MRI BRAIN FINDINGS IN PATIENTS WITH EFAVIRENZ-INDUCED ATAXIA

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A research report submitted to the faculty of health sciences, University of the Witwatersrand, in partial fulfilment for the degree of Master of Medicine in the division of neurology.

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i. DECLARATION

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FACULTY OF HEALTH SCIENCES

SCHOOL OF CLINICAL MEDICINE

DEPARTMENT OF NEUROSCIENCES

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- I confirm that this written work is my own work except where I have stated otherwise.
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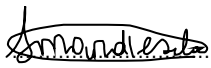
Signature:  ……

Date: ……22/09/2022……

ii. DEDICATION

To my late parents: Alfred and Nokuzola Mandlesilo, my wife, Mpho Mandlesilo and my two daughters Babalwa and Sibabalwe, thank you for your love and support.

iii. ETHICAL CONSIDERATIONS

Permission for this retrospective study was obtained from Professor Girish Modi (Head of Division of Neurology, Department of Neurosciences) and the human research ethics committee of the University of the Witwatersrand (Clearance number-M210871)

ABSTRACT

Introduction

There are millions of HIV positive patients on antiretroviral therapy (ART) who are still taking a Fixed-Dose Combination pill (FDC) containing efavirenz. Patients with efavirenz levels above the therapeutic range's upper limit have experienced an increased frequency of side effects. Some studies have shown patients with efavirenz toxicity presenting with a late-onset ataxia and encephalopathy syndrome. (1,2)

This study aims to examine the records of HIV positive patients on ART with efavirenz-induced ataxia and asses if the MRI brain is normal or abnormal. Because these patients usually present with some form of encephalopathy, ranging from delirium to frank psychosis, MRI brain is considered the best investigation.

Methods

In this study, we reviewed the records of 25 HIV positive patients on ART who presented with efavirenz-induced ataxia-encephalopathy. The MRI brain images were stratified into two groups: Normal and Abnormal. We then assessed the abnormalities and described them. We also documented socio-demographic data, clinical features, HIV history, and efavirenz levels.

Frequency tables were computed and reported, pie charts were used for MRI brain abnormalities and histograms for age, CD4 count, and efavirenz levels.

Results

Out of 25 HIV positive patients with efavirenz-induced ataxia, 15 (60%) MRI Brain images were normal, and 10 (36%) were abnormal. In terms of MRI brain abnormalities found, 3 (12%) had features of HIV-associated dementia, 2 (8%) had generalized atrophy, 2 (8%) had cerebellar atrophy, and 3 (12%) had other unrelated abnormalities.

Conclusion

Most MRI brain images of patients with efavirenz-induced ataxia are normal. Few MRI brain images were abnormal. The abnormalities found were not related to efavirenz-induced ataxia, and there were no features of encephalopathy on the MRI brain images.

V. ACKNOWLEDGEMENTS.

I would like to express my gratitude to my supervisors, Professor Girish Modi and Professor Andre Mochan; thank you for your guidance and support throughout this research project.

vi. Contents

Chapter 2: Proposed Manuscript

Chapter 3: Appendices

vii. LIST OF TABLES

viii. List of figures

ix. Abbreviations

MRI	Magnetic Resonance Imaging
FDC	Fixed-Dose Combination
HIV	Human Immunodeficiency Virus
ART	Anti-Retroviral Therapy
AIDS	Acquired Immunodeficiency Syndrome
UNAIDS	United Nations Program on HIV/AIDS
ARVs	Antiretroviral drugs
EFV	Efavirenz
CT	Computer Tomography
CSF	Cerebrospinal Fluid
NHLS	National Health Laboratory Services
WHO	World Health Organization

CHAPTER 1: PROTOCOL AND EXTENDED LITERATURE REVIEW

1.1 Introduction:

There are currently about 38 million people globally living with HIV/AIDS; according to UNAIDS statistics, about 26 million are taking antiretroviral therapy (ART).(1)

In South Africa, about 7,5 million people live with HIV/AIDS. Of these, 5,2 million are currently on ART.(1) Internationally, HIV treatment guidelines recommend the first-line use of two nucleoside reverse transcriptase inhibitors (NRTIs) with a non-nucleoside reverse transcriptase inhibitor (NNRTI). (2) The South African antiretroviral first-line treatment regimen is based mainly on a non-nucleoside reverse transcriptase inhibitor. The 2020 South African HIV/AIDS guidelines recommend Dolutegravir as the first-line drug regimen; previously, the Fixed-dose combination (FDC) pill contained efavirenz.(3)

There are millions of patients who are still currently on FDC-containing efavirenz. Efavirenz is also still recommended as an alternative drug for the first-line regimen for pregnant women who need ART in their first trimester. (3) Efavirenz is used because it is a good and effective antiviral.

1.2 Metabolism of Efavirenz

Efavirenz has a therapeutic plasma range between 1 and 4 microgram/millilitre. The mechanism of action of efavirenz is by inhibiting the reverse transcriptase enzyme. Efavirenz is mainly cleared in the liver by a process involving the cytochrome P450 system and the generation of inactive metabolites. (4) The enzyme CYP450 2 B6 is responsible for the hydroxylation of efavirenz to 8-hydroxyefavirenz, which is the most important of its metabolites. Oxidized efavirenz metabolites undergo glucuronidation by UDP-glucuronosyltransferase, an important hepatic phase II conjugation pathway. (4)

Variations in individuals' efavirenz pharmacokinetics appear responsible for some differences in clinical outcomes, with polymorphisms in CYP2B6 being the relevant genetic determinant. (5) There is a well-known association between CYP2B6 polymorphisms and a high plasma concentration of efavirenz. This genetic variance has been associated with more severe CNS toxicity. (5)

Several studies have demonstrated an association between the CYP2B6 single nucleotide polymorphism (SNP) G156T and an increased risk of EFV toxicity. (5) One study in Botswana found that the prevalence of the slow metabolizing genotype was 30% in Africans. (6)

1.3 Cerebellar Ataxia

Ataxia means "Absence of order" and denotes a clinical syndrome of incoordination.(7)

Ataxia can be classified according to the mode of development into (8):

Acute: Seconds to days.

Subacute: Days to weeks.

Chronic: Months to years.

There are many causes of ataxia, from inherited to acquired causes.

1.4a Medication and toxic causes of ataxia:

Medications and toxins can lead to reversible or permanent cerebellar ataxia(8). Most of them usually cause acute ataxia and should always be considered when the cause of ataxia is not clear. (8)

Common agents include:

Alcohol

Antiepileptic drugs: Phenytoin, carbamazepine, lamotrigine and lacosamide.

Chemotherapy: Cytarabine, fluorouracil, vincristine, and capecitabine.

Other toxins: Heavy metals, Carbon tetrachloride, and Toluene.

ARVs: Efavirenz

1.4b Efavirenz induced ataxia

Central nervous system-related side effects like sleep disturbance, nightmares, dizziness, headaches, and depression are common in patients' first few weeks of treatment. (4) Patients with efavirenz levels above the therapeutic range's upper limit have experienced an increased frequency of side effects. (4,5) Recently, there have been reports of patients presenting with late-onset ataxia and encephalopathy. (9)

These are patients who initially tolerated efavirenz, and after a few months or years, developed ataxia usually associated with encephalopathy.

Despite extensive workup for these patients, no other cause for ataxia is found except for toxic levels of efavirenz in the blood, and the symptoms resolved after the withdrawal of efavirenz.

Variava et al. reported 20 patients who presented with late-onset ataxia and encephalopathy. (9)

They were all women and had taken efavirenz for at least two years. They all had toxic blood levels of efavirenz. No other cause of ataxia was found, and ataxia resolved after efavirenz was withdrawn.

Hauptfleisch et al. described two paediatric patients who presented with late-onset ataxia; they had been on an efavirenz-based regimen for at least a year(10). They both had high efavirenz levels, above the therapeutic range and their symptoms resolved once efavirenz had been withdrawn. No other cause of ataxia was found after extensive investigations.

Encephalopathy is also common in these patients who present with late -onset ataxia. Variava et al. (9) described encephalopathy in these patients which manifests in different forms such as delirium, drowsiness and psychosis. (9)

The conclusion was that these patients are likely to be slow genetic metabolizers of efavirenz. There is currently no study dedicated to MRI brain findings of patients with efavirenz-induced ataxia.

1.5 Problem Statement

Patients with efavirenz-induced ataxia are usually extensively worked up, including blood tests, CSF investigations, CT Brain, and MRI of the brain. The most extensive study to date included 20 patients with efavirenz-induced ataxia, but an MRI brain was not done. Since it has been documented that these patients also present with some form of encephalopathy, an MRI brain would be the best investigation to confirm if there are any abnormal findings.

1.6 Aim

This study aims to review the records of HIV positive patients on ART with efavirenz-induced ataxia and asses if the MRI brain is normal or abnormal.

1.7 STUDY OBJECTIVES

To review the records of HIV positive patients on ART with efavirenz-induced ataxia admitted at the medical/neurology wards at Charlotte Maxeke Academic Hospital, Helen Joseph Hospital, and Chris Hani Baragwanath Academic Hospital, in

Johannesburg, between January 2016 to December 2020 and asses if their MRI brain were normal or abnormal.

To describe the socio-demographics of HIV positive patients with efavirenz-induced ataxia, clinical features, including HIV history, and biochemical investigations.

1.8 Methods

1.8.1 Study design

A retrospective case series

1.8.2. Study setting and population

Patients admitted with efavirenz-induced ataxia in medical/neurology wards at Chris Hani Baragwanath Hospital, Charlotte Maxeke Academic Hospital, and Helen Joseph Hospital in Johannesburg.

1.8.3 Inclusion criteria

- HIV positive patients on ART who developed ataxia while taking efavirenz, with confirmed efavirenz toxic levels from January 2016 to December 2020.

- Patients older than 18 years of age.

1.8.4 Exclusion criteria

Presence of an alternative cause of ataxia as indicated on the blood test, CSF or MRI.

1.8.5 Sample size and collection

Since it is a record review, all records of patients who are HIV positive on ART with efavirenz-induced ataxia between January 2016 – December 2020 will be considered eligible for the study. We will collect a rough estimate of about 30-40 patients (We usually admit about five patients per year with efavirenz-induced ataxia).

For this study, the patient records will be obtained from the hospital records and inspected for the patient's history and clinical examination. We will get discharge summaries and Redcap records, and then the patient's files will be drawn from the records storage facility. NHLS will be accessed to obtain laboratory test results, including:

Blood tests: Efavirenz levels, CD4 count, and Viral load

MRI brain images and reports will be accessed through the PACS system.

1.8.6. Methods and techniques

- Data collection will be performed on a data collection sheet (See appendix i).
- Data will be captured using an excel spreadsheet.

1.9. Variables:

-Variables will be measured as both categorical and continuous.

-Categorical variables include gender, race, ARV regimen, MRI brain: normal/abnormal, ataxia history: symmetrical/asymmetrical, cognitive impairment, delirium and psychosis and viral load suppressed/not suppressed.

-Continuous variables Include: Age, weight, CD4 count and efavirenz levels

1.10 **Statistical analysis:**

The stata 13.1 statistical package will be used to compute the data analysis.

A biostatistician will be consulted to assist with statistical analysis.

To fulfil objective 1 of assessing the MRI brain of patients with efavirenz-induced ataxia, the MRI brain will be stratified into normal and abnormal. Frequency tables and pie charts will be used.

To fulfil objective 2 of describing social demographics, HIV history, clinical features and biochemical investigations, and continuous variables such as age, weight, CD4 count and efavirenz levels, we will calculate the mean. For categorical values such as gender, race, clinical features, viral load and ARV regimen, frequency tables will be used.

1.11 Ethics

- The protocol will be submitted for ethics approval to the University of the Witwatersrand's Human Research Committee.
- Patient Confidentiality will be maintained by assigning each case a study number.

1.12 Study strength

- To my knowledge, this is the first study in South Africa focused on MRI brain imaging in patients with efavirenz toxicity.

1.13 Study Limitations

- Because it is a retrospective study, some information may be incomplete from the records.

1.14 F**unding**

Self-funded

1.15 Timing

Gantt chart showing the expected timing of each research component

	Jan-April 2021	May-2021	June-2021	July-2021	August-2021	Sept-2021	Oct-Dec 2021
Protocol preparation							
Protocol Assessment							
Ethics application							
Data Collection							
Data Analysis							
Manuscript							

1.16 References- Protocol extended literature review.

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CHAPTER 2: PROPOSED MANUSCRIPT

MRI BRAIN FINDINGS IN PATIENTS WITH EFAVIRENZ-INDUCED ATAXIA

2.1 Background

There are currently about 38 million people globally living with HIV/Aids; according to UNAIDS statistics, of these, about 26 million are taking antiretroviral therapy (ART).(1)

In South Africa, about 7,5 million people live with HIV/Aids. Of these, 5,2 million are currently on ART.(1) International HIV treatment guidelines recommend the first-line use of two nucleoside reverse transcriptase inhibitors (NRTIs) with a non-nucleoside reverse transcriptase inhibitor (NNRTI).(2) The South African antiretroviral first-line treatment regimen is based mainly on a non-nucleoside reverse transcriptase inhibitor. The 2020 South African HIV/AIDS guidelines recommend Dolutegravir as a part of the first-line drug regimen; previously, the Fixed-dose combination (FDC) pill contained efavirenz.(3)

There are millions of patients who are still currently using an FDC-containing efavirenz. Efavirenz is also still recommended as an alternative drug for the first-line regimen for pregnant women who need ART in their first trimester of pregnancy. (3)

2.2 Metabolism of Efavirenz

Efavirenz has a therapeutic plasma range between 1 and 4 microgram/millilitre.

The mechanism of action of efavirenz is by inhibiting the reverse transcriptase enzyme. Efavirenz is mainly cleared in the liver by a process involving the cytochrome P450 system and the generation of inactive metabolites. (4)

Variations in different individuals' efavirenz pharmacokinetics appear to be responsible for some differences in clinical outcomes, with polymorphisms in CYP2B6 being the relevant genetic determinant. (5)

There is a well-known association between CYP2B6 polymorphisms and a high plasma concentration of efavirenz. This genetic variance has been associated with more severe CNS toxicity. (5)

2.3 Efavirenz induced ataxia

Central nervous system-related side effects like sleep disturbance, nightmares, dizziness, headaches, and depression are common in patients' first few weeks of treatment. (4,5) Patients with EFV levels above the therapeutic range's upper limit have experienced an increased frequency of side effects. (4,7)Recently, there have been reports of patients presenting with late-onset ataxia and encephalopathy.

These are patients who initially tolerated efavirenz, and after a few months or years, developed ataxia usually associated with encephalopathy.

Despite extensive workup for these patients, no other cause for ataxia was found except for toxic levels of efavirenz in the blood, and the symptoms resolve after the withdrawal of efavirenz.

Patients with efavirenz-induced ataxia are usually extensively worked up, including blood tests, CSF investigations, CT Brain, and MRI of the brain. The most extensive study to date included 20 patients with efavirenz-induced ataxia, but the MRI brain was not done. Since it has been documented that these patients also present with some form of encephalopathy, an MRI brain would be the best investigation to confirm if there are any abnormal findings.

This study aims to review the records of HIV positive patients on ART with efavirenz-induced ataxia and asses if the MRI brain is normal or abnormal.

2.4 Methods

2.4.1 Design and setting

We performed a retrospective record review of HIV positive patients on ART admitted with efavirenz-induced ataxia in medical/neurology wards at Chris Hani Baragwanath Hospital, Charlotte Maxeke Academic Hospital, and Helen Joseph Hospital Johannesburg, South Africa, from January 2016 to December 2020. We obtained the hospital records from discharge summaries and Redcap records, and the hospital files from the hospital records storage facility. We recruited 30 patients; 5 were excluded because they only had CT brain scans, and no MRI brain scans were done. The patient records of the 25 remaining patients meeting the inclusion criteria were then included in the study. We inspected the files for the history and clinical examination findings. NHLS was accessed to obtain laboratory results, including efavirenz blood levels, CD4 count and viral load.

MRI brain images and the reports were accessed through the PACs system.

The Witwatersrand Research Ethics committee approved the study, clearance number: M210871

2.4.2 Variables

Variables were measured as both categorical and continuous.

Categorical variables: gender, race, ARV regimen 1 or 2, MRI brain normal or abnormal, ataxia history: symmetrical/asymmetrical, cognitive impairment, delirium, and psychosis and viral load suppressed/not suppressed.
Continuous variables: age, weight, CD4 count and efavirenz levels.

2.5 Statistical Analysis

The Stata 13.1 statistical package was used to compute the data analysis.

A biostatistician was consulted to assist with statistical analysis.

To fulfil objective 1 of assessing the MRI brain of patients with efavirenz-induced ataxia, the MRI brain was stratified into normal and abnormal. We then used Frequency tables and pie charts to show the abnormalities found on the MRI brain images.

To fulfil objective 2 of describing social demographics, HIV history, clinical features and biochemical investigations, and continuous variables such as age, weight, CD4 count and efavirenz levels, we calculated the mean and used frequency charts and histograms. For categorical values such as gender, race, clinical features, viral load and ARV regimen, frequency tables were used.

2.6 Results

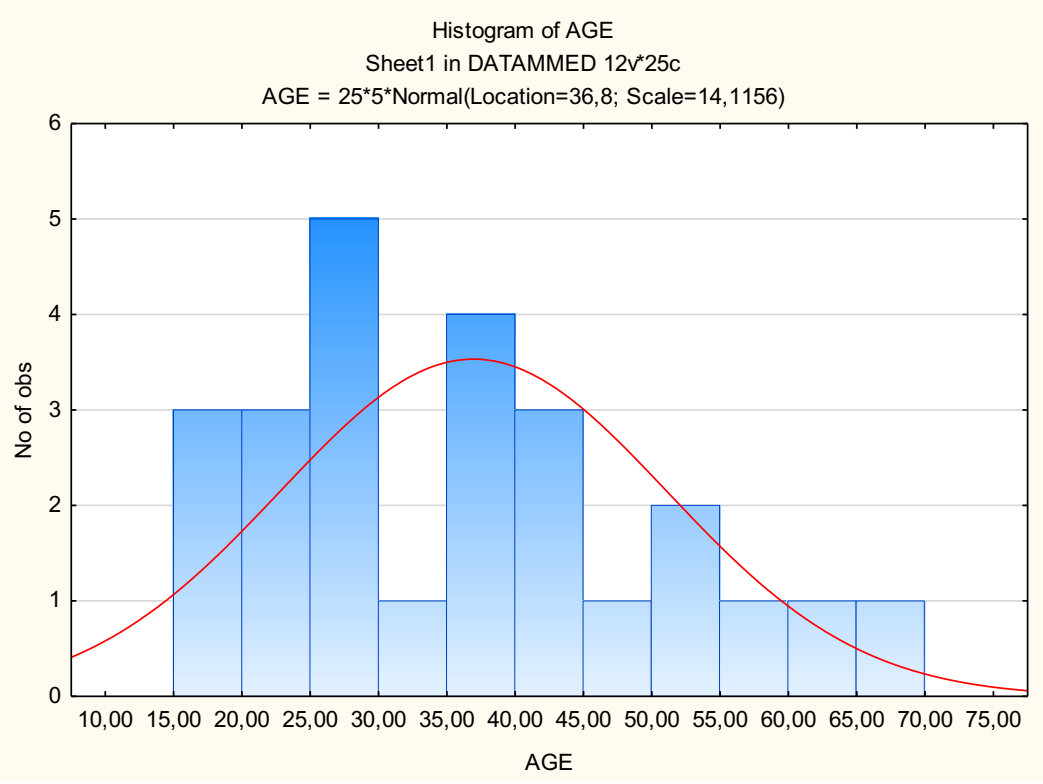
2.6.1 Demographics and data summary

There were 25 HIV positive patients with efavirenz-induced ataxia and MRI brain scans. Patients were between 18 and 66 years old with a median age of 36, the youngest patient was 18. Regarding gender, 21 (84%) were females, and 4 (16%) of the patients were males. All 25 (100%) of our patients were black Africans.

Table 1: Patient Demographics, gender.

	Frequency table: GENDER (Sheet1 in DATAMMED)			
Category	Count	Cumulative Count	Percent	Cumulative Percent
Female	21	21	84,00000	84,0000
Male	4	25	16,00000	100,0000
Missing	0	25	0,00000	100,0000

Figure 1: Histogram of age



No of obs = number of observations

Regarding the clinical features of ataxia, 23 (92%) patients had symmetrical ataxia, and 2 (8%) had asymmetrical ataxia.

Table 2: Clinical features of ataxia

	Frequency table: ATAXIA FEATURES (Sheet1 in DATAMMED)			
Category	Count	Cumulative Count	Percent	Cumulative Percent
Symmetrical	23	23	92,00000	92,0000
Asymmetrical	2	25	8,00000	100,0000
Missing	0	25	0,00000	100,0000

We also documented the higher cognitive functions; 8 (32%) were normal, 9 (36%) had cognitive impairment, and 8 (32%) had delirium.

Table 3: Higher Cognitive Functions

	Frequency table: HIGHER FUNCTIONS (Sheet1 in DATAMMED)			
Category	Count	Cumulative Count	Percent	Cumulative Percent
Delirium	8	8	32,00000	32,0000
Cognitive Impairment	9	17	36,00000	68,0000
Normal	8	25	32,00000	100,0000
Missing	0	25	0,00000	100,0000

Montreal Cognitive Assessment (MoCA) was used to screen for cognitive impairment and scores ranged from 18-25.

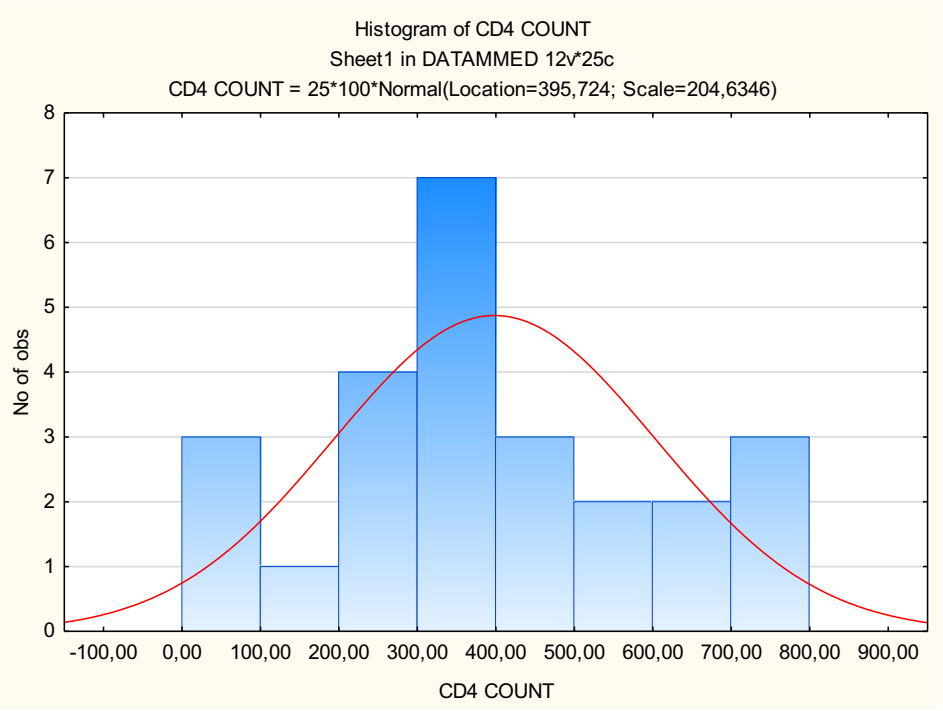
In terms of HIV history, all our patients were on regimen 1, most of our patients were virologically suppressed 24 (96%), and only 1 (4%) was not suppressed.

Table 4: Viral load

Category	Frequency table: VIRAL LOAD (Sheet1 in DATAMMED)			
	Count	Cumulative Count	Percent	Cumulative Percent
Suppressed	24	24	96,00000	96,0000
Not Suppressed	1	25	4,00000	100,0000
Missing	0	25	0,00000	100,0000

Regarding CD4 counts, the mean CD4 count was 395/mm^3, the minimum was 47,1/mm^3, and the maximum was 790/mm^3.

Figure 2: CD4 Count

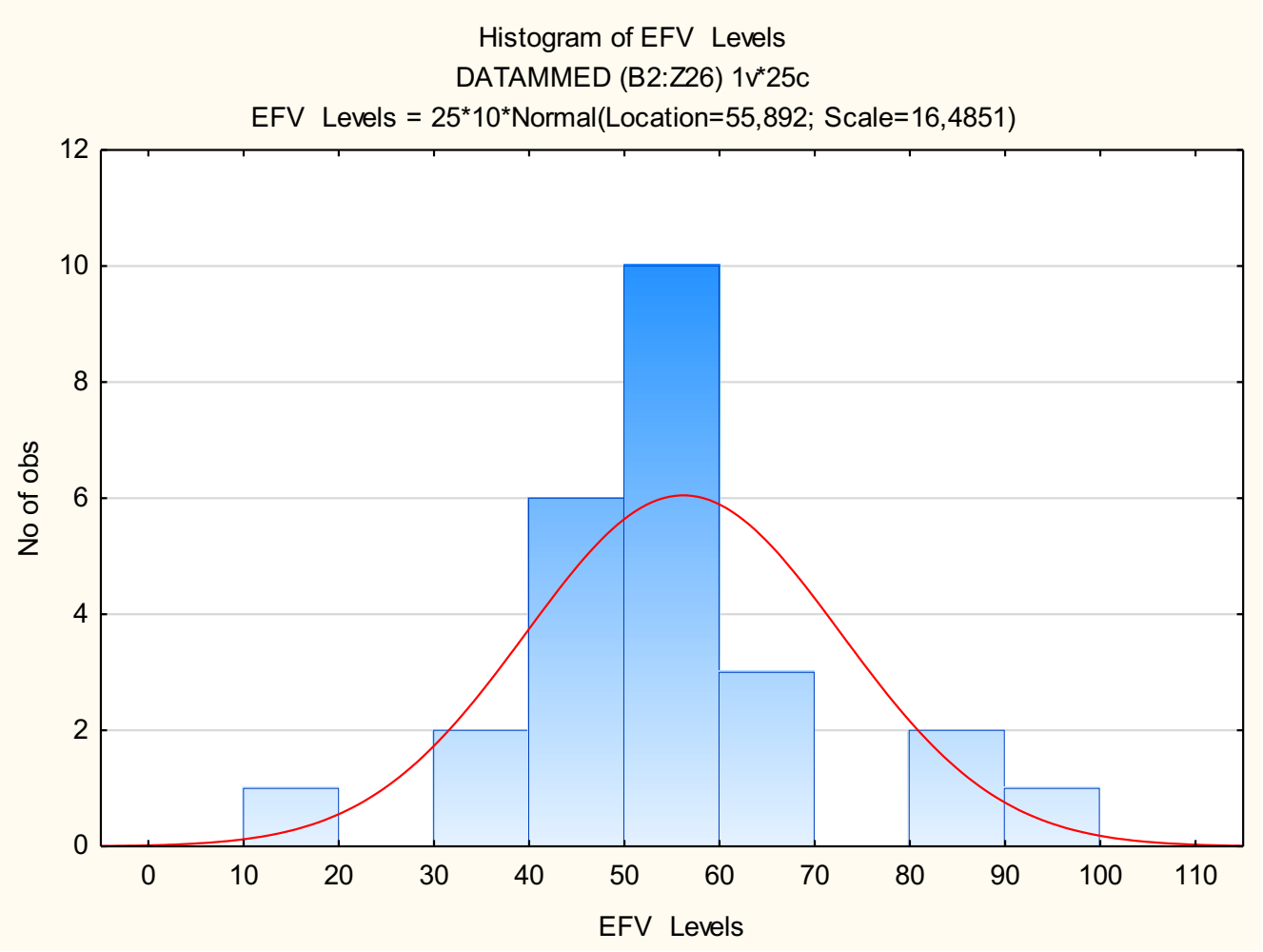


No of obs=number of observations

CD4 Count (cells/mm^3)

Pertaining to efavirenz levels, the mean was 55,8 mg/L, the minimum was 16,5 mg/L, and the maximum was 94 mg/L.

Figure 3: Histogram of Efavirenz levels



No of obs = number of observations

Efavirenz levels (mg/L)

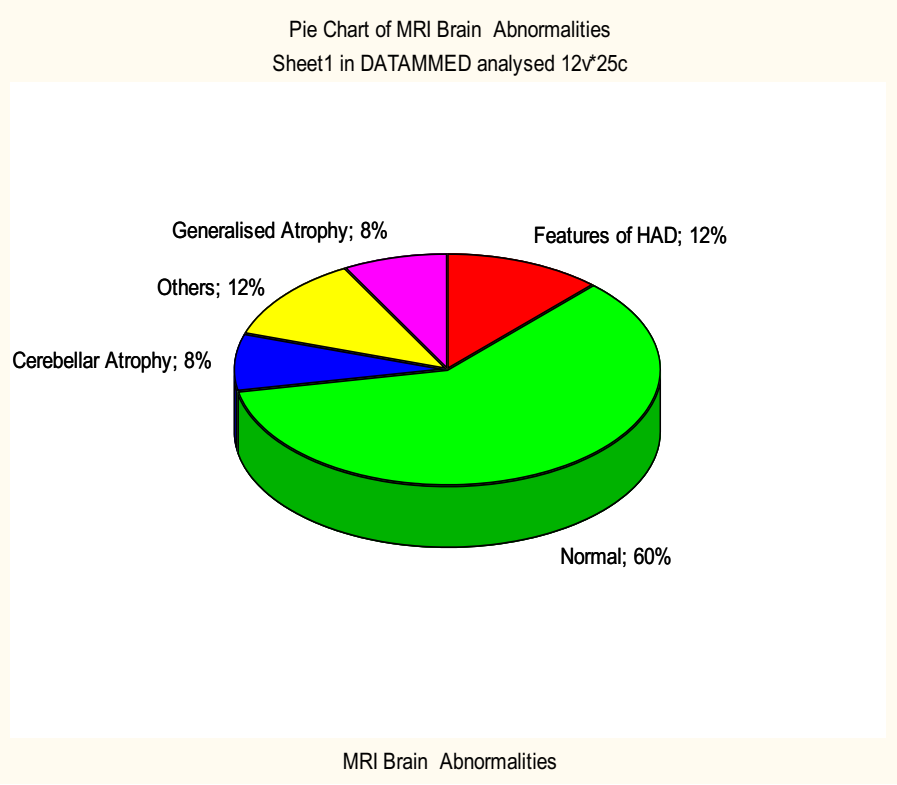
When analyzing the data for MRI brain images, 15 (60%) were normal, and 9 (40%) were abnormal.

In terms of MRI brain abnormalities, 3 (12%) had features of HIV-associated dementia (HAD), 2 (8%) had generalized atrophy, 2 (8%) had cerebellar atrophy, and 3 (12%) had other features (1 Cavernoma and two microvascular ischemic changes).

Table 5: MRI brain abnormalities

Category	Frequency table: MRI Brain Abnormalities (Sheet1 in DATAMMED)			
	Count	Cumulative Count	Percent	Cumulative Percent
Features of HAD	3	3	12,00000	12,0000
Normal	15	18	60,00000	72,0000
Cerebellar Atrophy	2	20	8,00000	80,0000
Others	3	23	12,00000	92,0000
Generalised Atrophy	2	25	8,00000	100,0000
Missing	0	25	0,00000	100,0000

Figure 4: MRI brain abnormalities



2.7 Discussion

2.7.1 MRI brain findings in patients with efavirenz-induced ataxia

The demographic profile of the patients with efavirenz-induced ataxia was young patients with a mean age of 36; 84% were females, and 16% were males. This observation suggests that patients with efavirenz-induced ataxia are mainly young females.

These results are in keeping with previous similar studies, where Variava et al. (9) found that efavirenz-induced ataxia was only seen in young females. Our study documented 2 (16%) males with efavirenz-induced ataxia.

It is worthwhile noting that other studies, Cross et al (11), had exclusively documented the syndrome in female patients; our study highlights that this condition can also occur in males, even though it is rare. We also observed that most patients had encephalopathy: 8 (32%) had delirium, and 9 (36%) had cognitive impairment; only 8 (32%) of patients had normal higher functions. Again, this observation is in line with the current literature; for example, in the study of Variava et al. (9), 11 (55%) of their patients had encephalopathy. This highlights that encephalopathy is common in these patients. When we compare our findings with Cross et al (11), 29% of their patients had encephalopathy. We did not observe any patients with psychosis in our study.

Regarding the clinical characteristics of the ataxia, we observed that 23 (93%) of our patients had symmetrical ataxia. We would have liked to also comment on the characteristics of nystagmus, but we could not because information on nystagmus was missing from most files. We could not assess patients' weight as it was not recorded in the files.

Regarding HIV history, all our patients were on regimen I, which contains efavirenz. Their mean CD4 count was 395 cells/mm^3, the minimum was 47,1 cells/mm^3, and the maximum was 790 cells/mm^3; this observation was also in line with current literature. Comparing our data with Variava et al. (9), the median CD4 count in their study was 299 cells/mm^3. Comparing our data with Cross et al. (11), their median CD4 count was 353 cells/mm^3, which shows that this condition commonly occurs in patients with fairly good CD4 counts. Concerning viral load, most of our patients had suppressed viral load (24 of 25). Again, when we compared it with other studies, we observed a similar occurrence; in the cohort of Variava et al. (9), 18 out of 19 patients had suppressed viral load, and in the study of Cross et al. (11), 6 out of 7 patients had suppressed viral load. This observation shows that efavirenz-induced ataxia commonly occurs in patients with good compliance to HIV treatment, as demonstrated by suppressed viral load and good CD4 count.

In terms of Efavirenz levels, all our patients had very high efavirenz levels. The mean efavirenz level was 55,8mg/l which is more than 13 times the upper limit of normal (1-4mg/l). The minimum was 16,5, and the maximum was 94. As we can see, these patients had very high toxic levels of efavirenz. Again, compared with the current literature, for example, Cross et al. (9) all their patients had efavirenz levels >20mg/l. Variava et al. (11) observed in their study that all their patients, 20 out of 20, had efavirenz levels>20mg/l.

The patients we described in our study are likely to be slow metabolizers of efavirenz. Efavirenz is mainly cleared in the liver by a process involving the cytochrome P450 system and the generation of inactive metabolites (6). Variations in different individual's efavirenz pharmacokinetics appear to be responsible for some differences in clinical outcome, with polymorphism in CYP2B6 being the relevant genetic determinant. Some studies have demonstrated an association between CYP2B6 single nucleotide polymorphisms and an increased risk of efavirenz. toxicity. (6)

Our study focused on the MRI brain images; 15 (60%) were normal compared to 10 (40%) that were abnormal. The MRI abnormalities observed: 3 out of 25 patients had features of HIV-associated dementia (HAD), 2 out of 25 patients had generalized atrophy, 2 out of 25 patients had cerebellar atrophy, 1 of the 25 patients had a cavernoma, and 2 of 25 patients had microvascular ischemic changes. Compared to the data of Variava et al.,10 of the 19 brain images showed abnormalities (7 had generalized atrophy, 1 had cerebellar atrophy, 1 had a pineal cyst, and one had features of encephalitis). Unfortunately, their study did not specify whether the brain imaging was CT Brain or MRI brain.

The study of Cross et al. (11)revealed 2 MRI abnormalities out of 7 patients they enrolled in their research, one patient had basal ganglia infarct, and one patient had non-specific parietal white matter intensity. Our study has shown that the MRI brain abnormalities observed in patients with efavirenz-induced ataxia are usually incidental findings and are non-contributory to the current condition. This observation is in line with existing literature as quoted above, although there is a lack of data on MRI brain findings in these patients.

From our limited experience, it may not be necessary to obtain MRI brain imaging in these patients, thus potentially saving on the cost of investigations. More, ideally, prospective studies will have to be done to assess the necessity and utility of MRI brain in these patients.

2.8 Study Limitations

This was a retrospective study, and we relied on the hospital records of patients; some information was missing. We wanted to assess the patients' weight, but we could not because of the incomplete records.

2.9 Conclusion

Efavirenz-induced ataxia is a common problem in HIV positive patients on ART. We hope to raise awareness about this condition that mainly affects young women and produces severe ataxia with encephalopathy, usually reversible. We suggest that for patients who still need to take efavirenz containing regimen, instead of 600mg, we recommend lowering the dose to 400mg nocte as per the current WHO guidelines.(2) We have also observed that MRI brain images in these patients were non-contributory, and even the abnormalities observed were not linked to encephalopathy that was observed clinically. More studies will need to be done with a bigger sample, but potentially, imaging with an MRI brain might not be necessary for this context.

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Appendix i: Data Sheet:

Demographic Data	
Study Number	
Age	
Gender	
Race	
Weight	

Clinical Features		
Asymmetrical		
Symmetrical		
Cognitive Impairment?	YES	NO
Delirium present?	YES	NO
Psychosis present?	YES	NO

HIV History and Investigations		
CD4 count		
Viral load	Suppressed	Not Suppressed
ARV Regimen	Regimen 1	Regimen 2
Efavirenz levels		

MRI Brain Findings	Normal	ABNORMAL
MRI BRAIN ABNORMALITIES		
Cerebellar atrophy		
Generalized atrophy		
Features of HIV-associated dementia		
Feature of encephalitis		
Others		

APPENDIX II: ETHICS CLEARANCE CERTIFICATE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R49 Dr SE Mandlesilo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M210871

NAME: (Principal Investigator)	Dr SE Mandlesilo
DEPARTMENT:	School of Clinical Medicine Department of Neurosciences Division of Neurology Medical School University
PROJECT TITLE:	*MRI brain findings in patients with Efavirenz-induced ataxia*
DATE CONSIDERED:	2021/08/27
DECISION:	Approved unconditionally
CONDITIONS:	
NOTE:	If contact information regarding student study participants is required, please contact the Registrar's office - <Nicoleen.Potgieter@wits.ac.za>
SUPERVISOR:	Professors G Modi and A Mochan
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2021/10/05

This Clearance Certificate is valid for 5 years from the date of approval. An extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office secretariat on the 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in August and therefore reports and re-certification will be due in the month of **August** each year. Unreported changes to the study may invalidate the clearance given by the HREC (Medical).

Signature of Principal Investigator

10/10/2021
Date

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FACULTY OF HEALTH SCIENCES

SCHOOL OF CLINICAL MEDICINE

DEPARTMENT OF NEUROSCIENCES

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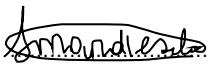
Signature:  .....

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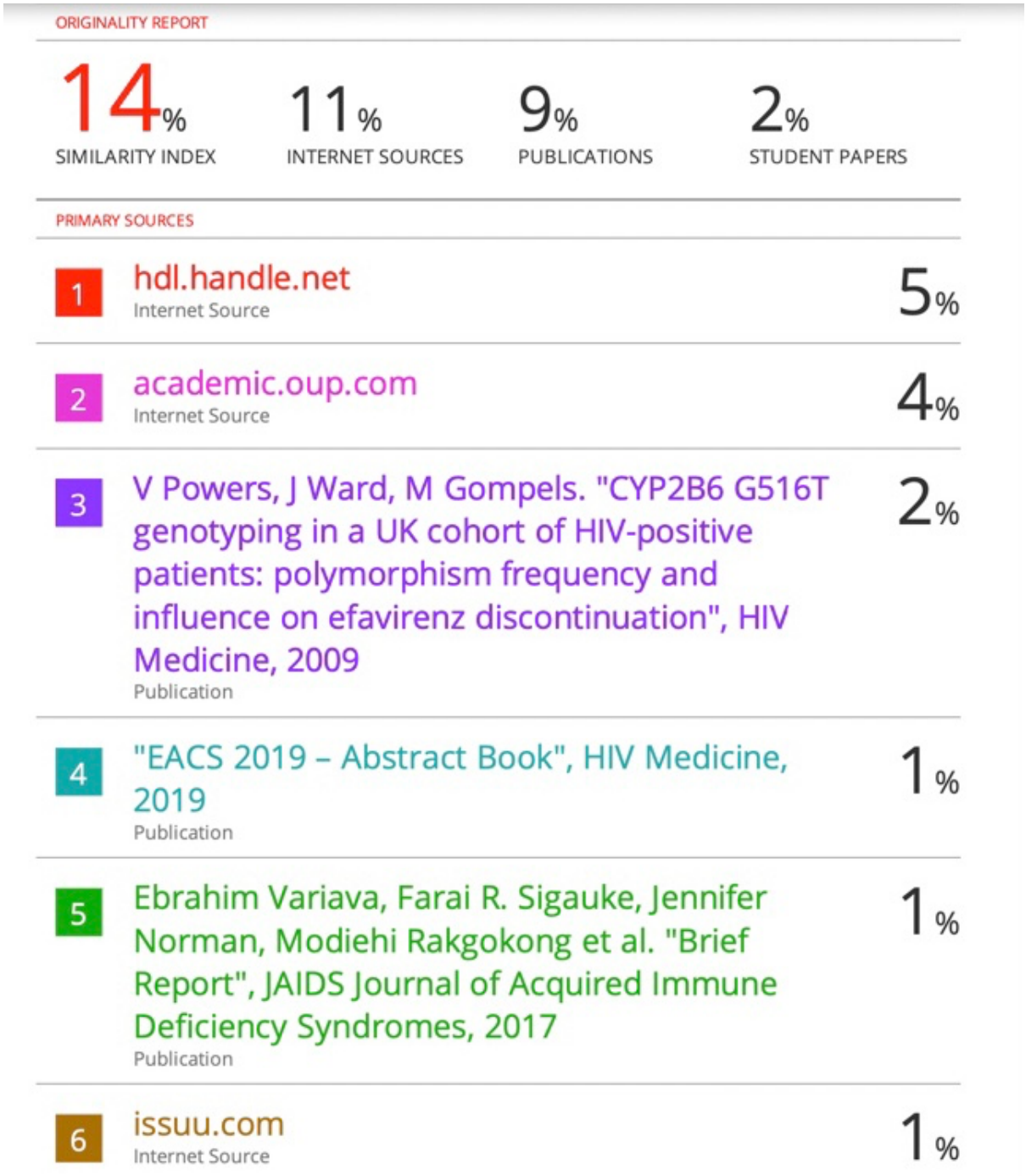
MRI BRAIN FINDINGS IN PATIENTS WITH EFAVIRENZ-INDUCED ATAXIA

SIMPHIWE EMMANUEL MANDLESILO



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