



Gaida, Razia and Truter, Ilse and Grobler, Christoffel and Kotze, Theunis and Godman, Brian (2016) A review of trials investigating efavirenz-induced neuropsychiatric side effects and the implications. Expert Review of Anti-infective Therapy, 14 (4). pp. 377-388. ISSN 1744-8336 , <http://dx.doi.org/10.1586/14787210.2016.1157469>

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A review of trials investigating efavirenz-induced neuropsychiatric side effects and the implications

Review Article

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(Accepted for publication in Expert Review of Anti-Infective Therapy. Please keep CONFIDENTIAL).

Abstract

Background: Efavirenz is part of the first-line treatment for HIV patients including South Africa with approximately 50% experiencing neuropsychiatric side effects. *Objective:* Systematic review of papers reporting neuropsychiatric side effects with efavirenz published between January 2001 and December 2014 to provide guidance. *Results:* 13 articles were reviewed. Patient ages ranged between 37 to 41 years, with a high percentage males. Scales used to measure incidence and severity of side effects were varied; with disease severity or stage not reported. Patients with psychoses were excluded. Most commonly reported side effects were a reduction in sleep quality, depression, dizziness and anxiety. These were generally mild and not warranting discontinuation of efavirenz. *Conclusion:* Difficult to directly compare the studies. Standardised methods need to be introduced and all patient groups represented including the elderly, children, patients with active symptomatic illness and more women especially among the African population.

Introduction

Efavirenz is part of the first-line treatment for human immune-deficiency virus (HIV) in countries such as South Africa¹. It is used as part of triple therapy involving three separate drugs as well as fixed-dose combinations. However, it has been shown in published studies that almost half of the patients initiated on efavirenz will experience some form of

neuropsychiatric side-effect^{2,3}. These side effects are said to occur most commonly within the first few days of treatment and resolve within the first four to six weeks of treatment⁴. However, it has been found that such symptoms may persist longer than initially thought⁵⁻⁷. The symptoms may persist for up to two years after initiation, although they may not be severe enough to warrant the discontinuation of efavirenz⁶. The aim of this review was to provide an overview of the neuropsychiatric side effects caused by efavirenz in order to determine the severity as well as their use in particular patient populations including, psychiatric patients, to provide future guidance.

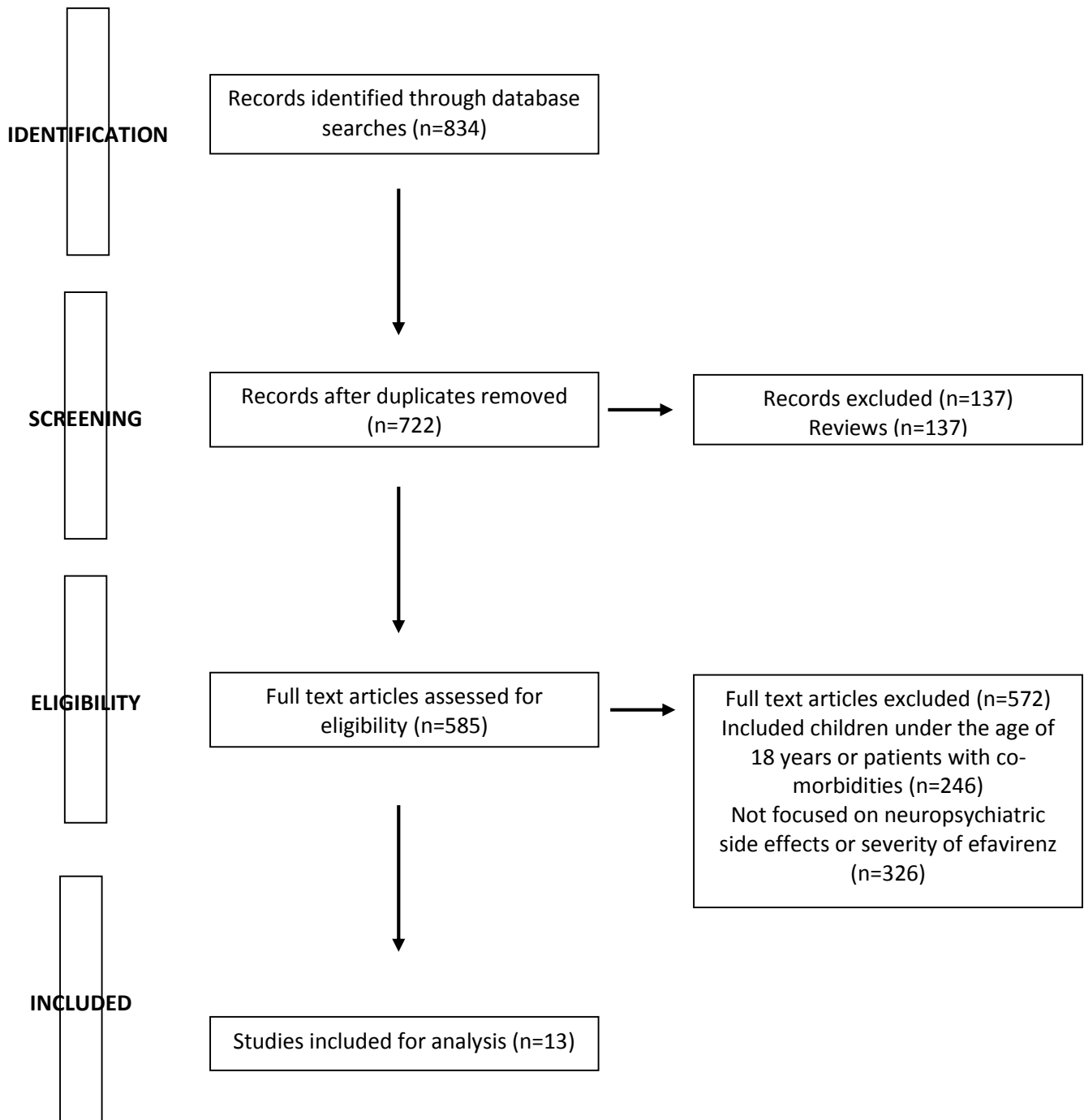
Methods

We undertook a systematic review of studies concerning HIV-positive patients on efavirenz reporting experiencing neuropsychiatric side effects. All primary studies published from January 2001 to December 2014 were included.

The inclusion criteria were that patients had to be over the age of 18 years who were HIV positive, the study had to follow patients who were using efavirenz either short term or long term and could be retrospective, prospective, cross-sectional or comparison studies. The primary outcome must indicate the incidence of neuropsychiatric side effects with a secondary outcome being the number of discontinuations due to these side effects. The electronic databases searched included; Biomed Central, EBSCOhost, Emerald, ISI web of knowledge, JSTOR, PubMed Central, SAGE, ScienceDirect and SpringerLink. The search terms used were; efavirenz, HIV-positive, neuropsychiatric, side effects, to find primary studies. A broad search was done initially using the keywords efavirenz, HIV-positive and side effects. The keywords were then refined (efavirenz, HIV, neuropsychiatric side effects) to identify more specific studies. Articles that contained these keywords in the title or abstract were extracted and their relevance was determined. Review articles as well as those including children under the age of 18 years and patients with co-morbidities were excluded.

Those that were considered relevant were read in entirety by the principal researcher (RG) to determine potential inclusion. The articles included and excluded are outlined in Figure 1. The search was limited to English language full-text articles published in journals accessible *via* the Nelson Mandela Metropolitan University database.

Figure 1. Articles included and excluded in the systematic review



Results

- *Overview of studies*

Of the studies analysed, two were randomised controlled trials, one was double-blind, but not randomised, four were cross-sectional cohort studies, four were prospective cohorts, one a retrospective analysis and another a longitudinal study. Four studies randomised patients to either efavirenz or another regimen. The other studies included patients who were already receiving efavirenz or a different regimen and were compared against each other. Five of the studies were conducted in Europe (Spain and France), four in the United States of America (USA) and one each in Australia, South Africa and the United Kingdom. Details of the studies are summarised in Table 1.

Insert Table 1

- *Patient populations*

Patients were recruited mostly from outpatient clinics (five studies). Two of the studies were a subset of a larger clinical trial. One study made use of a workplace HIV-programme to recruit patients and another recruited patients from the investigators' private practices. The studies all showed the patient population being at least 70% male with some studies showing as high as 90% male dominance. The average age of the patients across all of the studies was 37 years to 41 years old.

The inclusion criteria varied widely between studies. All participants had to be aged 18 years or older, however, the duration of efavirenz therapy varied from initiation up to at least one year of therapy. Fumaz and colleagues⁶ were considering the long-term side effects experienced with efavirenz and stated that the patient had to be on an efavirenz-containing regimen for at least one year in order to be included. Clifford and colleagues³ followed consenting patients for 184 weeks after being randomised to efavirenz. Other studies were considering the immediate effects and focused on patients who had just been initiated on efavirenz or were using efavirenz for three to six months.

The standard dose of efavirenz is 600mg daily generally taken at bedtime⁹. Only four studies explicitly stated the dose of efavirenz being received by the patients. One study made use of three 200mg tablets that had to be taken together at bedtime while others made use of single 600mg tablets and one study⁴ randomised patients to stepped dose of efavirenz or efavirenz 600mg daily. Although the standard dose of efavirenz is 600mg daily, it is dosed based on the weight of the patient. Patients weighing less than 40kg receive 400mg of efavirenz at bedtime as opposed to 600mg, which may impact on the incidence and/or the severity of side effects experienced.

- *Measuring protocols*

In terms of the instruments used to measure the neuropsychiatric side effects caused by efavirenz, there was some diversity. The instruments used are summarised in Table 2. The only common scales were the Symptom Checklist-90-Revised (SCL-90-R) and the Medical Outcome Study for HIV-positive patients (MOS-HIV) scale which were used by two studies.

Seven of the studies used clinicians to interview participants concerning side effects, whereas four studies allowed patients to answer questionnaires themselves. The exception was the study conducted by Fumaz and colleagues⁶ who used a combination of both. Further details are provided in Table 2.

Insert Table 2

- *Side-effects*

The most commonly reported side-effects included sleep quality (nine studies), depression (eight studies), dizziness (seven studies) and anxiety (seven studies). Some other notable problems reported included impaired concentration (five studies), abnormal dreams (four studies) and light-headedness (four studies). More serious side-effects such as suicidal ideation and paranoia were each reported just once. Studies tend to demonstrate that the symptoms are prominent in the first few weeks of therapy and then decline in severity, with the exception of the study by Fumaz and colleagues⁶ who showed that symptoms may persist for up to a mean of two years. Several studies^{7,9,11,12} also suggested that side-effects can persist for up to one year after the initiation of efavirenz and recommend that patient monitoring continue past the first few weeks of therapy. Hawkins and colleagues⁷ showed that the side effects of efavirenz can persist up to a year after the initiation of treatment. However, the side effects present after one year of therapy are not severe and are tolerated by patients. Gutierrez and colleagues¹² showed that patients who discontinued efavirenz were using the medication for a range of 16 months to 34 months. Detailed information is provided in Table 3. The package insert of efavirenz does mention that the drug can cause neuropsychiatric side effects; however, the incidence is stated as rare and includes only anxiety, apathy, emotional lability, euphoria, hallucinations and depression⁸.

Insert Table 3

- *Severity of side-effects*

The severity of the side-effects was recorded by five studies. Different scales were used to evaluate severity. Gutierrez and colleagues¹² utilised the World Health Organisation (WHO) severity scale, Hoffman and colleagues¹³ allowed providers to grade the severity of clinical side effects, Nelson and colleagues¹⁴ made use of the Division of AIDS Grading Table, and Rihs and colleagues¹⁰ used the Depression Anxiety and Stress Scale (DASS) to measure the severity of anxiety, depression and stress. Gutierrez-Valencia and colleagues⁴ did not state which scale was used to evaluate the severity of the side-effects.

Almost all of the studies reported patients discontinuing efavirenz treatment due to intolerable NPSEs; however, this occurred in the minority of patients. Generally though patients experienced mild symptoms as expressed by the various scales. However, it is worthy to note that some patients may experience intolerable side effects and require the discontinuation of efavirenz. Nelson and colleagues¹⁴ divided side effects caused by efavirenz into neurological and psychiatric. A total of 33.4% of patients on efavirenz were reported to have demonstrated at least one grade one to four neurologic side effect and 39% of patients using efavirenz reported at least one grade one to four psychiatric side effect. In both cases, these values were higher when compared to the group of patients receiving etravirine (20.2% neurologic side effect and 11% psychiatric side effects). Rihs and colleagues¹⁰ demonstrated that patients prescribed efavirenz had experienced severe to extremely severe anxiety, depression and

stress, although they were all small groups of patients. Gutierrez-Valencia and colleagues³ separated patients into a stepped dose and a full dose efavirenz group and explored a variety of side effects. They reported a higher number of patients (n = 6) from the full dose group experiencing severe side-effects at day 30 of the follow-up compared to the stepped dose group (n = 2).

The studies all showed that these side effects were transient in nature and not severe enough to warrant the discontinuation of efavirenz in the majority of patients. However, if the side-effects persist, as shown by Fumaz⁶, Hawkins⁷, Rihs¹⁰ and Leutscher¹¹, patient adherence to efavirenz may decline even if the side effects are mild or moderate in severity.

Discussion

Due to the varied nature of the measuring instruments used, it is difficult to directly compare these trials in a systematic review. However, in spite of the varying nature of these studies, there are some common findings. All published studies included in the review showed that the side effects caused by efavirenz can be tolerated by most patients and that these side effects tend to be transient in nature. There has not been any significant evidence of efavirenz causing suicidal ideation or paranoia in patients. In fact, a study by Napoli¹⁸ and colleagues employed a technique to identify associations between drugs and adverse reactions. The results showed that efavirenz was not associated with an increased risk of suicidality. Similarly, a study conducted by Smith and colleagues¹⁹ showed that there was no higher rate of completed suicide in patients using efavirenz. However, Mollan and colleagues²⁰ found that there is an increased risk of idealised, attempted, or completed suicide with efavirenz. Only one of the studies focused on in this review mentions suicide. This means that this particular side effect was not detected or not significant amongst the participants of the other studies. The neuropsychiatric symptoms have, however, been shown to persist for several years after the initiation of therapy and appropriate caution should therefore be taken. Continuing patient monitoring and counselling needs to be conducted in order to identify late-emergent side-effects.

Patients with a history of psychoses, active psychoses or depression were included in only one study²¹. Blanch and colleagues²¹ referred participating patients to be interviewed by a psychiatrist. It was found that only 54.8% of their patients had a psychiatric disorder, but 83.9% reported at least one psychiatric symptom at baseline, 71% reported some form of psychiatric symptom after the initiation of efavirenz and 13% dropped out of the study due to psychiatric side effects. The package insert of efavirenz does not state that efavirenz is contraindicated in patients with a psychiatric disorder⁸. As mentioned, the South African National consolidated Guidelines¹ state that an alternative may be used in place of efavirenz where the patient has significant psychiatric co-morbidity. However, the CD4 count has an impact on the alternative chosen. If a female patient has a CD4 count of less than 250 and a male patient has a CD4 count of less than 400, nevirapine may be used as an alternative. If the CD4 count of the female patient is equal to or more than 250 and the male patient has a CD4 count of 400 or more, the lopinavir/ritonavir combination should be used instead. It must be remembered that nevirapine has the potential to cause significant hepatotoxicity as well as skin abnormalities²⁰. However, there are significant drug interactions between ritonavir and psychotropic drugs such as clozapine, carbamazepine and sedatives and hypnotics such as diazepam, midazolam and zolpidem²¹. Also of note, a retrospective analysis that compared a large group of patients receiving efavirenz to a large group of patients receiving nevirapine showed that there were no significant differences between them in terms of treatment withdrawal. This further supports the idea that the neuropsychiatric side

effects caused by efavirenz are not severe enough to warrant its discontinuation in the majority of patients²⁴.

Even though efavirenz is no longer used as part of the first line treatment in the United States of America²⁵ or the United Kingdom²⁶, it still forms part of the treatment backbone in South Africa which has the largest HIV epidemic in the world²⁷. Several other countries in Africa with an HIV prevalence of more than 10% use efavirenz as part of the recommended first line treatment of naïve patients²⁷. Agents used as first line treatment in the United States of America and the United Kingdom are reserved for second or third line use in the African countries mentioned below. This demonstrates the importance of a thorough understanding of efavirenz as is it still widely used in developing countries. The various regimens are summarised in Table 4.

Table 4. First line ART regimens for treatment-naïve patients of various countries

Country	Date of Guidelines	Recommended first line treatment for treatment-naïve patients
Botswana ²⁸	2012	tenofovir + lamivudine + efavirenz (preferably as a single dose combination)
Lesotho ²⁹	2014	tenofovir + lamivudine + efavirenz (preferably as a single dose combination)
Malawi ³⁰	2014	tenofovir + lamivudine + efavirenz
Namibia ³¹	2010	tenofovir + lamivudine + nevirapine (if the CD4 count in women is >350cells/μl, or if the CD4 count in men is >400 cells/μl and the man is classified as WHO stage 3 or 4, efavirenz should be used instead of nevirapine)
South Africa ¹	2014	tenofovir + lamivudine + efavirenz (preferably as a single dose combination)
Swaziland ³³	2015	tenofovir + lamivudine + efavirenz
United States of America ²⁴	2015	abacavir + lamivudine + dolutegravir OR tenofovir + emtricitabine + dolutegravir OR tenofovir + emtricitabine + elvitegravir/cobicistat OR tenofovir + emtricitabine + raltegravir (a suitable regimen is to be chosen based on laboratory investigation results as stated in the full Guideline)
United Kingdom ²⁵	2015	tenofovir + emtricitabine + atazanavir/ritonavir OR darunavir/ritonavir OR dolutegravir OR elvitegravir/cobicistat OR raltegravir OR rilpivirine as preferred agents OR efavirenz as an alternative agent

		Alternative regimen abacavir + lamivudine + any of the above
Zimbabwe ³⁴	2013	tenofovir + lamivudine + efavirenz (preferably as a single dose combination)

The Malawian³⁰, South African¹ and United Kingdom Guidelines²⁶ state that if a patient has a history of, or current, mental illness that patient should not be given efavirenz. The Guidelines published in the United States of America²⁵ acknowledge that efavirenz causes a myriad of neuropsychiatric side-effects (NPSEs), some of which may be severe, but do not state that efavirenz should not be given to such patients or that therapy should be switched to an alternative agent. The HIV Treatment Guidelines of Swaziland³² suggest that patients with mental illness, even such severe conditions such as schizophrenia or schizoaffective disorder, should not be discriminated against in terms of antiretroviral treatment (ART). These patients should be assessed individually and appropriate decisions made using the screening tools provided in the Guideline. The Guidelines of Swaziland³² also warn that efavirenz is associated with mental health disturbances such as bad dreams and being in an altered state of mind, thus patients should be encouraged to take efavirenz before bedtime.

There have been suggestions that the plasma level of efavirenz may be a risk factor for the development of neuropsychiatric side effects; however, there has not been a consensus concerning the threshold concentration^{12,34}. Given that studies have shown that genetic variations, particularly of the enzyme CYP2B6, in patients affect the plasma levels of efavirenz^{9,35}, studies need to be conducted in a broader range of countries to determine region-specific guidelines for efavirenz dosing. These polymorphisms have been shown to be more common in patients of African descent and such patients should be monitored more closely as they are more likely to experience higher plasma levels of efavirenz and be susceptible to neuropsychiatric side effects³⁵. This is particularly important as only one of the studies included patients from South Africa¹³. This indicates that there is a need for further safety and pharmacovigilance studies in Africa to determine the clinical importance of this variation. This is endorsed by recent reports which showed that a nevirapine safety signal was detected in Namibia using their adverse reporting database - VigiFlow[®] - after shifting the initiation of nevirapine to patients with higher CD4 counts than previously recommended. This resulted in the Ministry of Health in Namibia halting this move and returning to the previous recommendations³⁶. This is important as the majority of people with HIV live in low- and middle-income countries, particularly sub-Saharan Africa, and HIV disproportionately affects young women in these countries^{37,38}. This compares with the high proportion of men in the published studies from Europe and the USA.

All of the studies included in this review had a majority male population and there was an average age range of 37 to 41 years. This implies a knowledge gap in special populations such as older patients, paediatrics and patients with a psychiatric illness as these factors will impact the treatment chosen. Such patients need to be included in studies in addition to including more women and patients in Africa in order to obtain a complete picture and representative sample. Consequently, it is difficult to provide additional guidance on the use of EFV especially in patients in Africa apart from that already documented.

None of the studies indicated the WHO stage of HIV. However, this has not been considered as a possible risk factor in the development of neuropsychiatric side effects of efavirenz. Determining risk factors for side-effects may assist with discerning possible causes of the

problem. The location and sample population has also shown to be of importance in studies concerning efavirenz and has to be taken into account when generalising results.

Limitations

There were only small numbers of female patients in the studies compared to males, with only limited follow-up. In addition, since only one of the studies was conducted in an Africa setting, the results may not be generalisable to all countries and settings due to the varied nature of efavirenz metabolism in patients of African descent. We are also aware that the methodologies of the included studies are varied and do not allow for direct comparisons and that the small number of studies sourced due to our strict methodology, which limited included studies to English language full-text articles published in journals accessible *via* the Nelson Mandela Metropolitan University database, does serve as a limitation to this study. However, we do not believe that the inclusion of more studies would have significantly altered the conclusions of our findings.

Conclusion

Standardised methods for measuring outcomes need to be determined. Similar studies need to be conducted in more countries to represent the various populations and their differences across continents. In the studies included in this systematic review, the neuropsychiatric side effects of efavirenz do not appear severe enough to warrant discontinuation of the medication, even if they may persist longer or emerge later than initially thought. Continuous pharmacovigilance, adherence counselling and support is important to these, and other patients, as efavirenz will form part of a lifelong regimen.

Key messages

- The neuropsychiatric side effects caused by efavirenz may persist longer than the first four to six weeks of treatment as initially thought
- These side effects are not generally severe enough to warrant the discontinuation of efavirenz
- Older patients, paediatric patients and patients with active symptomatic mental illness need to be included in studies to obtain a representative sample. Similarly for Africa there needs to be more women included in studies monitoring the side-effects of treatments for HIV
- Patients need to be provided with continuous adherence education to enhance the effectiveness of treatment

Expert commentary

HIV is a multifaceted condition, particularly among African regions where often patients need to make the choice between food and medication. Providing patients with medication that is effective, would cause limited side-effects and is simple to take is the aim of any healthcare programme. The introduction of the fixed dose combination has improved adherence to ART. The systematic review confirmed that efavirenz (EFV) does cause neuropsychiatric side effects in an appreciable number of patients, which include changes in

sleep quality, dizziness, anxiety and depression; however, the side-effects seen are generally mild and do not typically warrant discontinuation. They can though be severe in some patients, leading to discontinuation and switching to other treatments. Having said this, currently efavirenz forms a major part of HIV treatment in sub-Saharan Africa, which is likely to remain. Its utilisation would even appreciably increase in South Africa if the ‘test and treat’ option, i.e. if a patient tests HIV-positive, ART is started regardless of the CD4 count, was introduced, which South Africa is currently considering as a future treatment strategy. The situation in Southern Africa enhances the argument that efavirenz is still a medicine that requires more understanding among different African settings, given the likely increases in its utilisation as well as concerns with the make-up and the different genetic variations between HIV populations in Africa versus Western countries. In the meantime, patients will need to be appropriately screened before initiating efavirenz. They will also need to be continuously monitored for side effects and current adherence given the prevalence of side-effects with EFV.

Five-year view

Africa has the highest burden of HIV in the world. Given the various social aspects contributing to the spread of the disease, it is unlikely that this situation will change significantly over the next five years. The cost of medication will become even more of a determining factor in treatment decision-making. Adherence to treatment currently is, and will always be, a concern in patients expected to take lifelong treatment. Advances in medicine may result in a vaccine against HIV being developed and rolled out over the next five years. There may also be improvements in technology, leading to resistance testing in all patients testing HIV-positive before being initiated on treatment. However, for these advances to be implemented in countries with high HIV burden and limited resources, cost will continue to be a major factor leading to continued use of treatments such as EFV. It is hoped that more studies are conducted among HIV patients in Africa given the different patient patterns to Western countries and different genetic variations. This will help to further guide treatment choices.

Declaration of conflict of interest and acknowledgments

The authors have no conflict of interest to disclose. No funding was received for this study. However, there was a small grant from the Karolinska Institute to help with the writing of the paper. The write up of this paper was in part support by the Karolinska Institutet as well as VR-Link grant from Swedish Research Council (VR-Link 2013-6710).

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Table 1. Demographics of studies

Authors, publication year and country	Type of study	Setting	Follow-up period	Number of patients/controls	Average age of patients	% Male patients	Duration of efavirenz treatment
Blanch J et al. 2001 ²¹ (Spain)	Open-label, prospective, observational study	HIV hospital outpatients	12 weeks	31/-	41 years±10 years	71%	12 weeks
Clifford DB et al. 2005 ⁵ (USA)	Substudy of randomised, double-blind, controlled trial (A5095)	Multicentre academic clinical trial units	24 weeks	283/-	Median age – 37 years (efavirenz group), 38 years (non-efavirenz group)	82% (efavirenz group), 80% (non-efavirenz group)	184 weeks
Clifford DB et al. 2009 ¹⁵ (USA)	Substudy of A5095. Prospective, comparative, placebo-controlled study	Substudy	184 weeks	Efavirenz only – 86, Various regimens – 37, Late long-term efavirenz – 21, Non-efavirenz only - 33, Total - 177	Efavirenz only – 39.2 years, Various regimens – 37.4 years, Late long-term efavirenz – 40 years, Non-efavirenz only – 40.5 years	Efavirenz-only - 85%, Various regimens – 70%, Late long-term efavirenz – 81%, Non-efavirenz only – 81%	24 weeks
Fumaz CR et al. 2005 ⁶ (Spain)	Cross-sectional comparative study	Hospital	Cross-sectional study	Efavirenz – 60, Protease inhibitor – 60	Efavirenz - 41.4 years±8.05 years, protease inhibitor- 39.2 years±7.7 years	Efavirenz - 75%, PI – 70%	Average time 91.1±39.5 weeks for efavirenz patients and 119.9±67.4 weeks for the PI patients
Gutierrez F et al. 2005 ¹² (Spain)	Longitudinal study	Hospital	18 months	17/-	Median age - 40 years	82.4%	Median time was 18 months (range six months to 27 months)

Gutierrez-Valencia A et al. 2009 ⁴ (Spain)	Randomised, double-blind, controlled trial	Investigators' clinical practice	24 weeks	108 patients (Full dose group – 50, Stepped dose group - 58)	39 years	Full dose group – 80%, Stepped dose group – 77.6%	24 weeks
Hawkins T et al. 2005 ⁷ (USA)	Cross-sectional questionnaire-based cohort	Not indicated	Cross-sectional	77 protease inhibitor group and 75 efavirenz group	43 years ±7.4 PI group and 40 years ± 8.1 years efavirenz group	95% protease inhibitor group and 92% efavirenz group	345±250 days for patients on efavirenz and 582±445 days for patients on PIs
Hoffman CJ et al. 2008 ¹³ (South Africa)	Prospective cohort	Workplace	Included patients started on highly active antiretroviral therapy (HAART) over 3 years (2002-2005) and followed up until November 2006	853/-	Median age - 40 years	98%	378 days
Leutscher PDC et al. 2013 ¹¹ (Denmark)	Prospective cohort	University hospital outpatient HIV clinic	Patients initiated on therapy from January 2000 until December 2009 were included and followed up until December 2010	276 (168 on efavirenz)/-	Median age - 39 years	Efavirenz group – 71%, non-efavirenz group - 53%	Patients were on efavirenz between one and 11 years
Lochet P et al. 2003 ¹⁶ (France)	Cross-sectional study	HIV outpatients at hospitals	Cross sectional	174/-	Median age - 40 years	78.2%	Median duration – 14.5months (range 3 to 43.5 months)
Nelson M et al. 2011 ¹⁴ (UK)	Double-blind placebo controlled trial	Clinical trial	48 weeks (primary assessment of neuropsychiatric symptoms at 12 weeks)	157/-	38 years	81%	
Rihs TA et al. ¹⁰	Single-centre, cross-sectional case controlled	Outpatient HIV clinic	Cross sectional	32/32	Efavirenz group - 43 years±10 years Control -	Efavirenz -97% Control - 97%	Average duration - 14±5 months in the

(Australia)					44 years±10 years		efavirenz group and 24±14 months in the control group
Ward DJ and Curtin JM. 2006 ¹⁷ (USA)	Retrospective analysis	HIV-specialty private practice	3 years	40/-	Median age 41 years	97.5%	Average of 27 months on efavirenz (range 3-69 months)

Table 2. Statistical methods and outcomes

Primary author	Evaluation methods	Statistical methods	Primary outcome	Secondary outcome
Blanch J ²¹	<ul style="list-style-type: none"> - 100-point Karnofsky Scale (clinician administered) - Psychological and physical 10-point self-report scale (self-administered) - Structured Clinical Interview of the clinical version of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (psychiatrist administered) - Validated Spanish adaptations of the Symptom Check List-90-Revised (SCL-90-R) - Medical Outcome Study for HIV-positive patients (MOS-HIV) 	<ul style="list-style-type: none"> - Univariate repeated-measures ANOVA followed up with univariate simple contrast effects test - Friedman test - Wilcoxon signed-rank tests - Bonferroni adjustment - Univariate and multivariate regression analyses 	<ul style="list-style-type: none"> - Four patients discontinued efavirenz due to neuropsychiatric side effects - Patients who completed the follow-up demonstrated a decrease in SCL-90-R total score and in several subscales interpersonal sensitivity, depression and anxiety - No changes in MOS-HIV 	<ul style="list-style-type: none"> - Having fewer years of education - Having fewer baseline central nervous system symptoms - Reporting better baseline physical status - Having higher baseline scores in the Health Transition subscale of the MOS-HIV and in the Somatisation subscale of the SCL-90-R (associated with more neuropsychiatric side effects)
Clifford DB ⁵	<ul style="list-style-type: none"> - Trail Making Tests (series A and B) and the Digital Symbol Substitution Test 	<ul style="list-style-type: none"> - Nonparametric tests - Generalised estimation equation modelling - Wei-Johnson test - Spearman correlation coefficient 	<ul style="list-style-type: none"> - All components improved - Higher levels of efavirenz were associated with slightly lower responses - Efavirenz-related central nervous system scores increased - Median change of bad dream scores and anxiety increased while global depression score decreased 	<ul style="list-style-type: none"> - Neurocognitive performance was maintained without decline over the three years of the study - This provides some reassurance that chronic neurotoxicity is unlikely in many patients
Clifford DB ¹⁵	<ul style="list-style-type: none"> - Trail Making Tests (series A and B) 	<ul style="list-style-type: none"> - Wilcoxon signed rank tests 	<ul style="list-style-type: none"> - Efavirenz -related symptoms was higher than baseline at final 	None recorded

	<ul style="list-style-type: none"> - Digit Symbol Test - Pittsburgh Sleep Quality Index - State-Trait Anxiety Inventory for Adults - Center for Epidemiologic Studies Depression scale - Specially designed questionnaire 	<ul style="list-style-type: none"> - Wilcoxon rank sum tests 	<p>assessment.</p> <ul style="list-style-type: none"> - ‘Bad dreams’ detected a mean increase - Anxiety increased - When efavirenz-only patients are compared with those never receiving efavirenz, there is no statistically significant difference in changes over the study 	
Fumaz CR ⁶	<ul style="list-style-type: none"> - MOS-HIV questionnaire - Profile of Mood State 	<ul style="list-style-type: none"> - Kolmogorov-Smirnov test - Mann-Whitney nonparametric test - X² test - Fisher exact test - Spearman nonparametric test 	<ul style="list-style-type: none"> - 54% of efavirenz patients reported at least one neuropsychiatric disorder within the four weeks before the visit - Dizziness (21.7%), sadness (36.78%), mood changes (26.7%), irritability (30%), light-headedness (28.3%), nervousness (30%), impaired concentration (26.7%), abnormal dreams (48.3%), somnolence (15%) 	<ul style="list-style-type: none"> - Mean efavirenz levels showed no significant differences between those with and without neuropsychiatric disorders - 60% of efavirenz patients reported adherence and 55% of protease inhibitor patients
Gutierrez F ¹²	<ul style="list-style-type: none"> - Semi-structured interview (included questions exploring common presumptive efavirenz -related side effects) - WHO toxicity scale - Simplified Medication Adherence questionnaire 	<ul style="list-style-type: none"> - Student t test - Receiver operating characteristic values - Contingency tables - Multivariate analysis - Logistic regression 	<ul style="list-style-type: none"> - Four patients discontinued due to side effects - Adherence to efavirenz therapy was >90% for 16 of 17 patients - Ten patients reported neuropsychiatric side effects during the observation period, mostly sleep disturbances 	<ul style="list-style-type: none"> - Patients having plasma levels of more than 2.74µg/ml were 5.68 times more likely to experience central nervous system toxicity

			<ul style="list-style-type: none"> - Others include dizziness (6), insomnia or abnormal dreaming (5), impaired concentration and attention span (2), depression (2), obsessive disorder (1), drowsiness (1), irritability (1) and light-headedness (1) - Efavirenz plasma levels were higher for patients with neuropsychiatric side effects 	
Gutierrez-Valencia A ⁴	<ul style="list-style-type: none"> - 11 questions on common efavirenz - related neuropsychiatric side effects (dizziness, feelings of drunkenness, headache, impaired concentration, mood disorders, anxiety and depression) - Validated 13-item protocol that measured subjective sleep quality, somnolence, insomnia and nightmares 	<ul style="list-style-type: none"> - X² test - Student t test - Mann-Whitney-Wilcoxon test 	<ul style="list-style-type: none"> - During the first week, 55.5% developed efavirenz-related neuropsychiatric side effects (these were more frequent in the full dose group (66%) than the stepped dose group (46.5%)) - Incidences of dizziness (66% vs 32.8%), feeling of hangover (45.8% vs 20.7%), impaired concentration (22.9% vs 8.9%) and hallucinations (6.1% vs 0%) were higher and more severe in the full dose compared to stepped dose group 	- None recorded
Hawkins T ⁷	- SCL-90-R	<ul style="list-style-type: none"> - Univariate analysis - Student t test - X² test - Multivariate analyses 	<ul style="list-style-type: none"> - In the first six months, worse scores were seen in 39 of the 75 patients receiving efavirenz - The efavirenz group had higher scores for somatisation, anxiety, obsessive-compulsive disorder, the Global Severity Index and the Positive Symptom Distress Index with trends for higher 	<ul style="list-style-type: none"> - Efavirenz -related neuropsychiatric symptoms can last up to 200 days after the initiation of treatment - Severity of the side effects declined over time in efavirenz -treated patients compared to patients treated with a protease

			<p>scores in paranoid ideation and depression</p> <p>-After 12 months, the efavirenz group scored lower scores than the protease inhibitor treated group for somatisation, Interpersonal Sensitivity, Global Severity Index and Positive Symptom Total</p>	inhibitor-based regimen
Hoffman CJ ¹³	<ul style="list-style-type: none"> - Structured visit forms and results from routine and acute laboratory testing - Special side event reporting form 	<ul style="list-style-type: none"> - Pre-HAART person-years at risk were calculated from the first clinical evaluation or one year before the initiation of HAART - Person-years at risk on HAART were calculated from the time of HAART initiation to the earliest of the following: time of event, change or discontinuation of HAART, date of last clinical or laboratory encounter in the database or one year of follow-up on HAART 	<ul style="list-style-type: none"> - CNS effects with efavirenz – 187 patients - 37/100person years, 95% confidence interval 32-43 	- Subjects on co-trimoxazole had a higher rate of central nervous system symptoms
Leutscher PDC ¹¹	- Review of medical records	- X ² test	<ul style="list-style-type: none"> - 54% (n=90) of patients in the efavirenz group (n=168) discontinued efavirenz - Overall, 51% of patients discontinued efavirenz throughout the study - A small percentage of the 90 patients (n=17%) discontinued efavirenz during the first month of therapy, 32% discontinued 	<ul style="list-style-type: none"> - Other reasons for discontinuation of efavirenz were pregnancy, treatment failure or non-compliance - Once efavirenz was discontinued, there was resolution of the neuropsychiatric side effects in 61% of patients in the first-line efavirenz group

			<p>between one and 12 months and the remaining 51% discontinued after more than one year</p> <ul style="list-style-type: none"> - Neuropsychiatric disturbances was the most common reason for discontinuation among both patients discontinuing the initial efavirenz-based regimen as well as those discontinuing efavirenz as part of a second-line regimen - Among the first line treatment patients, 50% were discontinued after one year of therapy 	<p>- No differences in gender distribution, country of origin, history of HIV transmission or viral load or CD4 counts</p>
Lochet P ¹⁶	- SENSIO questionnaire	- None indicated	<ul style="list-style-type: none"> - Neuropsychiatric side effects occurred mainly in the first month of treatment - Sleep disturbances and dizziness occurred mostly at the beginning of efavirenz treatment - Neuropsychiatric side effects which persisted or worsened include anxiety, behavioural troubles, sadness and cognitive disorders - Late neuropsychiatric side effects included abnormal dreams, nocturnal waking, memory disorders, concentration difficulty, morning tiredness and daytime drowsiness 	- None recorded
Nelson M ¹⁴	- Division of AIDS grading table	- Logistic regression	- 13 of the 79 patients in the	- Change in HIV-RNA to week

			<p>etravirine arm and 36 of the 78 patients in the efavirenz arm showed at least one grade one to four drug-related treatment-emergent neuropsychiatric side effect</p> <p>- Four of 79 patients in the etravirine arm and 13 of 78 in the efavirenz arm showed at least one grade two to four drug-related treatment-emergent neuropsychiatric side effect</p>	<p>12 was $-2.9\log_{10}$ in both treatment arms</p> <p>- Median rise in CD4 cell counts was 146cells/μl in the etravirine arm and 121 cells/μl in the efavirenz arm</p>
Rihs TA ¹⁰	<ul style="list-style-type: none"> - Depression Anxiety and Stress Scale - Cognitive Failures Questionnaire 	<ul style="list-style-type: none"> - Paired t-tests - Wilcoxon's signed rank test - X² tests - Fisher's exact tests 	<ul style="list-style-type: none"> - Higher stress scores in the efavirenz group - 19% reported severe to extremely severe levels of stress - 19% of patients treated with efavirenz reported severe to extremely severe levels of anxiety - This group reported unusual dreams 	<ul style="list-style-type: none"> - No significant differences were found between the groups concerning cognitive impairment, fatigue, dizziness, derealisation or depersonalisation
Ward DJ ¹⁹	<ul style="list-style-type: none"> - No formal measuring tool used 	<ul style="list-style-type: none"> - Paired Student t test 	<ul style="list-style-type: none"> - 14 patients reported full recovery after switching - The other six patients reported significant improvement in symptoms - Three of the six patients had a history of depression before starting efavirenz 	<ul style="list-style-type: none"> - None recorded

Table 3. Side effects recorded

Primary Author	Side effects and consequences
Blanch J ²¹	Depression, anxiety, dizziness, light-headedness, feeling disengaged from reality. There were nine patients who dropped out of the study, four of whom did so due to intolerable NPSEs. Efavirenz was effective in decreasing viral load and improved the psychological distress level. Patients who maintained efavirenz treatment showed a decrease in interpersonal sensitivity during the first four weeks and a decrease in depression up to the first three months. The study found no association between NPSEs and personal psychiatric history.
Clifford DB ⁵	The significant increase in the NPSEs seen during the first week of treatment declined towards baseline levels during the study, but remained higher than baseline levels at the final visit. These side effects were not significantly associated with efavirenz trough levels measured at the final visit. Changes in the global sleep score over the study were not significant although the 'bad dreams' question detected a mean increase after 184 weeks. There was a statistically significant decrease in depression symptoms over the course of the study. The symptoms of anxiety increased by a median of four points as measured by the State Anxiety Index. There were 31 patients who discontinued treatment, 11 did so due to NPSEs.
Clifford DB ¹⁵	Sleep quality scores changed little over time. Patients who were not receiving efavirenz had significantly poorer sleep quality at week four as compared to the efavirenz group. All participants experienced anxiety throughout the study. Changes in depressed mood were similar in both groups.
Fumaz CR ⁶	Patients on efavirenz reported higher prevalence of dizziness, sadness, mood changes, irritability, light-headedness, nervousness, impaired concentration, abnormal dreams and somnolence. Other side effects included fatigue, headaches, euphoria, difficulty sleeping. There was no correlation between the plasma levels of efavirenz and the presence of NPSEs. There were no significant differences in quality of life between patients on efavirenz and those not.
Gutierrez F ¹²	Overall, 10 patients of the 17 experienced NPSEs, mostly sleep disturbances. CNS effects included dizziness, insomnia or abnormal dreams, impaired concentration and attention span, depression, drowsiness, irritability and light-headedness. In six of the 10 patients, NPSEs were mild. In the other four cases, CNS toxicity was moderate or severe leading to the discontinuation of efavirenz. This occurred at months six, eight, 11 and 13 of the study. Plasma levels of efavirenz were found to be higher in patients experiencing NPSEs.
Gutierrez-Valencia A ⁴	There were 12 patients who discontinued the study due to adverse effects. Five of these patients were in the stepped-dose group and seven in the full-dose group. Dizziness, feelings of drunkenness, impaired concentration and hallucinations, sleep disorders and nightmares were the most commonly recorded side effects. Other side effects included headache, mood disorders, disorientation, anxiety, depression. Throughout the second week of the study the incidence of NPSEs was similar in both groups, although the more severe NPSEs occurred in the full-dose group.
Hawkins T ⁷	Somatisation, obsessive-compulsive disorder, anxiety, depression and paranoid ideation were side effects more commonly seen in patients using efavirenz for less than six months. However, as treatment duration increased (199 to 365 days), even though the scores for patients using efavirenz were higher than PI using patients, it was not statistically significant.

Hoffman CJ ¹³	Dizziness, insomnia, bizarre dreams or hallucinations with efavirenz and was thought to be the responsible agent. The neurocerebellar toxicity affected 22% of patients at two weeks.
Leutscher PDC ¹¹	Of the 168 patients who started efavirenz, 90 later discontinued during the follow-up period. Of these 90 patients, 15 discontinued within the first month of treatment, 29 between month one and month 12 and the remaining 46 patients after one year. NPSEs are stated as the main reason for efavirenz discontinuation but no specific side effects were mentioned. A history of mental illness was reported in the same proportion of patients who continued efavirenz as those who discontinued.
Lochet P ¹⁶	Abnormal dreams, sleep disorders, memory disorders, restlessness, daytime drowsiness, impaired concentration, sadness, irritability, agitation, emotional instability, suicidal ideation, aggressiveness, headaches, feelings of drunkenness, euphoria, hallucinations, anxiety, behavioural troubles, sadness and cognitive disorders. At the time of the study, 23 (13.2%) of patients claimed to have frequent or very frequent suicidal ideation. Among these 23 patients, 18 (10.3%) did not report having this feeling before initiating efavirenz treatment, four patients did and one did not answer. There were 11 patients who discontinued efavirenz due to NPSEs.
Nelson M ¹⁴	The most common side effect of the nervous system was dizziness (19% in efavirenz arm and 4% in the etravirine arm). The most common psychiatric disorders were sleep disorder (abnormal dreams, insomnia, nightmares, sleep disorders) (9% of patients in the etravirine arm and 32% in the efavirenz arm). There were no deaths in the study.
Rihs TA ¹⁰	Patients on efavirenz experienced higher levels of depression, anxiety and bad dreams, but not regarding the quality of sleep. There were no differences between the groups in terms of cognitive impairment, feelings of derealisation, dizziness or light-headedness.
Ward DJ ¹⁷	Mental cloudiness, decreased memory, drunken sensations, difficulty concentrating, agitation, depression, fatigue, sleep difficulty and vivid dreams were experienced by patients on efavirenz before the switch to nevirapine was made

