

NEUROPSYCHIATRIC COMPLICATIONS OF EFAVIRENZ
IN CHILDREN WITH HIV-1 INFECTION

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DECLARATION BY CANDIDATE

I, Dr Charles Kumi Hammond (student number HMMCHA003), hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicates otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

No aspects of this work were reported or published prior to registration for the above-mentioned degree.

Signature:

Signed by candidate

Date: 16th February 2018

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LIST OF ABBREVIATIONS

3TC:	Lamivudine
ABC:	Abacavir
AEs:	Adverse effects
AIDS:	Acquired Immune Deficiency Syndrome
cART:	Combination Antiretroviral Therapy
CNS:	Central nervous system
CSF:	Cerebrospinal fluid
CT:	Computerized tomography
d4T:	Stavudine
EEG:	Electroencephalogram
EFV:	Efavirenz
GTCS:	Generalized tonic-clonic seizures
HAND:	HIV-associated neurocognitive dysfunction
HIV:	Human Immunodeficiency Virus
HIVE:	HIV encephalopathy
HAART:	Highly Active Antiretroviral Therapy
HREC:	Human Research Ethics Committee
IQ:	Intelligent quotient
LPV/r:	Lopinavir/ritonavir
MRI:	Magnetic resonance imaging
PCR:	Polymerase chain reaction
RCWMCH:	Red Cross War Memorial Children's Hospital
SNP:	Single nucleotide polymorphism
UCT:	University of Cape Town
UNAIDS:	Joint United Nations Programme on HIV/AIDS

CHAPTER 1: PUBLISHED REVIEW

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Neuropsychiatric complications of efavirenz in children with HIV infection

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Abstract

Efavirenz is an effective antiretroviral agent widely used as part of first-line regimen in HIV1-infected children and adults. Neuropsychiatric adverse effects are reported in up to 50% of users. These include dizziness, insomnia, abnormal dreams, headache and impaired concentration. The plasma level of efavirenz may be key in the development of these adverse effects. Even among individuals taking recommended doses for weight, the plasma levels vary widely. Genetic polymorphisms leading to different allelic variants of the CYP2B6 enzyme, making some individuals slow metabolizers may play a role. These allelic variants are highest in people of African descent. This report examines the neuropsychiatric adverse effects of efavirenz, and the strength of the data that the product may result in neuronal damage.

Keywords: adverse events, children, efavirenz, HIV, neuropsychiatric.

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Background

It is estimated that there were 2.6 million children <15 years of age worldwide living with HIV infection at the end of 2014, with approximately 88% living in sub-Saharan Africa [1]. Many of these children are orphans and live in poorly resourced settings and, thus, face huge socioeconomic challenges. With the improved availability of antiretroviral therapy (ART), these children now more often follow a chronic disease course and experience many long-term complications, some from the infection and associated comorbidities, and others as a result of therapy.

The neurologic and psychiatric manifestations in HIV-infected children may result from the infection itself, its secondary complications such as opportunistic infections of the central nervous system, seizures, cerebrovascular disease, as well as the adverse effect of ART. In addition, there is often a complex interplay between these processes and the multiple socioeconomic challenges faced by HIV-infected children living in low- and middle-income countries (LMIC) [2–5]. Frontal lobe dysexecutive function in HIV-infected children and adolescents is thought to be associated with poor virologic suppression (low CD4 count, high viral load) as well as poor socio-demographic and nutritional status (low haemoglobin and albumin levels). In these children, neuroimaging studies and neuropsychological testing have shown white matter micro-structural changes with associated cognitive decline and behavioural deterioration [6,7].

Efavirenz, a widely used non-nucleoside reverse transcriptase inhibitor, was approved in 1998 for the treatment of HIV-1 infection. It binds to a hydrophilic pocket located in the p66 subunit of the HIV reverse transcriptase, which directly inhibits its activity and, thereby, prevents the conversion of ssRNA into DNA during viral replication [8]. Thus, it prevents the formation of new viral particles, slowing down the damage to the host immune system and the occurrence of AIDS-defining illnesses.

It is well absorbed after oral administration. Following a single dose of 600 mg in adults, it reaches a plasma C_{max} of 4.1 mcg/ml in 3–5 h [9,10]. After multiple dosing, steady-state concentrations are achieved between 6 and 10 days [9]. It is 99% bound to plasma albumin [9,10] with an apparent distribution volume of 3.8 l/kg and a bioavailability of 40–45% [10]. Its bioavailability is much enhanced if taken with fatty food [11]. It crosses the blood–brain barrier, and adequate concentrations are reported in the cerebrospinal fluid (CSF) [9,10]. At steady state, its CSF:plasma ratio (also referred to as CSF penetration) is 0.61 (range: 0.4–1.3) [11]. It is metabolized mainly by the CYP450 isoenzyme CYP2B6 and to a lesser extent by CYP3A4, and has an apparent plasma clearance of 9.4 l/h and a long plasma half-life of 40–55 h [9,10]. However, it

induces its own metabolism through the induction of the CYP3A4 and CYP2B6 isoenzymes leading to decreased half-life and tolerance over time [9]. The general pharmacokinetic properties of efavirenz are influenced by many factors including age, sex, bodyweight, ethnicity, concomitant diseases and drug–drug interactions [9,11]. These interindividual variations appear to be responsible for some of the clinical outcomes of the drug. Due to its effectiveness, ease of administration and high tolerability, it is globally listed among preferred HIV treatment options [12,13] and recommended by the WHO as part of first-line ART [13]. However, there is clinical evidence supported by experimental data that it causes damage to neurons with resultant neuropsychiatric effects [14,15]. These adverse events (AEs) are reported in up to 50% of patients [16,17]. Patients report neuropsychiatric symptoms, such as dizziness, blurred vision, impaired concentration, sleep disturbance, headache and loss of memory. Less commonly reported neuropsychiatric AEs include seizures, depression, euphoria, delusions, hallucinations, paranoia, mania and suicidal ideation [16–19].

Though often reported as transient and mild, some neuropsychiatric AEs of efavirenz could be severe enough to lead to poor adherence or discontinuation of treatment, especially since they tend to occur early in the course of the treatment. Typically, the clinical symptoms of efavirenz neurotoxicity start within days of treatment initiation, peak after about a week or two and then finally resolve within 1–3 months despite ongoing treatment with efavirenz [16,17]. However, there is evidence of neurocognitive dysfunction associated with long-term efavirenz use in adults [20]. In children, some experts have predicted poor neurocognitive outcomes following efavirenz neurotoxicity [16]. There are also studies that suggest that the neuropsychiatric complications may persist for at least 2–3 years following efavirenz initiation [21,22].

The WHO does not recommend efavirenz use in children aged <3 years or weighing <10 kg [23]. However, in 2013, the US FDA approved its use to include children younger than 3 years but older than 3 months old. This prompted the Southern African HIV Clinicians Society (SAHIVCS) to release a statement in which they advised against the use of the drug in younger children within the subregion, citing the pharmacogenetic variances of children of African descent, as well as logistic constraints for therapeutic drug monitoring in resource-limited settings [24]. In this statement, the SAHIVCS noted that the *CYP2B6* G>T mutation is more common in the black African population putting these children at increased risk of toxicity especially with the higher doses that were recommended by the FDA. Moreover, genetic testing for the *CYP2B6* G>T polymorphism would not be available outside of research studies, and similarly the routine therapeutic drug monitoring to assess plasma levels of the drug and adjust doses accordingly [24].

This caution is not only useful in South Africa, but also in other parts of sub-Saharan Africa where the *CYP2B6 G>T* polymorphism is widely expressed [25–29]. As in South Africa, routine drug monitoring and genetic testing are not available in these countries. Some authors have recommended a systematic approach to the challenges of pediatric efavirenz dosing in sub-Saharan Africa, to include capacity building for therapeutic drug monitoring, treatment, laboratory and clinical monitoring for optimization of efavirenz in pediatric HIV programs in these regions [30,31].

It is still debated whether the neuropsychiatric complications noted with the use of efavirenz are severe enough for patients to discontinue the medication or to adhere poorly. While some authors have reported poor adherence or discontinuation of treatment following these complications [32–36], others have reported that these side effects are either mild or transient and do not lead to poor adherence or discontinuation of the drug [37–39].

Though CNS adverse effects are also reported in patients taking non-efavirenz-based ART regimens, they are most commonly reported in those on efavirenz. In a study of 408 HIV-infected children and adolescents in Uganda [39], a total of 378 patients were started on ART; 177 on efavirenz-based ART regimens and 201 on non-efavirenz-based ART regimens. There were a total of 39 reported CNS adverse effects including impaired concentration, dizziness, amnesia and nightmares. Twenty-five patients out of the 177 (14%) on efavirenz-based ART reported CNS-related AEs as compared with 14 patients from the 201 (7%) on non-efavirenz-based ART regimens [39]. Though some antiretroviral drugs including both nucleoside and non-nucleoside reverse transcriptase inhibitors (NRTIs and NNRTIs), as well as protease inhibitors (PIs), have been associated with CNS adverse effects [40,41], it must be noted that the incidence of neuronal toxicity in efavirenz is much higher [16,17].

This report will examine the neuropsychiatric AEs reported due to efavirenz. It will assess the strength of the data to support the suggestion that the product may result in neuronal damage. It will also examine the pharmacogenetic factors that may predispose children from some ethnic groups to neuronal toxicity.

Commonly reported neuropsychiatric AEs of efavirenz

While there are many clinical trials that report neuropsychiatric complications of efavirenz in adults [42–47], only one is published in children [27]. There are, however, a few case reports [34,48] and observational studies [33,36,37,39,49,50] that report neuropsychiatric complications of efavirenz in

children. The published case reports, observational studies and one randomized controlled trial in children are summarized in **Table 1**.

Sleep disturbances

Sleep disorders including insomnia, vivid dreams and nightmares are commonly associated with the initiation of efavirenz therapy in both children and adults [16,37–39]. In the first switch study in children aged 2–13 years old in 2003 in which protease inhibitors were substituted with efavirenz [37], the authors reported that two out of the 17 children studied had unusual vivid dreams after they were started on efavirenz while one child also reported insomnia. Mid-dose plasma efavirenz concentrations were not done [37]. In another prospective study to assess the safety and tolerability of ARTs among HIV-infected children and adolescents aged 3–18 years old in Uganda, nightmares were reported by eight out of 177 children who received efavirenz [39]. In adults taking efavirenz, a prospective study that assessed the quality of sleep through patient self-report showed an increase in vivid and unpleasant dreams, an increased recollection of dreams and an overall decrease in sleep quality [38].

The unusual vivid dreams following efavirenz initiation tend to decrease in frequency and intensity after the first 3 months [37], and often do not lead to treatment interruption, but are still potential reasons for some patients to discontinue the drug as they impact negatively on the quality of sleep. Out of five children who reported nightmares in an observational study in France, only one discontinued treatment [36]. In the Ugandan study, none of the eight children who reported nightmares discontinued treatment [39]. In a retrospective study of ten children aged 3–8 years, Funk *et al.* [50] reported efavirenz dose reduction in one child who experienced abnormal dreams and depression and whose plasma level was found to be 24.2 mg/l, over six times the upper limit of normal.

Impaired concentration

Impaired concentration, drowsiness or mental slowing are the most frequent CNS adverse effects of efavirenz, reported in up to 50% of people taking the drug, in both children and adults [18,33]. Mental slowing, drowsiness and later coma were reported in a black South African male adult who later succumbed to aspiration pneumonia [51]. In children, this effect is reported in two prospective studies from Uganda [39] and The Netherlands [33]. The mid-dose plasma efavirenz concentration was not done in the Ugandan study [39], but in the Dutch study it was reported to be increased in a total of 45 (14.7%) of samples tested, mainly from those who reported adverse effects [33].

The impaired concentration following efavirenz intake is thought to be due to a direct toxic effect of the medication on the brain and also the indirect effect of poor night-time sleep on initiation of the medication [33,38]. Thus, patients suffer poor concentration in the morning after a night-time dose. This coupled with visual blurring or dizziness makes it difficult for patients to go about their normal activities of daily living. In children, it is even more problematic when they need to go to school in the morning. In the Dutch study, six out of the eight children who reported AEs (five concentration problems, one sleep disorder, one psychotic reaction and one seizure) discontinued the medication [33].

Neurocognitive dysfunction

Poor neurocognitive outcomes have been reported in adults after long-term use of efavirenz. In a retrospective cohort study of 445 adults in which the long-term impact of efavirenz was compared with a comparator (lopinavir with ritonavir) [20], all patients completed standardized comprehensive testing that assessed various cognitive abilities namely speed of information processing, learning, recall, executive function, verbal fluency, working memory, attention and motor function. The mean duration of use was 1.5 years with good adherence in both groups. Overall, the efavirenz users had worse performance in most neurocognitive abilities than the lopinavir with ritonavir users, particularly verbal fluency, working memory and speed of information processing [20].

In children, the impact of efavirenz on neurocognitive outcome has not been reported. The poor neurocognitive ability of some children with perinatally-acquired HIV infection is largely attributed either to the direct effect of the virus on the brain, a condition termed HIV-related encephalopathy, or to one of the many comorbidities, such as neuroinfections, cerebrovascular disease and epilepsy [2–5]. However, with the current evidence that long-term efavirenz use causes neurocognitive dysfunction in adults, there is the potential that these manifestations could also occur in children.

Dizziness & visual disturbances

Dizziness is well documented as an adverse effect of efavirenz, usually reported as mild and often experienced only in the first few months of starting treatment [36,37,39,49]. In a randomized control trial of 57 children aged 3–16 years, Starr *et al.* [32] tested the safety and antiviral efficacy of an ART combination consisting of efavirenz, nelfinavir and one or more NRTIs. The children were monitored for 48 weeks after the initiation of therapy and pharmacokinetic studies were done to determine the mean values for 24-h area under the concentration-time curve at weeks 2 and 6. Dizziness, reported by eight out of the 57 children, was the only CNS AE noted. It was reported as mild and resolved once efavirenz was given at bedtime, and no child discontinued treatment as a result [32]. However, in an observational

study in 33 French children aged 10–14 years, one child reported persistent dizziness leading to discontinuation of the drug [36]. Ten others also reported dizziness but these were transitory and did not result in drug discontinuation [36].

The feeling of dizziness and mental slowing are usually most intense in the hours leading up to the peak in drug level, usually about 4 h after dosing. Thus, to minimize this effect on the patient's concentration and vision, it is recommended that the medication should be taken at bedtime [52]. However, night-time dosing also increases the incidence of sleep disorders particularly nightmares and unpleasant dreams and, as such, some patients prefer to take the medication in the morning to avoid these sleep disturbances [52].

Blurred vision has also been reported following efavirenz ingestion [48]. In the case of a 12-year-old Ugandan boy who accidentally ingested 3 g of efavirenz (7.5 times the recommended therapeutic dose for his weight), he had impaired vision to near objects that occurred within 1 h of ingesting the drug. He was admitted to hospital for 4 days and responded well to supportive treatment, though plasma levels of efavirenz were not done. Ten days following the ingestion of the drug, his vision had normalized [48].

Varying outcomes are reported following the visual disturbances or dizziness in children taking efavirenz; with either discontinuation of the drug [36] or continued adherence in spite of the dizziness and visual disturbances [37,39].

Psychiatric reactions

Psychiatric reactions including hallucinations, depression, suicidal ideation, aggression, paranoia and mania are described [33,35,36,50,53,54], but their association with efavirenz use is controversial with divided opinions. While some authors link these reactions to efavirenz use [36], others are of the opinion that these AEs are more common in people with a history of psychiatric disorders [53]. A third group of authors argue that there are no links between these effects and efavirenz use [54].

Out of ten children who received first-line triple therapy including efavirenz in a retrospective study, one child was reported to be depressed. There was no previous history of psychiatric illness in this child. Pharmacokinetic evaluation revealed high peak plasma efavirenz levels and the dosage of efavirenz was subsequently reduced with improvement in her condition [50].

In the observational study of 33 children in France who were given efavirenz in combination with other ART drugs, two children had a recurrence of pre-existing psychiatric problems. Efavirenz was discontinued in one child. A third child with no previous history of psychiatric disorder also presented with apathy and

confusion following two nights of nightmares leading the parents to discontinue treatment with efavirenz [36].

Hallucinations and paranoia are reported in adults leading to discontinuation of efavirenz treatment [35]. There is also a concern about an increased risk of suicidal ideation in adults who receive efavirenz, but this is also debated [17,18,54–56]. A recent meta-analysis of four large randomized clinical trials in ART-naive adults suggested that there is a two-fold increased hazard of suicidality (suicidal ideation, attempted suicide or completed suicide) in efavirenz users compared with non-efavirenz users [56]. However, no such association has been described in children.

In view of these psychiatric AEs described above, efavirenz is contraindicated in patients with significant psychiatric comorbidities [17,57], and in these patients, it is replaced by nevirapine or lopinavir/ritonavir. Adults with active psychiatric illness being considered for efavirenz therapy should be evaluated in terms of suicide risk [17].

Others CNS manifestations

Seizures, headache, amnesia, neuropathies and tremors are reported following treatment initiation with an efavirenz-containing regimen [33–37,39,48]. Absence seizures associated with efavirenz initiation were reported in a case of a 5-year-old black South African girl [34]. She was diagnosed with perinatally acquired HIV-1 at age of 52 days and started on an ART regimen containing a PI and two NRTIs. She had a good immune response and viral suppression on this regimen. At age of 4.5 years, she was enrolled into a clinical trial and randomized to substitute efavirenz for the PI. One month postrandomization, she was presented with staring episodes lasting less than a minute and occurring two to three times in a day. She always recovered completely from these episodes without any postictal drowsiness. Her EEG showed generalized burst of high amplitude slow waves and generalized polyspikes, and her mid-dose plasma efavirenz concentration was 19.62 mg/l, almost five times greater than the upper limit of normal. Efavirenz was discontinued and the PI restarted, and the staring episodes abated after 1 month. She also had normal EEG 2 months after discontinuing efavirenz [34].

In another case report, a 45-year-old female was reported to have multiple generalized seizures and later had status epilepticus following marked efavirenz toxicity [35]. Her mid-dose plasma efavirenz level was over fourfold greater than the upper limit of normal. On stopping the efavirenz, these symptoms resolved but recurred when the drug was reintroduced at a lower dosage. The efavirenz was again stopped and her symptoms resolved completely [35].

Headache is reported as one of the CNS adverse effects of efavirenz in children [36]. Six out of the 33 children who were treated with combination ART including efavirenz reported headaches, and two discontinued treatment as a result of the headache. The plasma levels of efavirenz were not determined in this study. Also, the authors did not give further details of the headache or whether it resolved after discontinuing the medication [36].

Tremors and motor deficits were reported in the 12-year-old African boy who accidentally ingested 3 g of efavirenz as a single dose. Additional neuropsychiatric AEs reported in this child include visual impairment and screaming at night [48].

It is important to note that some substances of abuse give similar CNS effects as those reported in efavirenz users. There are anecdotal reports that efavirenz may be misused by HIV patients and noninfected teens who crush the pill and smoke the powder for its psychoactive effects [58]. Animal studies have demonstrated similar mechanisms leading to the CNS effects of efavirenz and substances of abuse, such as lysergic acid diethylamide, cocaine and methamphetamine [58]. These findings correlate, in part, with the subjective experiences in humans who abuse efavirenz to generate specific neuropsychiatric events, such as hallucinations, vivid dreams and night terrors [58].

Pharmacogenetic factors leading to efavirenz toxicity

To be effective, antiretroviral drugs must reach therapeutic levels in the CNS, which is an important viral reservoir. There is evidence that efavirenz readily crosses the blood–brain barrier through simple diffusion [11]. It is hypothesized that the incidence of CNS adverse effects correlates more with the CSF concentration than with the plasma concentration. This, however, has not been tested in children. Even in adults, only a few studies have actually assessed efavirenz levels in the CSF [59–62]. In most pharmacokinetic studies, only plasma levels have been tested and the incidence of neuropsychiatric AEs has been found to correlate with the mid-dose plasma concentration measured at 12–15 h after taking the drug [33,34]. The exact plasma levels above which patients experience these AEs are reported differently from various studies [17,63,64], but mid-dose plasma concentrations between 1–4 mg/l have been observed to achieve maximal control/suppression of viral replication and are relatively safe in terms of short-term AEs [33,50].

In general, younger children often have increased metabolism of drugs compared with older children and adults and, therefore, require higher doses in order to maintain therapeutic plasma drug concentrations

similar to adults. In the case of efavirenz, dosing is done according to weight bands, with comparatively higher doses offered to younger children. For example, to maintain therapeutic plasma levels, the recommended doses for a 3-year-old child weighing 15 kg, an adolescent weighing 35 kg and an adult weighing 70 kg are 250, 400 and 600 mg once daily, respectively [65]. This means the dosage per bodyweight per day in these individuals will be 16.7, 11.4 and 8.6 mg/kg/day, respectively.

Although the mechanism of neuronal damage due to efavirenz remains unknown and requires more exploration, recent *in vivo* and *in vitro* studies have started to clarify these mechanisms. Animal studies have shown that efavirenz induces CNS effects through: upregulated production of proinflammatory cytokines; increase in serotonin levels; acting as partial agonist of the serotonin receptors; disruption of mitochondrial functions and neuronal handling of glucose and oxygen (bioenergetics); inhibition of creatine kinase activity in different regions of the brain; and inhibition of mitochondrial enzymes in the cerebral cortex, hippocampus and striatum [11]. In humans, recent *in vitro* studies have shown that efavirenz disrupts brain mitochondrial function and compromises cell viability by diminishing oxygen consumption rapidly in both neurons and glial cells [11,15,66]. As a result, there is a significant increase in the production of reactive oxygen species and a major decrease in mitochondrial membrane potential, negatively affecting cell viability. Further, it alters the cellular handling of glucose and oxygen leading to intracellular ATP reduction [11,15].

Efavirenz is mainly metabolized in the liver by the CYP450 isoenzyme CYP2B6 into 8-hydroxy-efavirenz. This isoenzyme CYP2B6 metabolizes over 90% of the drug. Another isoenzyme CYP2A6 metabolizes about 8% of the drug to 7-hydroxy-efavirenz and the remaining 2% is conjugated to efavirenz-glucuronide by the enzyme UGT2B7 [11,16]. In patients who ingest normal therapeutic doses of the drug, toxicity usually results from decreased metabolism due to expression of a genetic polymorphism in the CYP2B6 isoenzyme [67,68], drug–drug interactions [68,69] or hepatic or renal dysfunction [67].

Genetic polymorphism

A single nucleotide polymorphism in the CYP2B6 isoenzyme leads to a base change at the position 516 from G to T (CYP2B6–516G>T) and results in three different allelic variants (CYP2B6–516 G/G, CYP2B6–516 G/T and CYP2B6–516 T/T). Individuals with the heterozygous G/T and the homozygous T/T allelic variants express low levels of the CYP2B6 activity, compared with those with the homozygous G/G variant. This leads to decreased metabolism of the drug, and thus increased plasma concentrations putting these individuals at higher risk of efavirenz toxicity [11,68].

The CYP2B6–516G>T mutation is extensively described in the indigenous African (black) population in South Africa. In a study of 142 South Africans in which genotyping results were available from 122 participants (including 104 participants of indigenous African ancestry), 49% (50 blacks and ten other ancestries [nonblacks]) had the G/G genotype, 38% (40 blacks and ten nonblacks) were G/T heterozygotes and the remaining 13% (14 blacks and two nonblacks) were T/T homozygotes [68].

There were also differences in the median efavirenz plasma concentrations among the different genotypes. Individuals with the G/G genotype maintained a median efavirenz concentration of 1.6 mg/l (IQR: 1.0–2.7) while those with the G/T and T/T genotypes maintained higher median concentrations of 2.1 mg/l (interquartile range [IQR]: 1.6–4.7) and 5.9 mg/l (IQR: 3.6–6.8), respectively. Thus individuals with the T/T genotype (mostly blacks) had mid-dosing plasma concentrations higher than the recommended normal range of 1–4 mg/l, and also presented with higher incidence of neuropsychiatric complications, notably severe sleep disturbances [68].

The CYP2B6 516G>T polymorphism is also reported in black populations from other parts in sub-Saharan Africa [26–28,30], and in some nonwhite populations outside Africa [67,70]. In the USA, it is reported to be more common in African–Americans than in Caucasian Americans [67].

Drug interactions between antiepileptic drugs & efavirenz

Children infected with HIV are at increased risk of both infections of the CNS, and neurological deficits due to the direct effects of this neurotropic virus, with the result that seizures and epilepsy are common among these individuals [5]. As such, the concurrent use of ART and antiepileptic drugs (AED)s is inevitable, bringing with it issues of potential interactions between ART and AEDs. Of greatest concern is the P450 enzyme induction effect of the older-generation AEDs (phenobarbitone, phenytoin and carbamazepine) potentially interfering with effective plasma levels of ARTs metabolized by the P450 enzyme system, including efavirenz [71]. These drug interactions may either induce the metabolism of one drug and thereby decrease its plasma concentration or slow down its metabolism leading to toxic levels of the drug in the patient. Interactions that decrease AED levels could lead to loss of seizure control while those that reduce ART levels will result in virologic failure, resulting in immunologic decline, clinical disease progression and development of ART resistance [71].

These drug–drug interactions are even more important in resource-limited settings namely in many parts of sub-Saharan Africa where the management of seizures is still heavily dependent on the use of the older generation AEDs, which are also enzyme inducing. A joint panel of the American Academy of Neurology

and the International League Against Epilepsy (ILAE) made recommendations for the coadministration of ARTs (including efavirenz) and AEDs [71]. The panel found that the efavirenz levels defined as the area under the concentration-time curve were not significantly affected when coadministered with valproic acid. Based on this evidence, they recommended that the coadministration of valproic acid and efavirenz may not require efavirenz dose adjustment. This recommendation was graded level C evidence (derived from only one study with very limited populations evaluated). They, however, did not find sufficient evidence to support or refute pharmacokinetic interactions between efavirenz and the other enzyme-inducing AEDs (phenobarbitone, phenytoin and carbamazepine) and recommended that it may be important to avoid enzyme-inducing AEDs in people on ART regimens that include efavirenz [71].

The authors acknowledged that most of the evidence on which these recommendations were based, were from studies of limited adult populations [71], and so their application to the pediatric age group should be done with caution.

HIV/TB coinfection & impact on efavirenz metabolism

Many children with HIV infection also acquire TB infection and require concomitant treatments with anti-tuberculous and antiretroviral therapies. This scenario is also a potential source of drug–drug interactions as it includes the use of enzyme-inducing medications notably rifampicin and isoniazid.

Rifampicin, a widely used anti-tuberculous drug, induces hepatic enzymes including the CYP450 isoenzyme CYP2B6, the main enzyme involved in the metabolism of efavirenz [72]. Findings from studies that explored the effect of rifampicin-based anti-tuberculosis therapy on efavirenz mid-dosing interval plasma concentrations showed that in patients taking efavirenz, the addition of rifampicin-based anti-tubercular therapy decreases the mid-dosing efavirenz concentration, and this may have a negative effect on HIV viral suppression [68,73]. This has led to some authors suggesting an increase in the dosage of efavirenz in adults to 800 mg once daily when coadministered with rifampicin [73]. In children, recent pharmacokinetic studies found that rifampin-based anti-tuberculosis treatment was not associated with reduced plasma efavirenz concentrations, and did not support increasing efavirenz doses in the pediatric population [74,75].

Recent adult studies have reported that rifampicin-containing anti-tuberculosis regimens may on occasion cause a paradoxical elevation in plasma efavirenz concentration. This increased exposure, which may precipitate neurotoxicity, is the result of CYP2B6 loss-of-function polymorphisms [76–78].

Isoniazid coadministration with efavirenz in adults may cause a mild decrease in the efavirenz mid-dosing plasma concentration without clinically meaningful reduction in viral suppression [79]. However, recent evidence suggests that isoniazid may also contribute to elevated efavirenz concentrations by inhibiting CYP2A6, an important pathway for metabolizing efavirenz in individuals who are CYP2B6 slow metabolizers. Isoniazid is usually metabolized by the enzyme NAT2.

Loss-of-function polymorphisms in NAT2 causes increased isoniazid exposure, increasing the risk of CYP2A6 pathway inhibition. Furthermore, individuals with slow metabolizer phenotypes for both *CYP2B6* and *NAT2* genes have been shown to have markedly elevated efavirenz concentrations when cotreated with rifampicin-containing anti-tuberculosis therapy [77,80].

The WHO [81] and the CDC [82] have specific guidelines for the management of HIV and tuberculosis coinfections. They recommend that patients receive rifampicin during the initial and continuation phases of TB treatment, and efavirenz-based ART after the initial phase or as soon as the TB treatment is tolerated [81,82].

Conclusion & future perspective

Efavirenz commonly causes early neuropsychiatric AEs that are usually mild and transient, resolving within 1–3 months of starting treatment in most patients. However, some children are reported to have severe neuronal toxicity leading to poor adherence, discontinuation of treatment or poor neurocognitive outcomes. Some authors have recommended routine monitoring of therapeutic drug levels, but there is no strong evidence to support this. Also, there are controversies surrounding the use of efavirenz in children aged <3 years old or weighing <10 kg.

There is the need for further studies to better understand the scope and mechanisms of the neuronal damage hypothesized to be associated with efavirenz use in HIV-infected children, as well as the contribution of various pharmacogenetic factors and drug interactions that affect its metabolism. In low- and middle-income countries where second-line AEDs may not be available, priority should be given to further studies on the combinations of efavirenz and first-line AEDs.

Executive Summary

- Transient neuropsychiatric adverse effects are common in both children and adults who receive efavirenz.
- Commonly reported adverse effects in children include dizziness, insomnia, nightmares, impaired concentration and headache.
- Cases of seizures, ataxia and psychiatric reactions, such as depression and hallucination have also been reported. In some adults, the use of efavirenz has been associated with increased suicidality.
- Long-term efavirenz use may lead to poor neurocognitive outcome in children. Worsening performance in verbal fluency, working memory and speed of information processing have been reported in adults using efavirenz.
- The mechanism of neuronal damage due to efavirenz remains unknown but disruptions in brain mitochondrial function and altered cellular bioenergetics are thought to play a role.
- Bodyweight, age, sex, genetic factors and drug–drug interactions may influence efavirenz metabolism and play key roles in the neuronal toxicity.
- Dose adjustments have been suggested by some authors but the lack of routine therapeutic dose monitoring outside of research compounds the practice.

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Table 1: Published cases of efavirenz neurotoxicity

Publication	Type of study	No. of cases & demographic details	Dose of EFV ingested	Mid-dose EFV conc. (ref range: 1-4mg/L)	Neuropsychiatric manifestations	Outcome following AEs
Kenyon <i>et al.</i> [51] 2012 South Africa	Case report	N=1 adult Age: 38 years Male Race: B	Therapeutic doses	Increased (13mg/L 5 days after stopping EFV)	Vivid and unpleasant dreams Lightheadedness Mental slowing Headache Drowsiness, and later coma	EFV discontinued but patient died from aspiration pneumonia
Tukei <i>et al.</i> [39] 2012 Uganda	Prospective study	N=177 children and adolescents Age: 3-18 years Sex and races not specified	Therapeutic doses	Not done	Drowsiness (n=3) Dizziness (n=13) Nightmares (n=8) Amnesia (n=1)	None discontinued treatment. 8 lost to follow up
Nazziwa <i>et al.</i> [48] 2012 Uganda	Case report	N=1 child Male Age 12 years Race: B	Accidental ingestion of 3 grams of EFV	Not done	Visual blurring Nightmares Neuropathies Tremors	Given supportive treatment
Strehlau <i>et al.</i> [34] 2011 South Africa	Case report	N=1 child Female Age: 4.5 years Race: B	Therapeutic doses	Increased (19.62mg/L) 15h after the last dose	Absence seizures Subdued behavior	Discontinued EFV
Wintergerst <i>et al.</i> [33] 2008 Netherlands	Prospective cohort	N=33 children Sex: not specified Age: 2-16 years Race:7B, 24W, 2A	Therapeutic doses	Increased (>4mg/L in 14.7% of samples 8-20h after last dose)	Impaired concentration (n=5) Sleep disorder (n=1) Psychotic reaction (n=1) Seizures (n=1)	6 children discontinued EFV following AEs
Nijhawan <i>et al.</i> [35] 2008 USA	Case report	N=1 adult Female Age: 45 years Race: not specified	Therapeutic doses	Increased (29440 mcg/L by mass spectrometry, ref: 1200-7000 mcg/L) 12h postdose	Seizures (multiple GTCS and later status epilepticus) Insomnia Hallucinations Paranoia	EFV dose reduced and later discontinued

					Confusion	
Mckinney <i>et al.</i> [49] 2007 USA	Prospective study	N=37 children and adolescents Age: 3-21 years 17 females Race: 23B, 5W, 9H	Therapeutic doses (later adjusted upward for younger children who received liquid formulations)	Normal AUC for older subjects who received capsules, lower AUC for younger children who received liquid formulation	Dizziness (n=1)	2 children discontinued EFV (due to rash rather than dizziness)
Moyle <i>et al.</i> [38] 2006 UK	Prospective study	N=10 adults 10 males Age and races: not specified	Therapeutic doses	Not done	Nightmares Increased recollection of dreams Morning sluggishness	None discontinued EFV after AEs
Funk <i>et al.</i> [50] 2005 Germany	Retrospective study	N= 10 children 8 females Age: 3-8 years Races: not specified	Therapeutic doses	Cmin range 0.85-3.55mg/L, Cmax range 2.38-24.2mg/L)	Abnormal dreams (n=1) Depression (n=1)	EFV dosage reduced after plasma level was found to be high (24.2mg/L)
McComsey <i>et al.</i> [37] 2003 USA	Prospective study	N=17 children 10 females Age: 2-13 years Race: 15B, 2W	Therapeutic doses	Not done	Mild transient insomnia (n=1) Nightmares (n=2) Dizziness (n=1) Generalized seizures (n=1)	None discontinued EFV after AEs
Teglas <i>et al.</i> [36] 2001 France	Retrospective study	N=33 children Age: 10-14 years Sexes and races: not specifies	Therapeutic doses	Not done	Transitory dizziness (n=10) Persistent dizziness (n=1) Headache (n=6) Nightmares (n=5) Behavioral problems (n=3)	6 discontinued EFV due to persistent dizziness (n=1), headache (n=2), nightmares (n=1) and behavioral problems (n=2)

Starr <i>et al.</i> [32] 1999 USA	Randomized controlled trial	N=57 children 37 females Age: 3.8-16.8 years Race; 33B, 9W, 15H	Therapeutic doses (later adjusted if AUC was too small)	Mean value for 24 h AUC at weeks 2 and 6 were within normal limits	Dizziness (n=8)	25% discontinued EFV due to other non-CNS AEs
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Key: AE, adverse event; AUC, area under the concentration-time curve; Cmax, maximum plasma levels; Cmin, minimum plasma levels; EFV, efavirenz; GTCS, generalized tonic-clonic seizures; h, hours. Race: B, Black; W, White; A, Asian; H, Hispanic.

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Neuropsychiatric and Neurocognitive Manifestations in Children Treated with Efavirenz in South Africa

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Abstract

Background: Efavirenz is associated with transient neuropsychiatric manifestations but the impact on neurocognition is unknown. Genetically determined black South Africans who are slow metabolizers of efavirenz may be at risk of toxicity. This study describes neuropsychiatric and neurocognitive manifestations of South African children with suspected efavirenz neurotoxicity.

Methods: This retrospective study describes clinical features of 12 children with suspected efavirenz neurotoxicity (2008 – 2014).

Results: Twelve children were referred (aged 3 years 4 months to 12 years, mean 7 years 8 months; 8 indigenous African (black) and 4 mixed ancestry). Six had acute neuropsychiatric manifestations after 2-8 weeks (mean 5 weeks) on efavirenz including drowsiness, seizures, sleep disturbances, behavioural changes, ataxia and slurred speech. Symptoms resolved over a few weeks in four. Two black children were phenotypically slow metabolizers with high plasma efavirenz concentrations above normal range resulting in discontinuation of efavirenz. Nine children had neurocognitive concerns potentially exacerbated by long-term efavirenz (6-72 months therapy; mean 31 months), and showed poor performance in all neurocognitive domains.

Conclusion: Efavirenz causes transient neuropsychiatric adverse effects and may contribute to poor long-term neurocognitive outcomes in HIV-infected children. Genetically slow metabolizers are at risk of neurotoxicity. Prospective studies comparing efavirenz-treated and efavirenz-naïve children are needed.

Key words: Efavirenz, neuropsychiatric, neurocognitive, children, South Africa.

What this paper adds

- Transient neuropsychiatric manifestations are common in South African children receiving efavirenz.
- Efavirenz may contribute to poor neurocognitive outcomes seen in HIV-infected children often diagnosed as HIV-associated neurocognitive dysfunction (HAND).

By 2016 an estimated 320,000 children with HIV infection, between 0-14 years of age, were living in South Africa, with antiretroviral therapy (ART) coverage reaching about 55%.¹ Efavirenz (EFV), a highly potent non-nucleoside reverse transcriptase inhibitor, is a first-line ART drug widely used by HIV-infected children and adults. A once-daily dose is usually given at night. Despite its efficacy and ease of administration, there is emerging clinical evidence, supported by experimental data, that it causes damage to neurons with resultant neuropsychiatric adverse effects.²

Transient neuropsychiatric effects occur in up to 50% of people receiving efavirenz and include dizziness, blurred vision, impaired concentration or drowsiness, insomnia, nightmares, headache, mood changes and seizures.³⁻⁵ Psychiatric manifestations, more common in adults, include depression, euphoria, delusions, hallucinations, paranoia, mania and suicidal ideation.³⁻⁵ Symptoms often start within days of treatment initiation, peak after a few weeks and resolve within 1-3 months despite ongoing treatment.^{3,4} Poor long-term neurocognitive outcomes such as worsening performance in verbal fluency, working memory and speed of information processing in adults are reported after prolonged use of efavirenz.⁶

The mechanism of the neuronal damage in efavirenz toxicity remains unknown. Disruptions in brain mitochondrial function and altered cellular bioenergetics are suggested processes.^{2,7,8} There is wide inter-individual variation in efavirenz metabolism influenced by age, sex, body weight, ethnicity, concomitant diseases and drug interactions.^{7,9} The drug is mainly metabolized in the liver by the CYP450 isoenzyme CYP2B6.¹⁰ In people of African descent, a single nucleotide polymorphism (SNP) in the CYP2B6 isoenzyme results in three different allelic variants with some individuals expressing decreased enzyme activity. These individuals are slow metabolizers of the drug and at risk of neurotoxicity.^{7,11,12}

Although this SNP is widely reported in black (indigenous African) South Africans,¹² and cases of neuropsychiatric manifestations in this population are published,¹³⁻¹⁵ there is no study describing the central nervous system (CNS) complications of efavirenz in South African children. Thus, the scope and nature of the transient neuropsychiatric manifestations seen in children who receive efavirenz and how its long-term use impacts on their neurocognitive outcomes is unknown.

This study describes the neuropsychiatric and neurocognitive manifestations in children following treatment with efavirenz-based ART.

Method

This is a retrospective case series of 12 children who were referred to the Neuro-HIV clinic of the Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town, South Africa. RCWMCH is the largest children's hospital in sub-Saharan Africa, providing multidisciplinary care at an international level within the constraints of a resource-limited country. The Neuro-HIV clinic is a referral clinic for children with neurological complications of HIV. The service reviews an average of 50 new cases a year, with most children diagnosed with HIV-associated neurocognitive dysfunction (HAND), HIV encephalopathy (HIVE) or other specific neurologic conditions such as epilepsy, complications of secondary CNS infections, developmental delay, learning difficulties and behavior problems.¹⁶ Children are evaluated clinically and investigated with neuroimaging, electroencephalogram (EEG) and other neurophysiological testing where indicated. Neuropsychology assessments are completed where relevant. Children with suspected

efavirenz neurotoxicity have additional laboratory investigations including mid-dose plasma efavirenz levels.

Children were identified through the clinic database and were included if diagnosed with HIV infection, have received efavirenz, and had reported neuropsychiatric side-effects following efavirenz initiation. Children were excluded if they had CNS infection or other chronic neurological or psychiatric illness prior to efavirenz initiation. Data was collected on demographics, socioeconomic status, relevant medical histories, neuroimaging and laboratory reports. Neuropsychiatric manifestations following efavirenz initiation were noted. Duration on efavirenz-containing ARTs at the time of referral and the mid-dose plasma efavirenz concentrations which were analyzed at the University of Cape Town (UCT) pharmacology laboratory were recorded.

Neuropsychology reports, where available, were included for additional neurocognitive complications. All neuropsychology tests were conducted by a neuropsychologist. The test battery included all 10 core subsets from the Wechsler Intelligent Scale for Children – Fourth UK Edition (WISC IV) to obtain a full-scale IQ score as well as subscale scores in verbal comprehension, perceptual reasoning, working memory and processing speed. Aspects of executive functioning including visuospatial planning, problem solving, frustration tolerance and ability to understand and follow rules were assessed using the Delis-Kaplan Executive Function System Tower task (D-KEFS). Both the WISC IV and the D-KEFS are internationally recognized neuropsychological tests also used by neuropsychologists in South Africa. In children whose first language is not English, an interpreter was used during the testing. The developmental assessment reports were included for children who were assessed in the child development service using the Molteno Adapted Scale. School reports where available were also included.

All caregivers gave consent for inclusion of the child's details in the clinic database. The UCT Faculty of Health Sciences Human Research and Ethics Committee approved the study (HREC 479/2016) while the RCWMCH Research Committee granted permission for the study.

Results

Between 2008-2014, 12 children were referred with suspected efavirenz neurotoxicity. The children were aged between 3 years 4 months to 12 years (mean 7 years 8 months), and comprised of 5 males and 7 females. Eight children were of indigenous African (black) ancestry and 4 of mixed ancestry.

Table 1 summarises the study group demographics and key findings. Table 2 provides the individual case overviews, while table 3 summarises efavirenz usage and the neuropsychiatric and neurocognitive manifestations.

Acute neuropsychiatric manifestations were reported in 6 of the 12 children; namely impaired concentration or drowsiness (5/12), seizures (3/12), sleep disturbances (2/12), behavioural or personality changes (2/12), acute ataxia (1/12) and slurred speech (1/12). All 6 children had more than one complaint: four had 2 manifestations, one had 3 and another had 4. These manifestations occurred within 2-8 weeks (mean 5 weeks) after starting efavirenz. Patient 2 had seizures and impaired concentration 6 months after starting medication and patient 9 had behavioural and personality changes reported but the duration on efavirenz was not recorded. Of the 4 children who had seizures, 2 were generalized seizures and 2 were focal seizures. Five children had poor concentration and school performance with concern that symptoms

were exacerbated by efavirenz. Direct correlation with change in performance at the time of initiation of treatment was not documented by caregivers, limiting direct assumption of causality.

Eleven children had documentation on neurocognitive, developmental or academic assessments. These included neuropsychology assessments for 6 children, developmental assessments for 4 children and school reports for 7 children. These findings were captured as the long-term neurocognitive manifestations and included low to poor performances in processing speed (5/11), intelligent quotient (IQ) (5/11), attention span (4/11), working memory (4/11), verbal comprehension (3/11), perceptual reasoning (3/11), executive functioning (2/11), and visuospatial ability (1/11) as well as delayed fine motor skills (3/11) and speech/language development (3/11); all of which became evident after long-term use of efavirenz and ultimately led to academic underachievement in 6 children. Multiple complaints were common with one child having 6 manifestations, four had 5 manifestations and two had 3 manifestations.

The total duration on efavirenz at the time of referral to neurology was known for 10 children (range 6-72 months, mean 31 months) and unknown for 2 children but treatment was assumed to be established as neither reported acute manifestations.

Mid-dose plasma efavirenz concentration was done for 10 children. Levels ranged from 0.8 to 69 mg/L (normal reference range 1-4 mg/L). Two children (patients 1 and 6) had high (toxic) levels of plasma efavirenz concentrations (69.0 and >20.0 mg/L respectively). Mid-dose plasma efavirenz concentrations were within normal limits for 8 children.

Illustrative case summaries follow for patients 1 and 6 who had toxic plasma levels of efavirenz:

Patient 1 is a male child of indigenous African (black) ancestry referred to the neurology service in 2008 at 3 years 6 months of age with acute efavirenz neurotoxicity. After an unremarkable birth and postnatal course, he was diagnosed with pulmonary tuberculosis and HIV infection at 11 months of age. He commenced ART at 15 months with a CD4 count of 310 (11.2%). His ART regimen comprised stavudine (d4T), lamivudine (3TC) and efavirenz (EFV). Both his parents tested HIV-positive and his father died of HIV-related complications 2 years later.

One month after starting ART, he had his first GTCS during a febrile illness. At 2 years 11 months of age, he had multiple afebrile GTCS and was noted to be drowsy. He was ataxic, had slurred speech and regression of his motor milestones. His mother reported that the drowsiness was present since he started ART, but the ataxia and slurred speech were new. At this stage, his viral load was less than detectable and his CD4 count was 1549 (37%). His cerebrospinal fluid (CSF) had no cells, normal chemistry and was negative for herpes simplex viruses (HSV 1 and 2), John Cunningham (JC) virus and Cryptococcus neoformans. He had a normal brain CT scan. His EEG showed non-specific generalized slowing and no evidence of non-convulsive status epilepticus. Antiepileptic medication was not initiated. The ataxia resolved over a period of 1 month.

He was re-admitted to hospital at 3 years 6 months of age (7 months after the previous presentation) with acute ataxia and drowsiness. His mother was confused about his medication dosage and had given him 650 mg daily of efavirenz for 2 weeks instead of the prescribed 250 mg. His CSF and a repeat brain CT scan were normal. A repeat EEG showed no evidence of non-convulsive status epilepticus. His plasma efavirenz level was 69.0 mg/L (normal range 1-4 mg/L). Efavirenz was discontinued, leaving his ART regimen as

d4T/3TC. Over 2 weeks, repeated checks of his plasma efavirenz level showed a decrease from 69.0 mg/L to 54.4 mg/L, 36.9 mg/L and 15.2 mg/L. The ataxia resolved after 2 weeks of stopping the efavirenz.

Efavirenz was restarted after 3 weeks and repeated plasma efavirenz levels performed at 1 and 3 weeks remained elevated (12.9 mg/L and 12.0 mg/L respectively). The treatment with efavirenz was continued. Two months later, at age 3 years 9 months old, he was readmitted to the emergency unit with prolonged generalized seizures which required phenobarbital loading. After recovery, he was ataxic. EEG showed generalized slowing and no evidence of subclinical status epilepticus. Efavirenz levels were not performed during this admission. He commenced sodium valproate for seizure management.

At age 3 years 11 months, he was admitted again with GTCS and ataxia. Plasma efavirenz level was 36.4 mg/L. At this stage, he was diagnosed as efavirenz neurotoxicity and treatment with efavirenz stopped. Repeated plasma efavirenz level 5 days after stopping was 28.0 mg/L. He started lopinavir/ritonavir (LPV/r) together with d4T and 3TC. Two months after stopping efavirenz, there were no further seizures, drowsiness or ataxia. Plasma efavirenz level rechecked was 0.4 mg/L. He was thought to be a slow metabolizer.

Over the next 2 years, he remained virologically suppressed on d4T/3TC/LPV/r. His mother who herself continued on efavirenz was twice documented to be “slow” at clinic. Her mid-dose plasma efavirenz level performed during a clinic visit was 4.3 mg/L, just above the upper limit of normal.

This boy had no further complaints of seizures, drowsiness or ataxia. His antiepileptic treatment was stopped at age 7 years after a 2-year seizure-free period. At 8 years of age, he repeated grade 1 with a report from his school teacher indicating poor numeracy skills. Neuropsychology assessment documented a full-scale IQ score of 48 (extremely low range) with extremely low verbal comprehension, perceptual reasoning, working memory and processing speed, with poor executive functioning.

Patient 6 is a black female aged 8 years 4 months when referred in 2012. She was in foster care as both parents were deceased from HIV-related complications. She had prenatal exposure to alcohol and was diagnosed with pulmonary tuberculosis and HIV infection at age 3 years 9 months old.

She commenced first-line ART (d4T/3TC/EFV) at 6 years old. After 21 months of treatment, stavudine was changed to abacavir (ABC) due to lipodystrophy of her face. After 28 months on efavirenz, she was referred to the Neuro-HIV clinic because of poor memory, drowsiness during school hours and nocturnal enuresis. Despite sleeping adequately at night, it was difficult to arouse her in the morning and she often fell asleep in school. Drowsiness and sleep disturbances manifested within a few weeks after starting first-line ART. She struggled academically in second grade mainstream education, which her teacher attributed to poor concentration and memory. Although she had no formal cognitive assessment prior to efavirenz initiation, both foster parent and school teacher noticed changes in her cognition.

At presentation to the Neuro-HIV service, aged 8 years 4 months, she was stunted, underweight for age and had microcephaly. She had no features of foetal alcohol syndrome, was systemically well and had no focal neurological deficits. Her “draw-a-person score” was 5 years.

Her mid-dose plasma efavirenz concentration, performed 2 weeks prior to referral, was above 20.0 mg/L. Neurotoxicity was diagnosed and efavirenz was stopped, leaving her on ABC/3TC. A follow-up plasma efavirenz level was 0.72 mg/L. Brain MRI showed nonspecific T2-weighted signal abnormalities in the right peritrigonal white matter. Neuropsychology assessment showed poor performance in attention, working

memory and processing speed. Her overall IQ was 70 (borderline). Five weeks after stopping efavirenz, her level of concentration had improved, and she was no longer sleepy during the day. She continued treatment with ABC/3TC and recommendation was made for placement in special school.

Discussion

The children in this study were 8 indigenous African (black) and 4 mixed ancestry with complex socio-economic circumstances such as being orphans, uninvolved parents or in foster care. Prenatal alcohol exposure was reported with foetal alcohol syndrome probable in one child. These factors together with the neuroinflammatory effect of HIV itself and the secondary neurological complications result in a complex interplay which impacts on the behaviour of the affected children. Frontal lobe dysexecutive syndrome in HIV-infected children and adolescents may result from white matter damage leading to cognitive and behavioural challenges, including poor concentration and hyperactivity¹⁷ and could contribute to the neuropsychiatric manifestations seen in this cohort. However, most of the acute manifestations in this study were noticed within a few weeks of efavirenz initiation.

Among the suspected acute neuropsychiatric manifestations of efavirenz, drowsiness and impaired concentration were the most common, occurring in 5 out of the 12 children, including the two with high plasma EFV concentrations. In 4 of these children, drowsiness occurred a few weeks after starting efavirenz-based ART, and in the fifth child at 6 months. The medication was discontinued for the 2 children with high plasma efavirenz levels but continued in the other three with resolution of the symptoms over time. Drowsiness is the most common acute CNS manifestation of efavirenz accounting for up to 50% of reported cases.^{5,18} The adverse events seen a few weeks after starting efavirenz typically resolving within one to two months,^{3,4} and may be missed or not reported, especially in children. Night-time dosing is recommended to reduce the effect on the patient's concentration.³

Seizures were the second common manifestation in our cohort. They were reported in 4 out of the 12 children, all treated with valproate with good outcomes, although 1 child required efavirenz discontinuation in addition to AED treatment. The incidence of seizures is generally higher in HIV-infected children.¹⁹ Our study numbers were too small to establish a causal relationship between efavirenz initiation and seizures. However, there are 3 reported cases of seizures in black South African children following efavirenz initiation that required cessation of treatment before seizure control was achieved.^{13,15} All 3 children expressed the CYP2B6 polymorphism rendering them slow metabolizers. Status epilepticus is reported in an adult following marked efavirenz toxicity and required treatment discontinuation.²⁰ In other reports, children continued treatment with efavirenz as seizures were controlled.²¹

Sleep disturbances are commonly reported²² and were documented in 2 of our children. These included insomnia and difficulty waking from sleep in the morning despite adequate night-time sleep. In one patient, this resolved despite continued treatment with efavirenz, but in the other patient it persisted until efavirenz was discontinued. The assumption that sleep disturbances are transient and resolve with time despite continued treatment with efavirenz^{3,4,21} may not be true for slow metabolizers who maintain high and toxic plasma levels even after ingestion of therapeutic doses. There were no nightmares or vivid dreams reported by our children, but caregivers may not have been asked about their presence. These are commonly reported by adults or adolescents.^{22,23}

Ataxia was noticed in one patient with high plasma concentrations of efavirenz. On stopping the medication, there was a gradual improvement in the gait with a corresponding decline in the plasma levels. Ataxia is reported in other black South African children with supra-therapeutic efavirenz levels.¹⁴

Other acute CNS manifestations seen in our children included behavioural or personality changes such as emotional outburst and withdrawn behaviour. Other psychiatric reactions such as hallucinations, depression and suicidal ideation were not reported by our children, but are recognized more in adults and adolescents.^{24,25}

Long-term manifestations included poor working memory, attention span, verbal comprehension, perceptual reasoning, processing speed and visuospatial skills, as well as poor executive functioning and borderline to extremely low IQ (ranging from 48 to 70), all of which can lead to poor academic performance. Poor neurocognitive outcomes following long-term efavirenz use, particularly decreased verbal fluency, working memory and processing speed, are reported in adults.⁶ In children, such outcomes are often attributed to HIV-associated neurocognitive dysfunction (HAND) or HIV encephalopathy (HIVE).^{26,27} In our cohort, developmental assessments also revealed delayed fine motor, speech and language development in 3 children. While these developmental challenges cannot solely be attributed to efavirenz as children with HIVE typically have developmental delays,^{16,27} efavirenz may be exacerbating these outcomes. Nine of the 12 children were diagnosed as HIVE/HAND and 1 as attachment disorder. All 10 children continued their treatment with efavirenz-containing ART.

Mid-dose plasma efavirenz concentration in 8 children were within the normal reference range of 1-4 mg/L. Two patients both of indigenous African (black) ancestry, had high (toxic) levels. Their acute presentations included drowsiness, ataxia, slurred speech, seizures and sleep disturbance. In the long-term, they had low achievements in verbal comprehension, perceptual reasoning, attention, working memory, processing speed, executive functioning and full IQ score. School reports showed poor numeracy skills leading to academic underachievement. In both children, plasma EFV levels decreased weeks after stopping treatment with efavirenz. Their phenotype was compatible with the CYP2B6 SNP making them slow metabolizers of efavirenz and predisposing them to neurotoxicity.

Limitations of the study

The content of this case series is limited by the retrospective data collection. There were no cognitive or developmental assessments documented at the time of efavirenz initiation. Further, only 6 and 4 children respectively had these assessments as part of their evaluation after referral to neurology. Not all children had plasma EFV levels performed, and there was no controlled timing for the EFV levels. It therefore does not establish a causal relationship between efavirenz neurotoxicity and neuropsychiatric manifestations. Limited access to genetic testing did not allow CYP2B6 genotyping in this study.

Conclusion

In this retrospective study, 12 children with complex socio-economic status and on efavirenz-based ART were referred to neurology service for suspected efavirenz neurotoxicity. The acute presentations included drowsiness, seizures, sleep disturbances, ataxia, slurred speech and behavioural or personality

changes. The observed long-term outcomes included poor processing speed, attention span, working memory, verbal comprehension, perceptual reasoning, visuospatial ability, executive functioning and low IQ leading to poor academic performance. Delayed fine motor skills as well as speech/language delay were also noted.

Two children with toxic levels of efavirenz had neuropsychiatric manifestations related to efavirenz. An adverse efavirenz response was suspected for the remaining children. The complex interplay of the difficult socio-economic circumstances in these children, the neuroinflammatory effect of HIV and the secondary complications from opportunistic infections and other treatment besides efavirenz reflect the layering effect of HIV. To better understand the acute neuropsychiatric and long-term neurocognitive complications of efavirenz in South African children, a prospective study is needed to compare the manifestations of HIV-infected children treated with efavirenz and efavirenz-naïve controls. Pharmacogenetic analysis will be important to further understand the risk factors for efavirenz neurotoxicity in children including the role of the CYP2B6 polymorphism.

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Declaration of conflict of interest

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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Table 1: Study summary

Total no. of children referred (N)	12 children
Period of study	January 2008 – December 2014
Age distribution	Range 3 years 4 months to 12 years, mean 7 years 8 months, median 8 years 5 months
Sex distribution	5 males, 7 females
Racial distribution	8 blacks, 4 mixed, 0 whites, 0 Asians
Neuroimaging studies (n=8/12)	3 had brain CT scans: all normal (3/3) 5 had brain MRI; normal (3/5), non-specific signal changes (1/5), old infarcts (1/5)
Acute neuropsychiatric manifestations (n=6/12)	Reported within 2-8 weeks after EFV initiation (mean 5 weeks) and included drowsiness or impaired concentration (5/12), seizures (4/12), sleep disturbances (2/12), behavior and personality changes (2/12), acute ataxia (1/12), and slurred speech (1/12)
Neurocognitive or developmental assessment (n=11/12)	11 had some form of assessment including neuropsychology testing (n=6), developmental assessment (n=4) and school report (n=7). Neurocognitive and developmental difficulties were noted after 6-72 months on EFV (mean 31 months)
Neuropsychology reports (n=6/12)	All 6 children showed borderline, low or extremely low achievements in all domains including poor processing speed (5/6), attention span (4/6), working memory (3/6), verbal comprehension (2/6), perceptual reasoning (2/6), executive functioning (1/6), visuospatial ability (1/6) and borderline to extremely low IQ (5/6).
Developmental assessment reports (n=4/12)	Delayed fine motor development (3/4) Delayed speech/language development (2/4) Age-appropriate development (1/4)
School (or teacher's) reports (n=7/12)	6 children not coping with mainstream curriculum, with 5 repeating various grades 1 child had average performance in mainstream curriculum
Duration on efavirenz before presentation	Mean duration at the time of acute presentation = 5 weeks (range 2-8 weeks, median 4 weeks) Mean total duration at the time of neurocognitive or developmental assessment = 31 months (range 6-72 months, median 23 months) Total duration not known for 2 patients
Plasma EFV levels (n=10/12)	Levels within normal range of 1-4 mg/L (8/10) Levels above normal range (2/10)
Neurologic diagnoses and outcomes	EFV neurotoxicity, EFV stopped (2/12) HAND/HIVE, EFV continued (9/12) Behavioural disorder, EFV continued (1/12)

Key: CT, computerized tomography; EFV, efavirenz; HAND, HIV-associated neurocognitive dysfunction; HIVE, HIV encephalopathy; MRI, magnetic resonance imaging.

Table 2: Demography, relevant history and findings

No	Year presented	Age (y/mo) Sex Race	Socioeconomic status and relevant history	Reason(s) for referral to neurology	Clinical, Laboratory & Neuro-radiological findings	School report, Developmental assessment & Neuropsychology assessment (age at report)
1	2008	3y 6mo Male Black	Lived with mother (HIV+) and 5-year old sister (HIV-). Father died (HIV-related) when he was 3y old. Diagnosed HIV+ at age 11mo when he presented with FTT, PTB and pericardia effusion. Started ART at age 15mo.	Drowsiness and seizures (GTCS) few weeks after starting EFV. Had acute ataxia (with regression of motor milestones) and slurred speech after he was accidentally dispensed with high doses of EFV.	Clinical: Underweight for age and sex. WHO stage 3 disease. Lab: Low CD4 count = 310 (11%) at commencement of ART. EEG: non-specific generalized slowing (x2), normal (x1). Audiology: normal hearing Neuroimaging: normal brain CT scan	School report (grade 2, age 8y 6mo): Functioning below average in all areas. Poor numeracy skills. Neuropsychology report (age 9y 0mo): borderline to extremely low verbal comprehension, low average to extremely low perceptual reasoning, extremely low working memory and borderline to extremely low processing speed. Low achievement on executive functioning. Full IQ score 48 (extremely low).
2	2008	3y 4mo Male Black	Lived with mother who was diagnosed HIV+ during pregnancy. No antenatal PMTCT but had AZT after birth for 6 weeks. No NVP. Diagnosed HIV+ at age 4mo. Father was not involved with care. Started ART at age 21mo. History of poor adherence to ART	Reported insomnia 2mo after starting EFV. Seizures (GTCS) and impaired concentration reported 6mo after EFV.	Clinical: Well grown, hyperactive child with poor concentration. WHO stage 2 disease EEG: Normal awake and sleep EEG. Neuroimaging: normal brain CT scan	Not available
3	2009	4y 4mo Male Black	Diagnosed HIV+ at age 3mo. Mother was sole caregiver until she died of HIV-related condition. Father was not involved. Child placed in institutional care at age 3y. Started ART at age 78mo. Father came back into the picture when he was 7.6y old. He then moved in with father and step mother. History of PTB, FTT, delayed speech and ADHD. Started treatment with methylphenidate at age 6y 3mo.	Seizures (staring, GTCS) and impaired concentration. GTCS started before ART initiation but staring and impaired concentration started 6 weeks after EFV.	Clinical: Normal weight and height for age and sex, but microcephalic. Hyperactive with mild to moderate speech delay. EEG: Normal awake and sleep EEG. Audiology: normal hearing Neuroimaging: Brain CT scan showed calcified mastoid air cells, normal brain parenchymal	Developmental assessment (age 7y 2mo): Delayed fine motor and speech/language development. At chronological age of 86mo, his fine motor development was assessed at 64mo and his language development at 66mo. Conner's questionnaire: completed by both teacher and carer (at age 6y 3mo) suggestive of ADHD.
4	2010	10y Female Black	Forster care (lived with uncle). Mother deceased, no information on father. Pregnancy/birth history not known and no details on when and how HIV was diagnosed and duration on ART.	Poor concentration affecting school work	Clinical: Stunted with long tract signs in the lower limbs. Audiology: Normal audiogram (had poor concentration during testing) Neuroimaging: Not done	School report (grade 2, age 10y): Struggling with mainstream curriculum (repeating grade 2)

5	2012	6y 10mo Male Mixed	Forster care. Both parents deceased (HIV-related). History of alcohol exposure in utero, and FTT, PTB and parotitis at age 13mo. Started ART at 25mo. Diagnosed ADHD at age 6y and was being treated with methylphenidate.	Poor concentration and ADHD.	Clinical: Stunted and microcephalic. Had FAS facies, features of ADHD and long tract signs. Audiology: Normal hearing but slow in responses (needed lots of reinforcement during testing). Neuroimaging: normal brain MRI	Neuropsychology report (age 7y 2mo): Borderline verbal comprehension, borderline perceptual reasoning, low working memory, extremely low processing speed. Verbal IQ 70 (borderline), Performance IQ 70 (borderline), Full scale IQ 62 (extremely low) Conner's questionnaire: completed by foster parent and teacher (at age 6y) suggest ADHD
6	2012	8y 4mo Female Black	Forster care. Both parents deceased. Mother died of pregnancy-related complication when she was pregnant with younger sibling. Father died of HIV-related cause. History of prenatal alcohol exposure and PTB at age 3y + 10mo. Diagnosed HIV+ at age 3y + 10mo and started ART at 6y.	Drowsiness (during school hours), difficult to arouse during sleep, all noticed few weeks after starting EFV. Also has poor concentration and poor memory affecting school work.	Clinical: Stunted and underweight. OFC between 3rd-10th centile. No features of FAS. No focal signs. Noted to be drowsy during clinic visit. Audiology: Normal testing. Neuroimaging: Brain MRI showed non-specific T2W high signal abnormality in the right peritrigonal white matter.	School report (grade 2, age 8y): Not coping with mainstream curriculum. Repeated grade 2. Neuropsychology report (age 8y 9mo): Low performance on attention, working memory and processing speed. (Was drowsy during testing). Full scale IQ 70 (borderline)
7	2013	10y 1mo Female Black	Lived with both parents, (both HIV+) and 2 older siblings (both HIV-). Mother tested HIV- during pregnancy. Had normal early development and generally good health until age 8y when she was diagnosed HIV+. Started ART at 8y.	Poor concentration and poor memory affecting school work leading to school failure.	Clinical: Well grown. Had low central tone, brisk reflexes with spread and crossed adductors. Mirror movement with finger apposition. Audiology: Normal testing. Neuroimaging: Brain MRI showed old lacuna infarct	School report (grade 2, age 10y): slow learner. Difficulties with English language and Mathematics. Repeated grade 2 in mainstream curriculum. Developmental assessment (age 10y 1mo): Poor fine motor skills. Draw-a-person score of 5y (at chronologic age of 10y 1mo old). Neuropsychology report (age 10y 7mo): Extremely low attention, processing speed, verbal comprehension and perceptual reasoning. Intact memory. Verbal IQ 55 (extremely low), performance IQ 69 (extremely low) full scale IQ 60 (extremely low)
8	2013	12y Female Mixed	Lived with both parents (both HIV+). Had a younger sibling who is HIV-. Diagnosed HIV+ at age 4y. History of PTB at 5y. Started ART at 5y.	Poor concentration and poor school performance.	Clinical: Well grown. All growth parameters above 50 th centile. Had long tract signs in all limbs. Audiology: Normal testing. Neuroimaging: Normal MRI	School report (grade 3, age 12y): Struggling with mainstream curriculum (repeated grades 1 and 3)

9	2013	5y 5mo Female Black	Failed PMTCT. Separated from biological mother on day 2 of life and placed in “place of safety” until adopted at age 4mo. Normal early development. Diagnosed HIV+ before age 1y and started on ART at age 24mo.	Withdrawn behavior, emotional outburst (usually at home, never at school, and terrible on holidays)	Clinical: Well grown, normal neurologic and systemic examination. EEG: Normal background, sharply contoured activity noted bilaterally. Neuroimaging: not done	Developmental assessment (age 5y 5mo): Development assessed to be age appropriate. Draw-a-person score of 5y 7mo (at chronologic age of 5y 5mo old)
10	2014	8y 6mo Female Mixed	Lived with mother (HIV+), father was not involved. Diagnosed HIV+ at age 6y. Previous history of LRTI in infancy requiring hospital admission. Had normal early development. Has 2 older siblings from a different father, both HIV-. Started ART at age 8y.	Poor concentration, emotional outburst and personality changes noticed about 2 months after starting EFV	Clinical: Microcephalic. Weight and height above the mean for age and sex. Had brisk DTR with clonus. Audiology: normal hearing Neuroimaging: Brain MRI normal	Neuropsychology report (age 8y 11mo): Low average general intellectual functioning and processing speed, severe to profound impairment in attention and visuospatial ability, borderline working memory, visual memory and executive functioning
11	2014	9y 4mo Male Black	Lived with mother (HIV+). Father deceased (HIV status unknown). History of PTB and FTT at age 11mo when HIV was diagnosed. Started ART at 13mo. Developed hypersensitivity (rash) to ABC and lipoatrophy on AZT. At time of referral, was on 3TC/EFV.	Poor concentration leading to school failure.	Clinical: All growth parameters >50 th centile for age and sex. Normal neurologic examination. Audiology: normal hearing. Neuroimaging: Not done.	Developmental assessment (age 3y 9mo): At chronologic age of 45mo, had significant delay in speech (+/- 30mo) and fine motor development (30-36mo). School report (grade 3, age 9y): repeated grade 1, passed grade 2 and was struggling with mainstream curriculum in grade 3. Neuropsychology report (age 9y 9mo): Marked difficulty with attention, processing speed and language. Memory (verbal and visuospatial) spared.
12	2014	10y 6mo Female Mixed	Lived with grandparents. Mother (HIV+) was on illicit drugs (died when patient was 6y old). Father not involved. Previous PTB and FTT. Diagnosed HIV+ at age 14mo and started on ART at age 17mo. History of poor adherence to ART. Referred by school teacher who reported episodes of absent stares lasting briefly after which she becomes sleepy.	Seizures (staring) and drowsiness few weeks after EFV initiation.	Clinical: Microcephalic with long tract signs. WHO stage 4 disease. Lab: FBC showed pancytopenic picture. EEG: Awake EEG normal Neuroimaging: Not done	School report (grade 4, age 10y): Pursuing mainstream curriculum with average performance.

Key: 3TC, lamivudine; ABC, abacavir; ADHD, attention deficit hyperactivity disorder; ART, antiretroviral therapy; AZT, zidovudine; CT, computerized tomography; DTR, deep tendon reflexes; EEG, electroencephalogram; EFV, efavirenz; FBC, full blood count; FTT, failure to thrive; GTSC, generalize tonic-clonic seizures; HIV+, HIV-positive; HIV-, HIV-negative; mo, month(s); IQ, intelligence quotient; MRI, magnetic resonance imaging; NVP, nevirapine; OFC, occipito-frontal circumference; PMTCT. Prevention of mother to child transmission; PTB, pulmonary tuberculosis; WHO, World Health Organization; y, year(s).

Table 3: Details of EFV treatment and reported neuropsychiatric and neurocognitive manifestations

No	Total duration on EFV (months)	Acute neuropsychiatric manifestations [duration on EFV]	Long-term neurocognitive manifestations	EFV level (mg/L)	Treatment outcomes
1	20	Drowsiness [0.5 month] Seizures (GTCS) [1 month] Acute ataxia and slurred speech [after accidental ingestion of high doses EFV for 2 weeks]	Low verbal comprehension Poor perceptual reasoning Poor working memory Poor processing speed Low executive functioning Extremely low IQ Poor academic performance (poor numeracy skills)	69.00	Diagnosed as EFV neuro-toxicity. EFV discontinued. Levels rechecked 2 months after discontinuation was 0.4 mg/L. Seizures treated with valproate which was weaned after 2-year seizure-free period. Discharged from neurology at age 8y 6mo (5 years after seizure onset)
2	22	Insomnia [2 months] Seizures [6 months] Impaired concentration [6 months]	None reported	Not done	Diagnosed as HAND. Seizures treated with valproate with good seizure control once adherent. Continued treatment with EFV
3	9	Seizures (staring episodes) [1.5 months] Impaired concentration [1.5 months]	Delayed fine motor skills Delayed speech/language development	2.70	Diagnosed as HIVE. Treated with valproate and methylphenidate. Had speech therapy. Continued treatment with EFV + d4T/3TC with virologic suppression, and no worsening of seizures. Relocated to another province at age 8 years.
4	Not known	None reported	Poor academic performance	1.04	Diagnosed as HIVE/HAND. Continued treatment with EFV
5	Not known	None reported	Poor working memory Poor processing speed Extremely low IQ	2.04	Diagnosed as HIVE, FAS, ADHD. Continued treatment with EFV. Special needs school recommended
6	28	Drowsiness [0.5 month] Sleep disturbances [0.5 month]	Poor working memory Poor attention Poor processing speed Borderline IQ Poor academic performance	20.0	Diagnosed as EFV neurotoxicity Discontinued treatment with EFV. Levels rechecked 2 weeks later was 0.74 mg/L. Special schooling was recommended
7	24	None reported	Delayed fine motor skills Low verbal comprehension Poor attention Poor perceptual reasoning Poor processing speed Extremely low IQ	1.92	Diagnosed as HAND. Treatment with EFV was continued

			Poor academic performance		
8	64	None reported	Poor academic performance	3.90	Diagnosed as HAND/HIVE. Continued treatment with EFV. Discharged from neuro.
9	12	Withdrawn behavior [duration on EFV not clear] Emotional outburst behavior [duration on EFV not clear]	None reported	1.28	Diagnosed as behavioural disorder (attachment disorder). Referred to psychiatry
10	6	Emotional outburst [2 months]	Impaired attention Impaired visuospatial ability	Not done	Diagnosed as HIVE. Continued treatment with EFV
11	72	None reported	Speech/language delay Delayed fine motor skills Poor attention Poor processing speed Poor academic performance	0.8	Diagnosed as HAND. Continued treatment with EFV. Special schooling and speech therapy recommended. Further f/up at district hospital
12	26	Seizures (staring episodes) [0.5 month] Drowsiness [0.5 month]	None reported	1.7	Diagnosed as HIVE. Treated with valproate with good seizure control. Continued treatment with EFV

Key: 3TC, lamivudine; ADHD, attention deficit hyperactivity disorder; d4T, stavudine; EFV, efavirenz; FAS, foetal alcohol syndrome; FTT, failure to thrive; GTSC, generalized tonic-clonic seizures; HAND, HIV-associated neurocognitive dysfunction; HIVE, HIV encephalopathy; IQ, intelligence quotient.

APPENDICES

Appendix 1: Data Collection Form

Study ID: [] [] [] []

Patient's folder number: [] [] [] [] [] [] [] [] [] []

Referred from:

a. Demographic details and relevant histories

DOB: ___/___/_____ (dd/mm/yyyy)

Sex: [] Male [] Female

Race: [] Indigenous African (Black) [] Asian

[] European ancestry (White) [] Mixed ancestry

Date diagnosed as HIV positive: ___/___/_____ (dd/mm/yyyy) [] Not known

Age at diagnosis: months [] Not known

Social status at the time of referral: [] Orphan [] Semi-orphan

[] Not an orphan [] Not known

Primary caregiver(s): [] Parents [] Other family member/foster care

[] Institutional care [] Other (specify):

School type: [] Mainstream [] Special education (specify):

[] Not placed

School grade:

Teacher's report (if available):

.....

Other affected family members: [] Yes [] No [] Not known

If Yes, specify:

Comorbidities: [] PTB [] Meningitis [] Seizures ($\geq 2x$)

[] ADHD [] Developmental delay [] Other

Details of comorbidities:

.....

Other relevant histories:

.....

b. Physical findings (at the time of referral)

Anthropometry: Weight: [] [] [] kg Percentile:

Height: [] [] [] cm Percentile:

OFC: [] [] cm Percentile:

Neurological examination:
.....
.....

Other relevant findings:
.....
.....

c. Laboratory investigations and Neuroimaging (at the time of referral or within 3 months)

Absolute CD4 count: CD4%: WHO staging:

Viral load:

Blood counts: FBC: Hb g/dL MCV..... WBC..... PLT.....

LFTs: ALT..... AST..... GGT..... T.Bil.....

Electroencephalogram (EEG): [] Yes [] No

If yes, findings:
.....

Neuroimaging: [] Brain CT scan [] Brain MRI

Findings:
.....

Audiogram: [] Yes [] No

If yes, findings:
.....

2. Neuropsychiatric manifestation:

Date first reported/identified: __/__/____ Date resolved: __/__/____

- How was it managed:
-]EFV continued
 -]EFV dose modified at clinic
 -]EFV stopped temporarily by patient/caregiver
 -]EFV stopped temporarily at clinic
 -]EFV discontinued by parent/caregiver
 -]EFV discontinued at clinic

Other details:
.....
.....

3. Neuropsychiatric manifestation:

Date first reported/identified: __/__/____ Date resolved: __/__/____

- How was it managed:
-]EFV continued
 -]EFV dose modified at clinic
 -]EFV stopped temporarily by patient/caregiver
 -]EFV stopped temporarily at clinic
 -]EFV discontinued by parent/caregiver
 -]EFV discontinued at clinic

Other details:
.....
.....

f. Long-term neurocognitive outcome

1. Neuropsychology assessment: [] Yes [] No

Date of assessment: __/__/____

Chronologic age: (months)

Assessment tool/scale:

Results of assessment and interpretation

Verbal comprehension:

Similarities:

Vocabulary:

Comprehension:

Perceptual reasoning:

Block design:

Picture concepts:

Matrix reasoning:

Working memory:

Digit span:

Letter-Number sequencing:

Processing speed:

Coding:

Symbol search:

Executive functioning:

Visuospatial planning:

Problem solving:

Frustration tolerance:

Ability to understand and follow rules:

Attention span:

Intelligence Quotient

Verbal IQ score:

Performance IQ:

Full scale IQ:

2. Developmental assessment: Yes No

Date of assessment: __/__/____

Chronologic age: (months)

Assessment scale used:

Findings:

Gross motor:

Fine motor:

Communication:

Personal-Social:

Other findings:

.....

3. School reports: Yes No

Grade: Details:

.....

.....

Grade: Details:

.....

.....

g. Other relevant details:

.....

.....

.....

.....

h. Outcome and recommendations from neurology service:

.....

.....

.....

.....

Appendix 2: Human Research Ethics Committee (HREC) Ethical Approval



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: sumayah.ariefdien@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

04 August 2016

HREC REF: 479/2016

Prof J Wilmshurst
Division of Paediatric Neurology
Paediatrics & Child Health
ICH Building Room 514
Red Cross Children's Hospital
Rondebosch

Dear Prof Wilmshurst

PROJECT TITLE: NEUROPSYCHIATRIC COMPLICATIONS OF EFAVIRENZ IN CHILDREN WITH HIV INFECTION (MPhil candidate - Dr C Hammond)

Thank you for your response letter dated 22 July 2016, addressing the issues raised by the Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 August 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

We acknowledge that the student, Dr C Hammond will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

Yours sincerely

pp T. Burgess
PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.

HREC 479/2016

Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix 3: Ethics Renewal




UNIVERSITY OF CAPE TOWN
UNWELIKE FASIKANE - UNWELIKELETHI SAN GASTHUS

HUMAN RESEARCH ETHICS COMMITTEE
- 8 JAN 2018
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee



FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001638)			
This serves as notification of annual approval, including any documentation described below.			
<input checked="" type="checkbox"/> Approved	Annual progress report	Approved until next renewal date	30.1.2019
<input type="checkbox"/> Not approved	See attached comments		
Signature Chairperson of the HREC			Date Signed
			10/1/2018

Comments to PI from the HREC

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	06/01/2018		
HREC REF Number	478/2018	Current Ethics Approval was granted until	30/08/2017
Protocol title	Neuropsychiatric complications of efavirenz in children with HIV infection		
Protocol number (if applicable)	n/a		
Are there any sub-studies linked to this study?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.	n/a		
Principal Investigator	Prof Jo Wilmshurst		
Department / Office Internal Mail Address	Department of Paediatrics and Child Health, Division of Paediatric Neurology, ICH Building Room 514, Red Cross War Memorial Children's Hospital, Rondebosch, Cape Town		



1.1 Does this protocol receive US Federal funding?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
1.2 If the study receives US Federal Funding, does the annual report require full committee approval?	<input type="checkbox"/> Yes	<input type="checkbox"/> No

Note: Any annual approvals for Full Committee review MUST be submitted on the monthly HREC submission dates.

If yes in 1.2 please complete section 1.3 below for invoicing purposes

1.3 Annual Approval for full committee review - R 3420 (inclusive of vat)

For invoicing purposes, please provide:

Sponsor's name	
Contact person	
Address	
Telephone number	
Email Address	

2. List of documentation for approval

--

3. Protocol status (tick ✓)

<input checked="" type="checkbox"/>	Open to enrolment
<input type="checkbox"/>	Closed to enrolment (tick ✓)
<input type="checkbox"/>	Research-related activities are ongoing
<input type="checkbox"/>	Research-related activities are complete, long-term follow-up only
<input type="checkbox"/>	Research-related activities are complete, data analysis only
<input type="checkbox"/>	Main study is complete but sub-study research-related activities are ongoing
<input type="checkbox"/>	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

Number of participants enrolled to date	12
Number of participants enrolled, since last HREC Progress report (continuing review)	12
Additional number of participants still required	80


5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	0
---	---

6. Cumulative summary of participants

Total number of participants who provided consent	n/a
Number of participants determined to be ineligible (i.e. after screening)	n/a
Number of participants currently active on the study	0
Number of participants completed study (without events leading to withdrawal)	12
Number of participants withdrawn at participants' request (i.e. changed their mind)	n/a
Number of participants withdrawn by PI due to toxicity or adverse events	n/a
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	n/a
Number of participants lost to follow-up. Please comment below on reasons for loss of follow-up.	n/a
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	n/a

7. Progress of study

Please provide a brief summary of the research to date including the overall progress and the progress since the last annual report, as well as any relevant comments/issues you would like to report to the HREC:

The study has 2 components: a retrospective case series of 12 participants and a prospective study of 90 participants. So far, the retrospective review is completed and at the report writing stage. The prospective study is yet to start pending funding.

8. Protocol violations and exceptions (tick ✓ all that apply)

<input checked="" type="checkbox"/>	No prior violations or exceptions have occurred since the original approval
-------------------------------------	---

<input type="checkbox"/>	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved
<input type="checkbox"/>	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review

9. Amendments (tick ✓ all that apply)

<input checked="" type="checkbox"/>	No prior amendments have been made since the original approval
<input type="checkbox"/>	Prior amendments have been reported since the last review and have already been approved
<input type="checkbox"/>	New protocol changes/ amendments are requested as part of this continuing review (See note below)

Note: If new protocol changes are being requested in this review, please complete an amendment form [\(FHS008\)](#).

Specific changes in the amended protocol and consent/assent forms must be bolded, *italicised* or tracked and all changes must include a rationale.

10. Adverse events

10.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC). Please comment on whether causality to any study procedure or intervention could be established.

n/a

10.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?

<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input checked="" type="checkbox"/> Not applicable
------------------------------	-----------------------------	--

If yes, please describe:

11. Summary of Monitoring and Audit Activities (tick ✓)

11.1 Was this study monitored or audited by an external agency (e.g. MCC, FDA)?

<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input checked="" type="checkbox"/> Not applicable
------------------------------	-----------------------------	--

11.2 Did a Data and Safety Monitoring Board publish a report?

<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input checked="" type="checkbox"/> Not applicable
------------------------------	-----------------------------	--

11.3 If yes, please identify the agency and attach a summary of the findings.

Agency Name		Report attached	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Not applicable
		DSMB report attached	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Not applicable



11.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
If yes, please explain:	

12. Level of risk (tick ✓)

12.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
<input type="checkbox"/>	Increased
<input type="checkbox"/>	Decreased
<input checked="" type="checkbox"/>	Shown no change
If there has been a change, please explain:	

12.2 Please provide a narrative summary of recent relevant literature that may have a bearing on the level of risk.
n/a

13. Statement of conflict of interest

Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
If yes, please explain and if necessary attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form FHS013):	

14. Signature

My signature certifies that the above is complete and correct.			
Signature of PI		Date	05/01/2018

Appendix 4: Red Cross War Memorial Children's Hospital Research Committee Approval



Dr AS Booysen
Manager: Medical Services
Email: Tony.Booyesen@Westerncape.gov.za
Tel: +27 21 658 5788 fax: +27 21 658 5166
RXH: RCC40

Dr C Hammond
Red Cross War Memorial Children's Hospital

Dear Dr C Hammond

APPROVAL OF RESEARCH

PROJECT TITLE: NEUROPSYCHIATRIC COMPLICATIONS OF EFAVIRENZ IN CHILDREN WITH HIV-1 INFECTION

It is a pleasure to inform you that approval is hereby granted to conduct the above-mentioned study at Red Cross War Memorial Children's Hospital.

Yours sincerely,

A handwritten signature in black ink, appearing to read "A. Booysen", written over a horizontal line.

Dr AS Booysen
Manager: Medical Services
Date: 07.10.16

Appendix 5: Reviewers' comments for published paper (chapter 1)

Title: Neuropsychiatric complications of efavirenz in children with HIV infection

Reviewer: 1

1. Several sections of this MS should be broadened/expanded as both the cell count and the number of references are quite below the suggested maximum limit. There is a lot of information that is simply mentioned without being analyzed in detail.
2. The authors discuss together “visual disturbances” and “dizziness” but these two effects are different and need to be clarified in greater detail. Please address this in the manuscript.
3. The section “Future perspective” does not correspond with the title of this work as it is only general information and no reference to children is made.
4. The MS would benefit for a global check of the language style. At some points there is repetition of information. At other points, the information presented does not flow smoothly. These corrections will add value to the MS and make it easier to read.
5. It would be very helpful to state in the text the plasma concentration of EFV in the clinical studies referenced. Is there a link between the EFV plasma concentration and the adverse effects observed?? Is there evidence for this in children?
6. In the main text, the authors should state exactly the age of the children in the studies in question if that information is available. The age difference in children may be a crucial factor for the side effects detected. The authors should discuss this.
7. Is there any evidence associating EFV-linked CNS effects and drugs of abuse in pediatric population?
8. Is there evidence that EFV-induced AEs are related to the other ARV drugs in the multidrug regime?
9. The authors state that “Efavirenz is mainly metabolized in the liver by the cytochrome P450 isoenzyme CYP2B6...”. What is known about this metabolic system in children (in the case of other drugs)? Are there changes in the EFV metabolism between adults and children?
10. What other factors regarding the pediatric subjects studied and referred to in this MS may be interfering with the effects recorded for EFV use. Body weight? Sex? Other comorbidities? Concomitant confections?
11. Several statements in the paragraph. “It is well absorbed after oral administration. Following a single dose of 600 mg in adults, it reaches a maximum plasma concentration (C_{max}) of 4.1

mcg/mL in 3-5 hours. After multiple dosing, steady-state concentrations are achieved between 6-10 days. It is 99% bound to plasma albumin with an apparent distribution volume...” lack references. Please add in relevant references to support the data.

12. The mechanistic studies regarding the mechanism by which EFV interferes with brain function includes assays performed in vitro (ref 8,9, 48). This needs to be clearly stated in the MS. Also, there are several other studies performed in vitro or in vivo that have to be mentioned (reviewed in Apostolova N et al., JAC, 2015; doi: 10.1093/jac/dkv183).
13. The paragraph starting “These drug interactions are even more important...” and the one starting with “The panel found that the efavirenz...” should not be separate ones but a continuation of the previous paragraph in each case.
14. In the table legend, “No. of cases & demographic details” should stand “N° of subjects and demographic studies”.

Reviewer: 2

This Review summarizes papers concerning neuropsychiatric complications in children receiving efavirenz within HAART regimes. Efavirenz is recommended by the WHO as a first line drug and became therefore the most common anti-HIV drug in sub-Saharan countries. It is known that one of the most predominant adverse events of efavirenz are neuropsychiatric complications in diverse forms. The magnitude often correlates with plasma peak concentrations. These known adverse events are quite complicated in children due to body weight and body surface related drug dosing and different active CYP2B6 metabolizing enzyme system. All these points are well reflected by the authors of this review who did a very good job.

1. In the introduction (Page 3, line31), the authors should consider that efavirenz is supposed to induce its own metabolism via CYP2B6 induction, which may shorten its half-life over time. Additionally, efavirenz combination with tuberculosis drugs (rifampicin) in HIV/TB co-infected patients may result in reduced efavirenz plasma levels due to the CYP induction by rifampicin. The authors should mention this in the introduction.
2. In the chapter 'drug interactions', the authors should consider extending it with a focus on the HIV/Tuberculosis co-infection, since rifampicin is a strong influencer of efavirenz plasma levels.

Appendix 6: Author Guidelines for *Developmental Medicine & Child Neurology*

Updated January 2018

All papers should be submitted online at <http://mc.manuscriptcentral.com/dmcn>. Please email the editorial office with any queries about the process (dmcn@editorialoffice.co.uk).

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1. Good publication practice

The journal follows the guidelines of the International Committee of Medical Journal Editors (www.icmje.org) and Wiley's Best Practice Guidelines on Publication Ethics (www.wiley.com/bw/publicationethics/). In particular, please note the following points.

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1. substantial contributions to research design, or the acquisition, analysis or interpretation of data;
2. drafting the paper or revising it critically;
3. approval of the submitted and final versions.

The corresponding author must state that all the authors have read the manuscript and agreed to its being submitted for publication. The covering letter should state that all individuals listed as authors meet the appropriate authorship criteria, that nobody who qualifies for authorship has been omitted from the list, that contributors and their funding sources have been properly acknowledged, and that authors and contributors have approved the acknowledgement of their contributions. The covering letter should include a short description of each author's contribution and should state whether he or she had complete access to the study data that support the publication.

Up to ten authors may be included on the title page. When there are more than ten authors, nine may be included on the title page and the tenth slot given to an appropriately named group; the members of this group will be listed in an appendix published online only. The authors listed in the study group will still be recognised as collaborators of the paper in search engines such as PubMed.

Contributors who do not qualify as authors should be listed, and their contribution described, in an acknowledgement section at the end of the article.

b) Reporting guidelines:

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Submissions must be accompanied by the appropriate checklist, fully completed with page numbers where applicable. Please select the most suitable checklist from the following and download the appropriate checklist:

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3. Presentation and formatting of your paper

a) Maximum length requirements

Article type	Abstract	“What this paper adds”	Text words (excl refs)	References	Figures/ tables
Original article	Structured, 200 words	1 to 5 points	3000	30	4
Systematic review	Structured, 200 words	1 to 5 points	As appropriate		
Other review	Unstructured, 150 words	1 to 2 points	3000	30	4
Case report	Unstructured, 150 words	1 to 2 points	1500	15	2
Letter to the Editor	None	None	600	5	1
Editorial, commentary, opinion	None	None	600	5	0
Clinical Insights	None	None	200-300	2	1

b) All papers

Title page Include the title of the paper, authors’ full names, main appointments and primary affiliations, and word count. Identify the corresponding author and give his or her postal address and e-mail address.

We encourage corresponding authors to provide an ORCID (Open Researcher and Contributor ID) identifier. ORCID is a registry that provides researchers with a unique digital identifier. Some funding

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Abstract On the second page of original articles and systematic reviews, provide a full structured abstract of no more than 200 words, with the following headings: Aim; Method, Results, Interpretation. The Aim and Interpretation sections should use plain language, as they will be available openly—that is, independent of the main paper. Where relevant the Method section should follow Equator guidelines (<http://www.equator-network.org/>), and should include means (sd) or medians and sex for study and control groups, definition of clinical characteristics, entry criteria for study, assessments used, duration and frequency of intervention, and timing of outcome assessments. Where relevant “Results” should follow Equator guidelines and should summarize significant results with statistical values, including negative findings if related to the study hypothesis. Non-significant trends should not be noted in the abstract.

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On the abstract page, also provide a shortened form of the title (up to six words) for use as a running footer.

‘What this paper adds’ All original articles and systematic reviews should have a section ‘What this paper adds’ after the abstract. This should comprise up to five bullet points up to 12 words. Other articles should have one or two similar bullet points.

The bullet points should contain only new results offered by the paper (i.e. not the paper’s design or implications), presented in a direct way. They should be succinct, and preferably they should use plain language because the ‘What this paper adds’ section will be openly accessible (that is, free to view by anyone).

General Include tables and figure legends in your main article file, after the references. Submit figures (illustrations) as separate files, as described below. Name all files using the surname of the first author (e.g. Smith.doc, Smith fig1.tif, etc.).

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Articles should comprise an introductory section (but not headed ‘Introduction’), followed by ‘Method’ (with optional subheadings, such as ‘Participants’ [rather than ‘Subjects’] and ‘Statistical analysis’), ‘Results’, and ‘Discussion’ sections. The Discussion section should include the limitations of the study. Subheadings should otherwise be kept to a minimum.

Authors are encouraged to submit video material supporting their papers, where appropriate, for publication in the Journal.

Papers longer than 3000 words, such as those reporting randomized controlled trials, may be published at the Editors’ discretion.

Randomized controlled trials should include a short trial protocol as supplementary information.

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We publish two types of review. One is a fully detailed comprehensive review of a subject, such as a systematic review, with full referencing and a word-count appropriate to the topic and amount of material to be covered. The other is intended to be a more personal view providing the reader with up-to-date information about the subject in question in a relatively brief format, referring to significant international papers but not forming a comprehensive overview of the literature.

Authors are advised to refer to the paper by [Grant et al: A Typography of Reviews published in Health Information and Libraries Journal, 2009](#), 26:2, before submitting a review paper to DMCN.

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DMCN accepts a very limited number of case reports. These should significantly add to our understanding of a condition or present a novel finding. They should comprise an introductory section as above, followed by the 'Case Report', then a 'Discussion' section.

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Letters are published at the Editors' discretion. They may comment on a published paper, or raise issues that are new to DMCN. In the case of letters commenting on a published paper, normally the author of that paper will be invited to comment on the letter, with both letter and comments being published in the same issue. The editor may suggest the letter is made available online on the Mac Keith Press website, without formal publication, to encourage debate (see <http://www.mackeith.co.uk/journal/letters-to-the-editor/>).

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Journal Article

Abrams RA, Tsai AM, Watson B, Jamali A, Lieber RL. Skeletal muscle recovery after tenotomy and 7-day delayed muscle length restoration. *Muscle Nerve* 2003; **23**: 707–14.

Auvin S, Joriot-Chekaf S, Cuvellier JC, Vallée C. Familial alternating hemiplegia of childhood or channelopathy? [letter]. *Dev Med Child Neurol* 2004; **46**: 500.

Journal Article, online only

High PC; the Committee on Early Childhood, Adoption, and Dependent Care and Council on School Health. School readiness. *Pediatrics* 2008; **121**: e1008–15.

Journal Article, e-pub/online early

Forsyth R, Basu AP. The change we want to see: the promotion of recovery after acquired brain injury. *Dev Med Child Neurol* 2014 Sep 8. doi: 10.1111/dmcn.12575. [E-pub ahead of print].

Book, whole

Mesibov GB, Kunce L, Schopler E. Asperger syndrome or high functioning autism? Current issues in autism. New York: Plenum Press, 1998.

Book, chapter

Finnegan LP, Kaltenbach K. Neonatal abstinence syndrome. In: Hoekelman RA, Nelson NM, editors. Primary pediatric care. 2nd edition. St. Louis: Mosby Yearbook, Inc., 1992: 1367–78.

For references to online sources, supply the author names, full title, and full URL including the date on which the site was accessed.

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Note that the Editors may decide that large figures or tables should be published online-only.

Tables, figure legends and short appendices Set out on separate pages at the end of (and as part of) the main document, after the references.

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The Editors advise reading “Statistical recommendations for papers submitted to *Developmental Medicine & Child Neurology*” ([Rigby AS, Dev Med Child Neurol 2010; 52: 299–304](#)) for guidelines on appropriate use and reporting of statistical analyses. Authors are recommended to work with a statistician where appropriate.

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4. Selection and publication

a) Editorial review

Submissions are subjected to an editorial discussion about their general suitability for the journal. This may lead to the decision to not accept the paper, or to send for review by at least two independent referees. During the submission process, authors have the opportunity to suggest up to three suitable independent referees (with their contact details), but the choice of referee rests with the Editors. At a later stage in the review process, papers with statistical analyses undergo specific statistical review.

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5. Style points

Jargon Avoid it strenuously. The journal aims to communicate across disciplines, and many of its readers do not have English as their first language, so plain language is preferred. The Editors may clarify and shorten manuscripts accepted for publication as necessary.

Abbreviations These should be kept to a minimum and restricted to those that are generally recognised. They must be spelled out in full on first usage in text and again in figure captions and table footnotes. They should be avoided in titles, headings and subheadings.

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