative ability was quantified by the area under the receiver operating characteristic (ROC) curve. Survival was represented using Kaplan-Meier plots with censoring at 3 months after initial supratherapeutic EFV concentration. Time to development of EFV toxicity after ART initiation was represented as an empirical cumulative distribution function, stratified by severity. Statistical analysis was performed using R software, version 3.6.1.

Ethics

Ethical approval for this study was obtained from Human Ethics Research Committee of the University of Cape Town 843/2016.

Results

Clinical phenotype and outcomes

109 patients with supratherapeutic EFV concentrations were identified over the study period; data from 81 patients were included in the analysis, distributed as follows: Brooklyn Chest Hospital 1, DP Marais 16, Groote Schuur Hospital 56, Mitchell's Plain District Hospital 8, and New Somerset Hospital 2 (See consort diagram supplementary appendix, Figure 1). Patients were excluded if their clinical records were missing or if they were under the age of 18 years at the time of EFV sampling. 1 patient had chronic diarrhoea and no other indication for having had an EFV concentration performed, so was also excluded.

62 patients had a neuropsychiatric syndrome and 19 had hepatitis as a reason for EFV sampling. Overall, 28 (34.6%) patients were male and the median age was 37.5 years (interquartile range (IQR) 29.3-45.0). Median CD4 count was 261 cells/mm^3 (IQR 101-412); 42 (74.6%) had undetectable plasma HIV RNA.

Compared to patients with hepatitis, those with neuropsychiatric manifestations had a lower median weight (50 vs 71kg), lower median CD4 (195 vs 449 cells/µL) and higher EFV concentrations (16.1 vs 6.6mg/L); a higher proportion of patients with neuropsychiatric presentations were exposed to INH (44 (74.6%) vs. 5 (26.3%) with hepatitis) (Table 1). Although 5 patients in the hepatitis group also used INH, all the hepatotoxic cases were reviewed by a hepatology team and concluded to have EFV-induced liver injury.

Of those with available results, (n=44) 7 (15.9%) patients with neuropsychiatric symptoms had abnormal CSF findings at the time of index presentation, six with raised protein (> 0.45 g/dL) and variable pleocytosis, and one with isolated polymorphonuclear pleocytosis. Neuroimaging (either CT or MRI) was performed for 39 patients with neuropsychiatric symptoms, with 18 being reported as abnormal. Abnormalities included ring enhancing lesions (n=4), generalised atrophy (n=5), infarcts (n=3), and non-specific white matter changes (n=3). Fourteen patients had positive serum treponemal tests, but only one had a positive rapid plasma reagent (RPR), titre 1:1.

Table 1: Clinical characteristics at time of supratherapeutic EFV concentration

Variable		Neuropsychiatric n= 62	Hepatitis n = 19	P-value
Male sex[a]	[n=81]	28 (45.2%)	0	<0.01
Weight[b] (kg)	[n=63]	50 (42.1-56.5)	71 (65.5-82.5)	<0.01
Age at toxicity[c] (years)	[n=81]	39.1 (30.9-46.1)	32.8 (27.7-38.5)	0.12
CD4[d] (cells/µL)	[n=81]	195 (74 -320)	449 (320-517)	<0.01
EFV concentration (mg/L)	[n=81]	16.1 (7.5-20.0) Range: 4-20	6.6 (4.9-8.8) 4-16	<0.01
HIV RNA copies/mL[e] < 40	[n=55]	30 (71.4%)	11 (100%)	0.05
Duration of EFV therapy[f] (months)	[n=74]	5.9 (2.1-40.8) Range: 0.7-113	5.9 (2.6-10.4) 0.4-17.2	0.27
Exposure to INH[g] TB treatment INH prophylaxis	[n=78]	44 (74.6%) 33 (55.9%) 11 (18.7%)	5 (26.3%) 3(15.8%) 2 (10.5%)	<0.01 0.003 0.50
Duration of TB therapy or IPT (days)[h]	[n=79]	48 (30.0-108.2) Range: 7-554	30 (26.8-38.2) Range: 17-63	0.19
Laboratory parameters[†] Hb (g/dL)[i] Cr (umo/l)[j] ALT (U/L)[k]	 [n=81] [n=80] [n=75]	 11.8 (9.5-13.5) 59 (47.5-70.5) 32 (20-54.5)	 13.5 (11.8-14.2) 51 (46.5-62.5) 665 (274-1353)	 0.03 0.12 <0.01

Data are n (percent) or median (interquartile range). Continuous variables compared using Wilcoxon rank sum and categorical variables using Fishers test.

Abbreviations: EFV, efavirenz, HIV, human immunodeficiency virus, DAIDS, Division of Allergy and Infectious Diseases, INH, Isoniazid, TB, tuberculosis, IPT, isoniazid preventative therapy, Hb, haemoglobin, Cr, creatinine, ALT, alanine transaminase

[†]Investigations performed within one month of index presentation

Psychomotor slowing (n = 24) was the most common neuropsychiatric symptom, followed by ataxia (n = 20), psychosis (n = 17), other cerebellar signs (n = 13), and mood disturbances (n = 11). DAIDS Grade 3 or higher symptoms for ataxia, altered mental state, and psychiatric disorders was present in 47 (75.8%). Median time to neurotoxicity was 5.9 months (IQR 2.1-40.8); those with milder manifestations presented later (9.8 months (IQR 1.6-19.0)) compared with patients with severe symptoms (5.7 months (IQR 2.7-42.3)), although this difference was not statistically significant (p=0.73) (Fig 1).

Median efavirenz concentration was 20.0 mg/L (the upper limit of assay detection, IQR 13.0-20.0) in those with severe versus 7.0 mg/L (IQR 4.5-11.8) in those with mild neurotoxicity ($p<0.01$).

14 of the hepatitis group (74%) and 46 (74%) of those with neuropsychiatric presentations improved on withdrawal of EFV ; the condition remained unchanged at one month in 6 (8%) patients. Among those with severe neurotoxicity, there was complete resolution of symptoms within 1 month in 29 (94%) who discontinued efavirenz.

A total of fourteen (17%) patients died within the three-month follow-up period, 9 (64%) of them were associated with neuropsychiatric presentations, 5 (55.6%) of which were categorised as severe. 4 patients had drug-resistant TB, two patients had sepsis, and three had generalised seizures. 5 (36%) patients without neuropsychiatric symptoms died in hospital, all secondary to fulminant liver failure, 2 of whom were less than 3 months post-partum. Median time to death after diagnosis of EFV toxicity was 21 days (IQR 10.0-36.0) overall; 20 days (IQR 9.0-42.3) for neuropsychiatric presentations; and 22 days (IQR 12.5- 35.5) for non-neurological presentations (Fig. 2).

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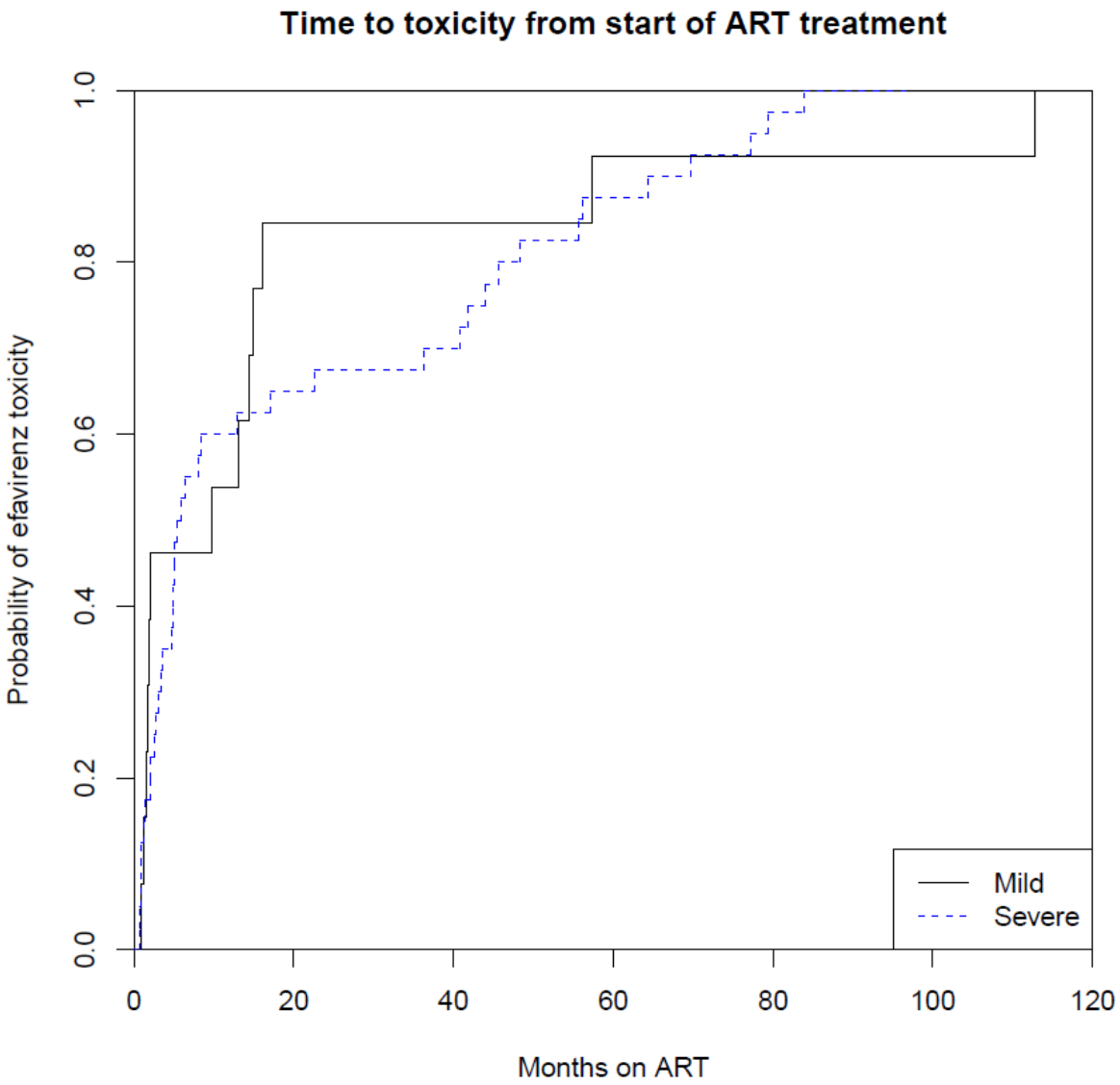

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182 **Figure 1: Empiric Cumulative Distribution Function showing probability of EFV toxicity over time**

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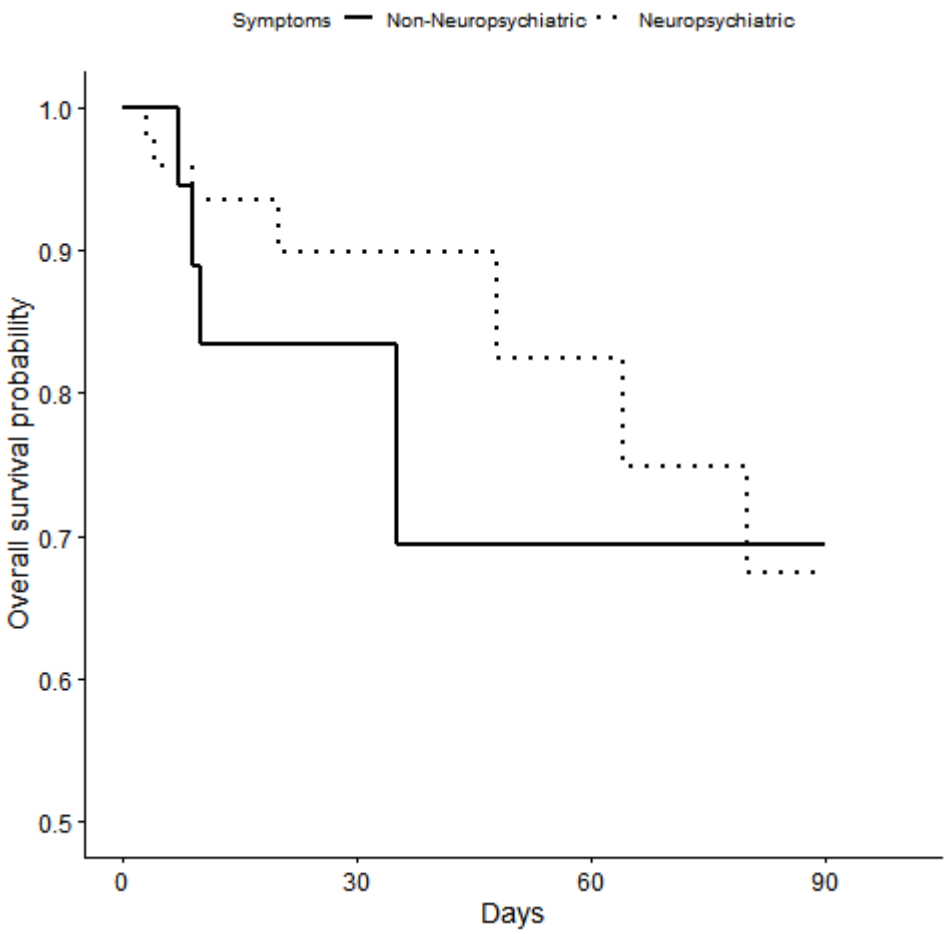

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185 **Figure 2: Kaplan Meier plot comparing survival probability of neuropsychiatric and non-**

186 **neuropsychiatric/hepatitis symptoms**

Predictors of neurotoxicity

INH exposure (aOR 8.2; 95% CI, 2.5 – 26.7), longer duration, per 180 days, of EFV therapy (aOR 1.3; 95% CI, 1.0-1.7), and increasing EFV concentrations per 1mg/L increase (aOR 1.2; 95% CI, 1.1-1.4) were independent predictors of neuropsychiatric symptoms (Table 2). An increase in the CD4 count, per 50 cells/µL, (aOR 0.8; 95% CI, 0.7-0.9) as well as an increase in weight per 10kg (aOR 0.3; CI, 0.1-0.5) was protective against the development of neuropsychiatric symptoms. We could not analyse any relationship between male sex and neuropsychiatric effects as the hepatitis group had only female patients.

Table 2: Associations with neuropsychiatric symptoms

	Univariable OR (95% CI)	**p-value**	**Multivariable OR (95% CI)**	**p-value**
Age	1.0 (1.0-1.1)	0.29		
Weight (per 10kg increase)	0.3 (0.1-0.5)	<0.01		
EFV concentration (per 1 mg/L increase)	1.2 (1.1-1.4)	<0.01	1.3 (1.1-1.6)	0.01
Duration of EFV therapy (per 180 day increase)	1.3 (1.0-1.7)	0.06	1.99 (1.1-3.7)	0.03
Duration of TB therapy (weeks)	1.2 (0.9-1.6)	0.24		
INH exposure	8.2 (2.5-26.7)	<0.01		
CD4 cell count, per 50 (cells/µL)	0.8 (0.7-0.9)	<0.01	0.70 (0.6- 0.9)	<0.01

In blue: backward elimination using AIC = (54.5→52.5) Chi-squared: 3.49; Hosmer-Lemmeshow p=0.89 g=10 (n=69 for multivariable model)

Higher EFV concentrations were associated with severe neuropsychiatric symptoms, with 1.2-fold higher odds (95% CI, 1.1-1.4) with every 1 mg/L increase and 3.1-fold higher odds (95% CI, 1.4 – 6.8) for every 5 mg/L increase (Table 3).

Table 3: Associations with severe neuropsychiatric symptoms

	Univariable OR (95% CI)	**p-value**	**Multivariable OR (95% CI)**	**p-value**
Age	1.0 (0.9-1.0)	0.34		
Weight (10kg)	0.6 (0.3-1.2)	0.18		
EFV concentration (per 1 mg/L increase)	1.2 (1.1-1.4)	<0.01	1.3 (1.1-1.5)	<0.01
Duration of EFV therapy (per 180 days)	1.0 (0.9-1.2)	0.73	0.9 (0.8-1.1)	0.30
Duration of TB therapy (weeks)	0.9 (0.9- 1.0)	0.10		
INH exposure	2.3 (0.6-9.5)	0.26		
CD4 cell count, per 50 (cells/µL)	1.0 (0.8-1.2)	0.93		
Male sex	0.4 (0.1-1.5)	0.17		

In blue: backward elimination using AIC = (47.0→39.3) Chi-squared: 4.9; Hosmer-Lemmeshow: p=0.76 g=10 (n= 47 for multivariable model)

Discussion

We describe a distinct clinical phenotype and factors that may contribute to higher risk of neurotoxicity among 81 patients with elevated EFV concentrations. There were duration- and concentration-dependent effects, as well as higher risk with concomitant INH exposure and those with lower CD4 count. Most patients with severe neurotoxicity had symptom resolution within 1 month after stopping EFV, although overall 3-month mortality was high in this population.

Prior adult studies have involved smaller case report series' of neuropsychiatric symptoms with only female patients (13, 14) but our study is the first to include 45% males in the neuropsychiatric cohort. Female sex has been associated previously with higher EFV concentrations compared with men, possibly due to a higher dose for weight with a standard fixed drug combinations (17,18). However, more recent epidemiological data shows a shift towards higher body weight in women in South Africa, potentially resulting in lower EFV concentrations (19). Men did have a higher median EFV concentration (15.7 mg/L; IQR 6.9-20 vs 10.8 mg/L; IQR 6.6-20) p=0.27, see supplementary figure 2, but we could not ascertain weights from many of the folders, so we cannot conclusively say this difference is due to weight alone.

The protective effect of a higher CD4 count against neuropsychiatric symptoms may also be linked to weight – lower CD4s are associated with lower weights (20). Lower CD4s are also linked to more opportunistic infections including TB (2), placing patients at a higher chance of being exposed to INH, either as part of TB treatment or prophylaxis, which would also increase their risk of EFV toxicity and neuropsychiatric symptoms.

The association between longer duration of EFV therapy and neuropsychiatric symptoms may be linked to direct toxicity of glial cells from EFV metabolites (6), with a cumulative exposure threshold necessary for symptom appearance. Although the exact mechanism of EFV hepatitis symptoms remains unclear, suggested mechanisms include an EFV-induced mitochondrial dysfunction pathway (21). This potential difference in toxicity mechanism may explain why patients with hepatitis appeared to have poorer survival outcomes in the earlier part of their illness, with fulminant liver failure being the cause of death. Decreased survival from neurotoxicity occurred later, coinciding with the later onset of toxicity with prolonged course. A higher EFV concentration was associated with neuropsychiatric but not non-neuropsychiatric symptoms, also adding to the suggestion that there may be different pathological mechanisms in the clinical manifestations of EFV toxicity.

Higher EFV concentration was the only independent risk factor for severe neuropsychiatric symptoms. Symptoms of neuropsychiatric toxicity can be vague and non-specific – patients may have presented later as they only sought medical assistance once symptoms were severe enough to cause impediment to daily functioning, and similarly clinicians may have only done EFV concentrations when they thought symptoms were serious enough to change to alternative ART.

Consistent with other case reports, cerebellar signs and changes in mentation often co-exist or pre-date one another (13,14). The relatively large proportion (41%) of patients with a pre-existing diagnosis of suspected HAND is also in keeping with the finding of long-term neurocognitive depression associated with EFV toxicity (15,22).

Although patients with neuropsychiatric symptoms had abnormalities on their LPs and CT scans, on reviewing the totality of the clincial information, we are fairly certain (acknowledging the limitations of retrospective analysis) that EFV was an important contributor. We did exclude other conditions to the best of our ability, but as the patient cohort was hospitalised in-patients with multiple co-existing comorbidities, an undiagnosed or untreated contributor cannot be excluded.

The median time to EFV neurotoxicity was 6 months in our study, but other case series have noted much longer delays of up to 2 years (14), which might reflect a greater awareness of the presentation of EFV toxicity at the time of our study, as lack of clinician awareness was cited previously as a reason for delayed diagnosis (14).

INH is known to be a risk factor for increased EFV toxicity in those with SNPs (5,23,24) for slow metaboliser genotypes, and in our population INH exposure was a significant risk factor for the development of EFV toxicity and neuropsychiatric symptoms. Pharmacokinetic and pharmacogenetic studies have shown that clearance of INH in patients taking both EFV and INH is highly dependent on the *NAT2* or *CYP2B6* polymorphisms, with presence of the *NAT2* and *CYP2B6* mutations having as much as a five-fold difference in EFV clearance between “slow” and “normal” metabolisers (5,24). With an estimated 20% of South Africa’s population having a slow *NAT2* mutation, and our data suggesting concentration-dependent toxicity, genotyping should ideally be performed prior to co-administering EFV and INH. The association with INH co-administration may also explain why some patients also have a prolonged period of being symptomatic – patients became toxic once INH was co-administered and symptoms took a month to resolve after EFV had been stopped.

Limitations

Inability to obtain accurate, complete data from medical records is a limitation of all retrospective studies. Pre-specified predictors were dropped from multivariable models because of missing data, potentially influencing outputs. Statistical analysis was also further complicated by certain subsets within the cohort being much larger than others, which also likely influenced the outputs of both univariate and multivariate models. Clinical notes detailing the neuropsychiatric condition of patients were not recorded in a standardised manner, so symptom severity may have been misclassified. Interobserver variation was, however, limited by one researcher collecting all the data. Potential cases with neurotoxicity but within the therapeutic EFV concentration range would not have been identified within this cohort, but the finding of a dose-dependent relationship suggests that supratherapeutic concentrations are more likely to lead to neuropsychiatric symptoms.

Ethnicity, a surrogate for metaboliser phenotype, was not included as a parameter in this study as this variable was not consistently recorded and could not be inferred from the available demographic information in the hospital records. We were unable to collect samples for genotyping because of difficulties contacting patients.

Conclusion

This study highlights the clinical heterogeneity of EFV-associated neurotoxicity. EFV toxicity is a reversible condition and recognition is critical to avoid misdiagnosis with potentially fatal outcome with continuation of EFV. Our findings support replacement of EFV by integrase inhibitors as a first line drug in ART programmes (22,23).

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Competing interests

The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.

Author contributions

S.W. and K.C. conceived of the presented idea and were in charge of overall direction and planning. S.W., K.C., and P.A designed the study framework. P.A. collected the data and added to the database, performed the analysis, and wrote the manuscript with input from all authors. R.C. and J.S. assisted in data collection. Z.M. assisted in capturing data onto the database. S.P. assisted in data analysis.

Data Availability

Data supporting the findings of this study are available from the corresponding author P.A. on request.

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Disclaimer

The views expressed in the submitted article are the authors' own and not an official position of the institution or funder.

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Supplementary Appendix

Supplementary Figures

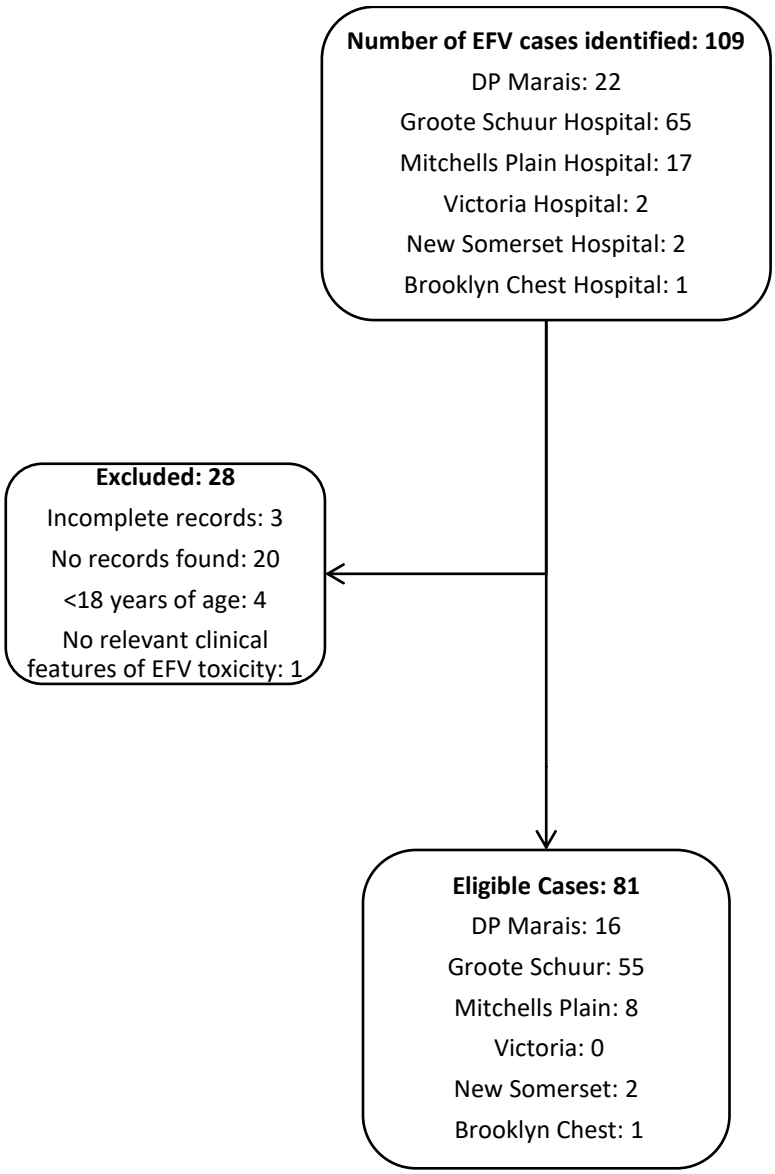
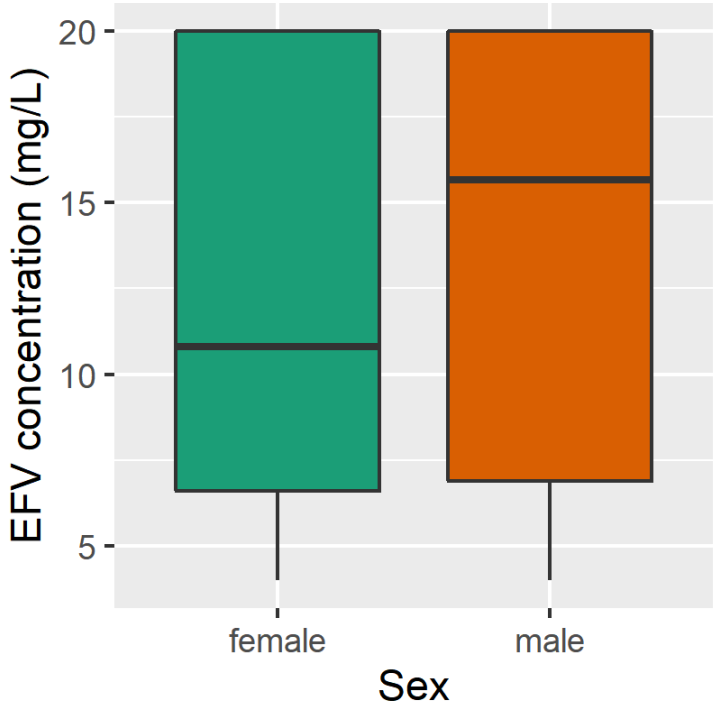


Figure 3: Consort diagram showing selection of cases for study



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418 Figure 4: Box and whisker plot showing distribution of EFV concentrations by sex