

# HIV and mental illness in Malawi and the neuropsychiatric sequelae of efavirenz

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## Abstract

### Introduction

Little is published about mental disorders in Malawi, specifically in relation to Human Immunodeficiency Virus (HIV) and its treatment. Efavirenz is a medication commonly used as part of triple therapy for HIV treatment. Indeed, in 2013, Malawi introduced 5A with Efavirenz as part of its 1st line treatment for HIV. There exists some literature documenting known psychiatric side effects of Efavirenz, which include anxiety, mood changes, nightmares, psychosis and suicidal ideation. Little is known about what features are most common in the presentation and what factors in the patient and drug which may make this reaction more likely.

### Aim

The aim of this commentary is to review the association between HIV and psychiatric disorder, and consider the neuropsychiatric side-effects of Efavirenz.

### Method

An evaluative literature review was completed by means of multiple electronic database search as well as an additional manual search to obtain published works identified through the electronic search. Search terms used were: Efavirenz, Acquired Immunodeficiency Syndrome, Africa, Antiretroviral Therapy, Developing Countries, Malawi, Mental Disorders, Public Health, and Psychiatry.

### Conclusion

This is an important area of study, as potentially large numbers of individuals with HIV are being placed on Efavirenz as first line treatment, yet 60% may experience some form of neuropsychiatric side effects.

## Introduction

Acquired Immune Deficiency Syndrome (AIDS) is a disease caused by the Human Immunodeficiency Virus (HIV), as described by the Center for Disease Control in 1981<sup>1</sup>. More than 36 million people are currently living with HIV, the vast majority of whom are in low and middle-income countries<sup>2</sup>. About 35 million people have already died of this disease<sup>2</sup>. In 2012, an estimated 2.3 million people were newly infected with the virus and 1.1 million people died of AIDS-related illnesses in 2015<sup>2</sup>. According to the 2010 Malawi Demographic Health Survey (MDHS), the prevalence of HIV in adults aged 15 to 49 in Malawi is approximately 10-11%, and the number of people living with HIV is 1.1 million<sup>3</sup>. The Joint United Nations Programme on HIV and AIDS (UNAIDS) recorded 36,000 new HIV infections and 24,000 AIDS-related deaths in 2016, although both of these figures represent a decrease from the 2010 figures<sup>4</sup>.

There is a dearth of large-scale prevalence studies exploring mental illness in Malawi. Studies examining this have tended to be relatively small in scale and completed in the Southern region of Malawi. The prevalence of mental, neurological and substance use disorders for primary care attendees is usually between 15% and 30% and in some cases reaches as high as 45%<sup>5</sup>. Wright *et al* found that 28.8% of people attending primary care clinics have a common mental disorder including depression,<sup>6</sup> and Stewart *et al* found a 30.4% prevalence of depressive episodes among women with

young infants in Thyolo, as well as associations with poverty, relationship problems, HIV-infection and poor infant health<sup>7</sup>. Furthermore, the Malawi Health Sector Strategic Plan 2011-2016 indicates that mental illness accounts for 4% of the total burden of disease in Malawi<sup>8</sup>.

Zomba Mental Hospital (ZMH) is the only government-run tertiary psychiatric referral hospital in Malawi. The commonest reasons for admission at ZMH are schizophrenia, bipolar disorders, intellectual disability, epilepsy, substance-related and HIV-related conditions<sup>9</sup>. Data from inpatients at Zomba suggests that 90% of patients admitted at ZMH are diagnosed with Schizophrenia or related illnesses<sup>10</sup>.

### Association between HIV and Psychiatric disorder

#### *HIV infection in those with pre-existing mental disorder*

It has been hypothesized that mental illness is a risk factor for developing HIV-infection. This is mainly based on indirect evidence<sup>11</sup> and is thought to involve multiple factors, including; high-risk behaviours such as infrequent condom use, multiple sex partners and intravenous drug use,<sup>12,13</sup> social exclusion that may lead to exchange of sex for money or goods, or forced sex,<sup>14,15</sup> cognitive deficits leading to impaired judgment and/or the ability to negotiate safe sex<sup>16</sup>. In addition, the consequences of mental illness may lead to insufficient money to purchase condoms, no privacy for safer sex negotiation and considerable periods of hospitalization that may interfere with long-term sexual relationships and the opportunity to obtain condoms<sup>17</sup>.

Depression has been identified as a major contributor to sexual risky behaviour resulting in HIV infection in Botswana and other countries<sup>18-24</sup>. It has been associated with steeper declines in CD4 counts, greater risk of developing HIV dementia, decreased antiretroviral medication adherence and more rapid progression to AIDS and death<sup>18</sup>. Manic symptoms such as increased energy, grandiosity, hypersexuality, impulsivity, and poor judgment often lead to risky behaviours<sup>25-27</sup>. Over half of individuals with bipolar disorder also have lifetime substance use disorders, which further increase the risk of HIV infection<sup>25,27-28</sup>. Cognitive dysfunction in patients having primary psychiatric illness like schizophrenia has been well documented<sup>9</sup>. Cognitive deficits such as lack of planning, impaired judgement, lack of motivation to engage in safer sexual behaviours and inability to acquire and/or use information about HIV/AIDS increase risk of contracting HIV<sup>9</sup>.

Studies from Africa, United States of America (USA) and elsewhere, investigating the link between mental illnesses and HIV, report varying but consistent results that adults with severe mental illness have higher rates of HIV infection<sup>29-34</sup>. Prevalence rates of HIV in those with mental illness range from 2 – 76 times higher than the general population<sup>32,35-38</sup>.

There is less data available about the relationship between mental illness and the risk of contracting HIV in low-income countries. One systematic review found that the HIV-prevalence varied between 0 and 23.8%, which appeared to correspond to the prevalence in the general population<sup>39</sup>. The latter figure represented a study in Zimbabwe<sup>40</sup>. In Malawi, psychiatric outpatients in Thyolo had an HIV-prevalence of 14.8%, compared to the general population of 21%<sup>41</sup>.

#### *Rates of mental disorder in those with pre-existing HIV*

Mental illness and neuropsychiatric manifestations of HIV are often a combination of complex biological, psychological and social circumstances associated with HIV infection<sup>42</sup>. The following mechanisms have been hypothesized to be important: the psychological burden arising from the acute trauma of the diagnosis, difficulties posed on daily life, the longer-term threat of physical decline and shortened life expectancy<sup>11</sup>. Others are: the necessary life style changes, complicated therapeutic regimes, aversive symptoms and stigma leading to guilt and loss of social support,<sup>11</sup> as well as the direct effects of the virus on the central nervous system causing neuropsychiatric complications,<sup>43</sup> opportunistic infections of the nervous system,<sup>44</sup> and side effects of antiretroviral therapy (ART) on the central nervous system<sup>45</sup>. Documented information about mental health disorders among HIV-positive people in low and middle-income countries is less extensive. A systematic review from developing countries shows a wide range of prevalence of depression among people infected with HIV (0-64%)<sup>15</sup>. This wide range is most likely representative of the wide variation in research methods applied. The review suggests that people infected with HIV are more often psychologically distressed and that this may be related to the severity of physical symptoms, the quality of family relations and the support of the partner<sup>15</sup>. This finding has been repeated in a Malawian setting<sup>46</sup>.

Depression has been documented among patients with HIV at 17.9% in Salima and 20% among adolescents with HIV in Lilongwe<sup>24</sup>. Prevalence of major depression was also significantly higher in those with HIV in the over 50 age

group in rural South Africa<sup>47</sup>. Females, particularly those in the urban residency and those receiving a government grant, were affected<sup>47</sup>. Depression associated with HIV/AIDS has been linked with faster disease progression and reduced drug adherence<sup>48</sup>. It has also been shown to be associated with less social support, worse quality of life, as well as higher HIV plasma viral loads, increased disease progression and higher mortality<sup>23,36,37,41,49,50</sup>. Suicidal ideation may be a cause for psychiatric referral in subjects who have been informed about a diagnosis of HIV/AIDS, and was found at 12.6% and 10% prevalence in studies done in Lilongwe and rural Zambia<sup>24</sup>.

In patients with HIV, prevalence of mania is elevated though less so than depression<sup>21,25,34</sup>. Patients with mania secondary to HIV tend to present at a more advanced stage, are more likely to have developed AIDS, have a low CD4 count and have a higher prevalence of co-morbid dementia or cognitive slowing when compared to HIV-positive patients with primary mania<sup>20,23,26,34</sup>. The prevalence of mania in a population of HIV-positive patients was found to be similar to that of the general population, at 1.2 - 1.4%, whereas the rate in patients with AIDS was 4.3 - 8 %<sup>20,26</sup>. Patients with mania secondary to HIV had more irritability, aggression, cognitive impairment and dementia and had higher rates of psychotic symptoms<sup>25</sup>. The frequency of affective episodes may increase following HIV infection in bipolar patients, and mania may occur having been given a diagnosis of HIV<sup>25</sup>.

The prevalence of generalized anxiety disorder, and adjustment disorder is increased in HIV-positive patients compared to HIV negative individuals<sup>26,50</sup>. These may arise from the distress associated with being diagnosed with the infection and from the implications of the diagnosis<sup>26,50</sup>.

Psychosis may occur as a direct result of HIV infection on the CNS, with the highest incidence reported among patients in later stages of HIV disease<sup>26</sup>. Cognitive dysfunction is also common among patients with HIV associated psychosis<sup>24,34,35</sup>. Cognitive impairment has also been found to be worse among HIV-positive individuals with psychosis in comparison to HIV negative individuals with psychosis<sup>21</sup>.

Dementia is commonly seen in patients with HIV, particularly when ART medication is not taken regularly<sup>51</sup>. Patel et al found a prevalence of HIV-associated dementia of 14.0% among HIV-positive adults<sup>51</sup>. Cognitive impairment in HIV has been associated with greatly increased mortality independent of other factors such as baseline clinical stage, CD4 count, serum haemoglobin concentration, ART use, and social and demographic characteristics<sup>52</sup>.

HIV infection has a number of psychiatric sequelae associated with it. Psychiatric illness is commonly the first presentation of HIV infection, as highlighted by a study in Uganda in which 43% of HIV-positive individuals did not have a prior episode of mental illness<sup>21</sup>. Several studies from high-income countries indicate a higher prevalence of major depressive disorder, milder depressive symptoms, anxiety disorder,<sup>53-55</sup> mania, psychotic disorders,<sup>53,56-57</sup> and substance abuse,<sup>58</sup> as well as cognitive impairment<sup>56</sup> among people infected with HIV. HIV infection may also exacerbate existing conditions such as Schizophrenia<sup>59</sup>.

#### *Adherence to Testing and Treatment*

It is thought that individuals with severe mental illness may lack competence to refuse testing or treatment for HIV. In a study in Thyolo, Malawi, 93.7% had the capacity to provide

consent for HIV testing in outpatient settings, but other studies have found that only 80%-87% of patients with severe mental illness had adequate capacity to provide consent<sup>60</sup>. Co-morbid diagnosis of mental disorder and HIV are associated with poorer ART adherence, faster disease progression and increased mortality<sup>61</sup>. Adhering to ART therapy requires, amongst other things, insight and capacity. Evidence from high-income countries shows that adherence may be negatively affected by depression, cognitive impairment, and alcohol and substance abuse, although adherence increases with close medical observation<sup>11</sup>. Poor adherence to ART may also be closely related to the central nervous system's adverse effects caused by these drugs, including Efavirenz, although this relationship is multi-factorial<sup>62</sup>. Adherence to ART is important in achieving viral suppression of HIV, thereby reducing infectiousness and helping prevent disease progression<sup>63</sup>. Public health policies should therefore strive to maximize adherence<sup>50</sup>.

### *Treatment of HIV*

The mainstay of HIV treatment is the so-called anti-retroviral therapy (ART) drugs. These drugs either interfere with the transcription of viral RNA into complementary DNA (dependent on reverse transcriptase), or when viral proteins are produced and broken down into subunits via the protease enzyme<sup>64</sup>. These drugs have significantly improved the clinical outcomes for patients with HIV. At the end of 2012, close to 10 million people were receiving ART in low and middle-income countries<sup>2</sup>. However, almost 19 million other people who were eligible for ART under new 2013 guidelines still did not have access to antiretroviral drugs<sup>2</sup>. Treatments consist of 'combination treatments,' which are classified as the nucleoside reverse transcriptase inhibitors, the non-nucleoside reverse transcriptase inhibitors and the protease inhibitors,<sup>64</sup> as well as the entry inhibitors, fusion inhibitors, and the integrase inhibitors<sup>65</sup>. These are exemplified as highly active antiretroviral therapy (HAART), which are a combination of protease and reverse transcriptase inhibitors. These aim to reduce viral loads and increase lymphocyte numbers, thus helping to decrease mortality and morbidity including HIV associated dementia and the incidence of opportunistic infections affecting the central nervous system (CNS)<sup>67</sup>. HIV infection has thus become a chronic disease with patients surviving for many years. It is important that one of these combination drugs crosses the blood brain barrier, yet this may paradoxically pre-dispose patients to neuropsychiatric side effects. Efavirenz is known to be one such agent that does cross the blood brain barrier<sup>68</sup>.

### *Efavirenz*

Efavirenz is a medication commonly used as part of combination therapy for HIV treatment, and has been shown to be not inferior at reducing the viral load in HIV-positive patients compared to other preparations<sup>69,70</sup>. Hence, in Malawi, its use is now recommended as first line treatment, despite the noted side-effects. Current ART guidelines in Malawi recommend that those with symptoms of/or a history of mental illness should be commenced on the 6A regimen, of which Efavirenz is not included<sup>71</sup>. These guidelines also advise that Nevirapine replace Efavirenz in those patients who experience severe side-effects such as psychosis<sup>71</sup>. All those living with HIV should be initiated on ART irrespective of their CD4 count or clinical stage<sup>71</sup>.

Efavirenz is a selective non-nucleoside analog and non-

competitive inhibitor of the reverse transcriptase enzyme of HIV. It attaches directly to this enzyme blocking DNA-RNA polymerase, causing the destruction of this catalytic site of the enzyme<sup>72</sup>. It is highly protein bound (around 99.7%) to human plasma proteins, and is predominantly metabolised by the cytochrome P450 system. It has a prolonged half-life, permitting once daily dosing that has obvious benefits in terms of adherence and has good antiretroviral efficacy<sup>68</sup>.

### *Neuropsychiatric side effects of Efavirenz*

Existing literature suggests a widely repeated association between antiretroviral drugs and psychiatric disorder, with Efavirenz being the most frequently cited. It may cause adverse psychiatric events ranging from 61-90% of patients,<sup>73-76</sup> Reported side effects include: nightmares, headache, light-headedness, insomnia, confusion, lethargy, impaired concentration, amnesia, hallucinations, abnormal dreams, anxiety, de-personalisation, de-realisation, personality change, stream of thought troubles, mania, depression, suicidal thoughts, psychosis and hallucination<sup>74,76-87</sup>. In 2008, Marwaha found that African children and teenagers were experiencing hallucinogenic effects from smoking Efavirenz<sup>88</sup>.

Many of these adverse effects can be provoked by the virus itself,<sup>44-46</sup> making it difficult to fully ascribe them to the effects of Efavirenz. Regardless of their origin, these side effects may lead to discontinuation of HAART therapy, but have been reported to resolve following discontinuation of Efavirenz and by adding appropriate psychiatric medication<sup>79</sup>. Spire *et al* found that female gender, unemployment, steady sexual partners and multiple episodes of depression were social, demographic and psychiatric risk factors for Efavirenz discontinuation<sup>89</sup>.

Some of these adverse effects may be associated with elevated serum levels of Efavirenz. Marzolini *et al* found that low levels predicted treatment failure and high levels were associated with CNS side effects<sup>90</sup>. The neurochemical mechanisms responsible for these adverse effects are not well understood. Side effects commonly appear within the first week of treatment, and some will disappear or diminish after several weeks<sup>91</sup>. Others may not diminish until after 200 days,<sup>92</sup> whereas others may persist indefinitely<sup>78</sup>.

Several studies have highlighted the role of underlying psychiatric illness in predicting side effects to Efavirenz. Boly *et al* found that pre-existing depressive symptoms predicted neuropsychiatric side effects in HIV-1 positive patients treated with Efavirenz<sup>93</sup> and Moreno *et al* suggested that pre-existing psychiatric diseases, such as Post Traumatic Stress Disorder (PTSD), could predispose to Efavirenz side effects<sup>94</sup>. Others have indicated that young age and history of depression could be involved,<sup>95</sup> as well as a history of chemical dependency.<sup>96</sup>

Allavena *et al* speculated that the combination of ART regimen may be of importance, since neuropsychiatric side effects were seen when switching from an Efavirenz ART regimen to an Efavirenz-Tenofovir combination<sup>97</sup>.

Of relevance, Efavirenz undergoes transformation by the CYP liver enzymes (mainly CYP2B6 and CYP3A4), and is thus subject to interactions with psychiatric medications<sup>88</sup>. For example, Fluoxetine and Fluvoxamine elevate the plasma level of Efavirenz and, thus, accentuate its effects on the CNS<sup>86</sup>. This is important in the Malawi context since Fluoxetine is one of the few commonly used anti-depressant

medications. Also, genetic polymorphisms resulting in deficient alleles of the CYP2B6 isoform has been shown to be more prevalent in African populations<sup>98</sup>.

## Future Considerations

As yet, there have been no case control studies undertaken in this population to establish more systematically which factors are associated with Efavirenz related psychiatric presentations. Little is known about what features are most common in neuropsychiatric presentation and what patient factors are associated with increased risk of developing these side effects or precipitating acute mental illness. One retrospective study by Von Giesen *et al* found no significant differences between Efavirenz and Nevirapine containing ART regimens with respect to memory, attention, psychomotor speed, CD4 count, and the manifestation of depression<sup>99</sup>. The study participants had similar demographic characteristics prior to therapy and a comparable outcome including adverse effects and neuropsychiatric symptoms.<sup>99</sup> It is therefore important to be able identify characteristics of neuropsychiatric presentations secondary to Efavirenz that distinguish this presentation from other forms of mental illness or characteristics of HIV infection itself; elucidating this will aid in the management of mental illnesses in those taking Efavirenz for co-morbid HIV infection. It would help determine those who may be at risk of this adverse reaction, and help to inform future HIV treatment strategies at local and national level, and contribute to the international evidence in this area.

Before initiating Efavirenz, patients should be screened for the presence of any mental disorder, or a history of one. Patients should be encouraged to attend follow-up clinics regularly, and clinic staff should be trained in recognizing neuropsychiatric side-effects. Follow-up should also be prolonged. The neuropsychiatric sequelae of Efavirenz should be treated according to severity, with intolerable ones warranting substitute therapy. This should consider interactions with psychotropic medications.

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