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Systematic Review

The association between depression and efavirenz-based antiretroviral treatment in people living with human immune-deficiency virus: a systematic review

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ABSTRACT

The neuropsychiatric disturbance such as depression in people living with (PLHIV) requires serious attention as this affects their health outcome. Efavirenz (EFV)-based treatment has been associated with neuropsychiatric adverse events, but its mechanism still unknown. The purpose of this systematic review is to dissect recent studies regarding EFV and depression, in the hope to discover reasonings behind this association. PRISMA flow chart was used to search for the related literatures in the last five years (2018-2023). Targeted population was PLHIV on EFV-based ART only and/or compared with non-EFV-based ART. Relevant keywords used to search were HIV, efavirenz and depression. Five eligible articles were selected which included a total of 3272 PLHIV. Overall, three studies agreed that EFV-based ART was related to depression, while the other two studies did not. It was shown that EFV-based ART did cause neuropsychiatric adverse effects in the first few weeks of treatment, but subsided after several months. However, longer-term research is needed to determine its long-term effects. Variation of results in different studies must be influenced by the possible genetic factors, baseline depression, different social and psychological circumstances throughout the treatment and different assessment tools for depression. Depression on EFV-based treatment in PLHIV may manifest in the initial few weeks of treatment, and additional research is still needed to determine its effects throughout longer treatment durations. Early diagnosis of depression in PLHIV is essential to decide the best choice of ARV for better outcome.

Keywords: HIV, Efavirenz, Depression, PLHIV

INTRODUCTION

Because of the effects of AIDS, including the loss of social support, mental health issues, prejudice, and cognitive impairment, persons living with HIV (PLHIV) have greater challenges than those who are not infected do.[1] More research is needed on the mental disorders in PLHIV. Worldwide, PLHIV are more likely to experience neuropsychiatric conditions such anxiety, insomnia, and depression.[2] A meta-analysis among PLHIV in China found the prevalence of depression to be 54%, up to seven times higher than the general population, in stark contrast to the general population, where the prevalence of depression was 21.1% during the COVID-19 epidemic in China.[3] Anti-retroviral therapy (ART) is commonly made ineffective by these conditions, and depression significantly lowers treatment compliance and raises death rates.[4]

People living with HIV (PLHIV) encounter more difficulties than uninfected people do because of the consequences of AIDS, such as a loss of social support, mental health problems, discrimination, and cognitive impairment.[1] The neuropsychiatric abnormalities in

PLHIV require more attention. Worldwide, PLHIV are prone to neuropsychiatric issues such depression, sleeplessness, and anxiety. In striking contrast to the overall population, where the prevalence of depression is 21.1% during the COVID-19 outbreak in China, a meta-analysis among PLHIV in China estimated the prevalence of depression to be 54%, up to seven times higher than the general population.[2,3] These illnesses frequently reduce quality of life and anti-retroviral therapy (ART) is rendered ineffective by depression, which also decreases treatment compliance and increases mortality.[4] HIV neurotoxicity, recreational drug use that harms the CNS by changing brain hemostasis, HIV stigma, social factors, and unfavorable effects of antiretroviral treatment (ART) are possible causes of neuropsychiatric problems in PLHIV.[5]

Although highly active anti-retroviral therapy (HAART) has improved survival rates and turned HIV infection into a chronic illness requiring lifetime medication, about one-fourth of HIV-infected people still experience chronic sadness or anxiety.[6] Despite being extensively used, efavirenz (EFV) has been linked to neuropsychiatric adverse effects, with a frequency of these occurrences in PLHIV as high as 25-70%.[7] One of the most often reported adverse effects was depression. However, it is still unclear how it relates to depression or brain physiology.[8] A study found that efavirenz was linked to a five-fold increased risk of depressive symptoms in patients with a history of depression over the course of a year rather than an increased risk of depressive symptoms in HIV-infected patients without a history of depression. This difference in risk became particularly obvious after 24 weeks of follow-up.[9] According to a research, PLHIV receiving efavirenz were nearly twice as likely to experience suicidal thoughts or attempt suicide as those taking other medications.[10] This particular study found that efavirenz users had an increased risk of depressive symptoms, including suicidal thoughts and attempts. These contradictory study results indicate that there is currently a lack of knowledge regarding the connection between efavirenz and mental disorder in PLHIV. The goal of this systematic review is to explain recent data from the last five years regarding the EFV-based treatment and depression in PLHIV in order to determine the cause of conflicting results on the topic.

METHODS

Literature searching was conducted according to preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart. The targeted population in this systematic review was all PLHIV on EFV-based ART alone and/or non-EFV-based ART. We did not limit the choices of depression assessment tool, as there have been various types of assessment tools used in different countries depending on the feasibility.

All literatures or studies were selected based on the inclusion criteria: studies published in English; cohort or cross-sectional studies; literatures of publication year from August 2018 to November 2022; and available in full original version. Literatures without clear method and design of study were excluded.

We used Pubmed, Google Scholar and medRxiv to look for eligible. Relevant keywords used to search for literatures were: HIV, efavirenz and depression. Literatures were then selected based on our limit of time range of publication. Initial assessment on the title, abstract and keywords were conducted. Further assessment was done by scanning through the full-text literatures to match with the inclusion criteria. Selected literatures were then preceded for systematic review. Out of all 79 studies found, we selected 5 studies to be systematically reviewed.

Extraction of the data from selected literatures including the first author's name, country of origin of the study, year of publication, total sample size, the mean/median age of all participants, the depression assessment tool and types of ART. The assessed outcome was the occurrence of depression based on the results of each depression assessment tool. Risk of bias assessment was done by Cochrane collaboration's risk-of-bias method (Figure 2).

RESULTS

We selected five articles within the last five years (2018-2023) that matched our eligibility criteria with a total of 3272 PLHIV.[5,11-14] Three studies are cohort prospective and two studies are cross-sectional studies, all of which were selected to represent different perspectives of the results. Two studies were from America, another two studies came from Asia and one study was from the Africa continent. Most of the studies' participations were from men, except for one study that intentionally included only male participants. Most participants from all studies were in their thirties. The depression assessment tool used in each study was also different from one another depending on the feasibility at each site. In fact, due to those variabilities, the results from all articles were quite diverse and add up to more insight regarding the association between efavirenz and depression. Overall, three studies agreed that efavirenz-based ART was related to depression, while the other two studies did not.

Two studies that assessed the correlation between the duration of EFV-based therapy consumption and the occurrence of depression (Yijia et al and Xiao et al) agreed that time-on-EFV did not associate with depression.[5,12] Those never on EFV, currently on EFV or even have switched off from EFV were found to be no different for their risk of depression. Moreover, those who had discontinued their EFV-based treatment did not show significant changes in depression severity.[12] Longer term on EFV-based ART (more than 6 years) also did not affect the risk of depression when compared to shorter term of medication (0.5-6 years).[5] This is contrary to another similar study by Checa et al that also focused on the time-on-EFV, which revealed that patients on EFV-based

therapy after 8-12 weeks since initiation had risk of severe or very severe depression.[13]

Another study that looked at the risk of depression by Chang et al when comparing EFV to non-EFV-based ART (nevirapine or NVP) actually showed that patients on EFV had less risk about 38% to suffer from a depression than those on NVP.[11]

This is however, in contrast with a study from Indonesia that strongly stated that EFV was a significant independent factor for suicidal ideation related to depressive symptoms in Indonesian population.[14]

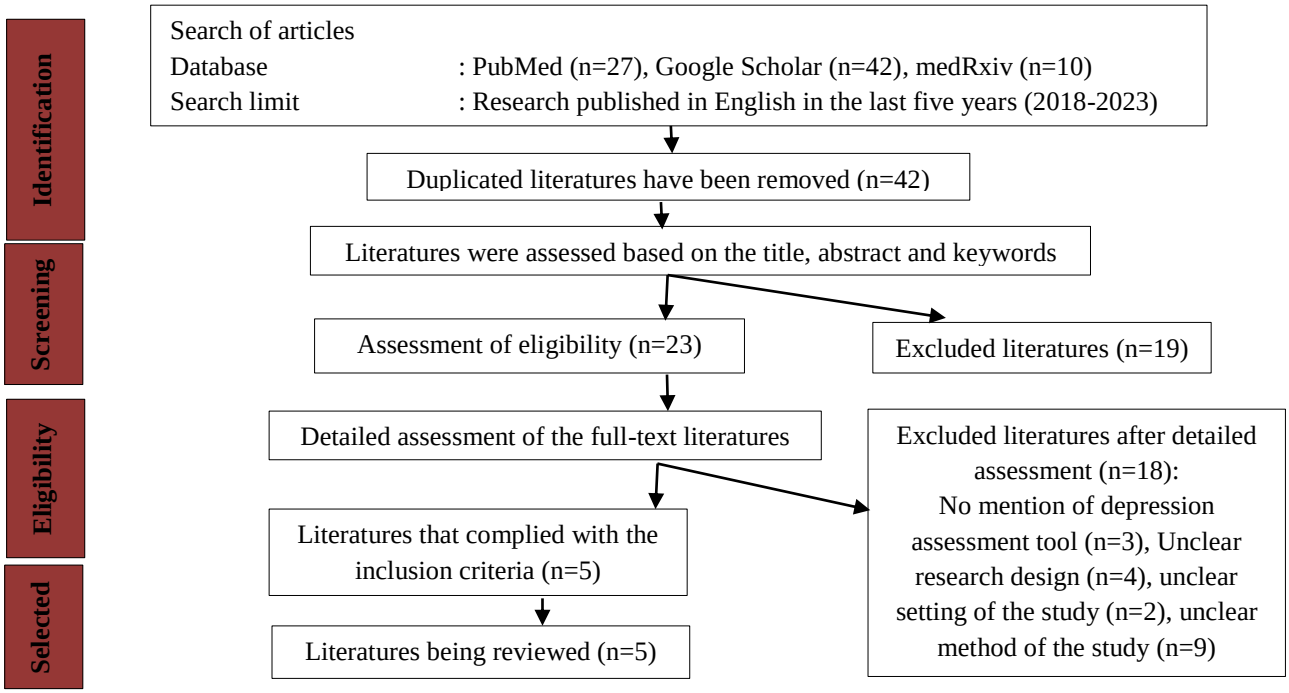

Figure 1: Literatures selection according to PRISMA flow chart.

Table 1: Summary of the reviewed literatures.

First author (publication year)	Design of study	Country of research	Sample size	Mean/ median age	Depression assessment tool	ARV treatment	Summary of findings
Chang et al[11]	Prospective cohort	Uganda	694 (305 on efavirenz, 389 on nevirapine) By gender: female 65.9% on efavirenz, 72.8% on nevirapine	33	The Hopkins symptom checklist	Efavirenz versus Nevirapine	No difference in baseline was found for depression between those who were ever exposed to efavirenz and those who were receiving nevirapine (P>0.80). Participants who received efavirenz had less occurrence of depression compared to those with nevirapine (20% vs 32.1%). Efavirenz use was found to show decreased odds of depression compared to nevirapine (adjusted odds ratio (AOR)=0.62, 95%CI 0.40-0.96)
Li et al[12]	Prospective cohort	USA	1989 (men only)	37	Center for epidemiological studies-	Efavirenz	Participants were grouped into three different categories: never on EFV, currently on EFV and ever been on EFV and then

Continued.

First author (publication year)	Design of study	Country of research	Sample size	Mean/ median age	Depression assessment tool	ARV treatment	Summary of findings
					depression (CES-D) scores		switched off. CES-D scores did not show any significant change over two years before and four years after switching in the switch-off group. CES-D scores were also found to be no different among the three different groups in 3.2 years of follow up.
Checa et al[13]	Prospective cohort	Ecuador	79 (female 13.9%)	28	The Hamilton rating scale for depression	Efavirenz	Most of the participants had TDF/FTC/EFV. Baseline score of the Hamilton Rating Scale showed that only less than 30% of the participants had no depression symptoms, where almost 40% of them had suffered from mild depression. Furthermore, the second assessment done 8-12 weeks after the ART initiation revealed a score in tune with severe or very severe depression (Relative risk (RR)=1.58, 95%CI 1.09-2.28).
Ophinni et al[14]	Cross-sectional	Indonesia	86 (42 on Efavirenz-based therapy, 32 on NNRTI-based therapy and 12 on PI-based therapy) By gender: female 34.9%	35	Symptom checklist-90 (SCL-90)	Efavirenz-based, other NNRTI-based, PI-based	Participants with suicidal ideation were found to have higher mean SCL-90 T-score for depressive symptoms (60.75±12.0, p=0.000). It was found that suicidal ideation in their lifetime was related to efavirenz use. Efavirenz was also considered as a significant independent factor (AOR=5.00, 95%CI 1.02-24.6) for suicidal ideation among Indonesians in this study.
Xiao et al[5]	Cross-sectional	China	424 (female 1.9%)	34	- 12-item short form health survey (SF-12) - hospital anxiety and depression scale (HADS)	Efavirenz	All participants were divided into three groups based on their time on EFV-based ART: group A (in between 0.5-2 years), group B (in between 2-4 years), group C (in between 4-6 years) and group D (equal to or more than 6 years). Overall mental component summary scores of SF-12 showed 50.2, meaning lower score than general population. 15.3% of all participants experienced depression and did not differ significantly between all groups of time-on-ART. There was no correlation between depression and time on EFV

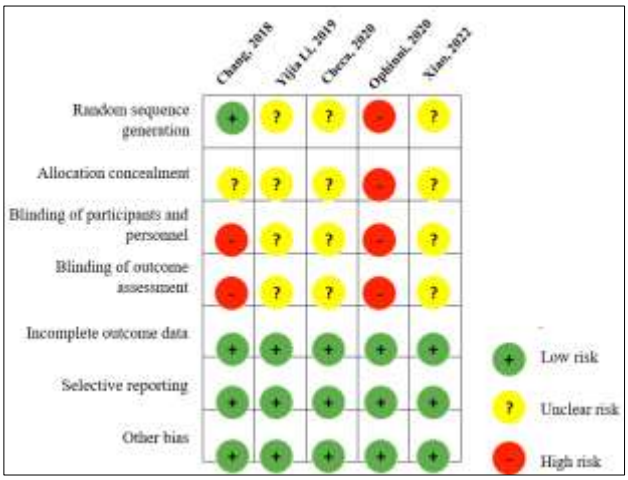

Figure 2: Risk of bias assessment of all selected studies.

DISCUSSION

Varying results regarding the association between EFV-based ART and depression could be explained by several factors that potentially affected the outcome. One is genetic difference in different ethnics that might explain different effects of EFV in these different populations. Previous studies on African decendants and Caucasians showed slower EFV clearance along with greater CNS toxicity in Caucasians than Africans.[15,16] This is in line with our systematic review; we reviewed one study from Africa (Uganda),[11] which showed favorable action of EFV that had lower odd ratio of depression than another type of ART (NVP). Chang et al explained in their study that EFV is metabolized slower compared to NVP, causing the drug to have lower peak levels and cause less toxicity to the CNS. Long duration of the drug use is also considered to induce the tolerance towards the CNS-related side effects.[5,12-14] Nonetheless, compared to other reviewed studies coming from American and Asian countries, the results from those countries rather showed correlation between EFV and depression. Efavirenz has been demonstrated to interact with various neurotransmitter pathways, and host genetic modification of these pathways may have an impact on the phenotype.[17]

We also could not get rid of the fact that baseline depression might possibly affect the outcome. Yijia et al in their study proved no difference of incidence of depression between those who were never on EFV and currently on EFV.[12] While Xiao et al showed how different duration of treatment did not affect the occurrence of depression in PLHIV who had already experienced the symptoms.[5] Both study signal that the event of depression is not solely influenced by the use EFV, and that the possibility of baseline depression must be taken into account. Depression and suicidal ideation in patients early after HIV diagnosis are usually due to their inadaptation and scarce of effective coping mechanism to cope with their health status. This influences their ability to bear with the treatment, causing them more prone to neuropsychological symptoms such as depression on treatment.[18] Therefore baseline depression in participants of the study should be considered to control confounding factors and avoid bias of results. This is also highlighted in two reviewed studies (Chang et al and Ophinni et al), which explained that depression screening is rarely done in routine clinical practice and the use of screening instrument needs to be carefully calculated, since an instrument might be overly sensitive.[11,14]

The time-on-EFV must also be studied further in the future. Checa et al showed in their study that 8-12 weeks on EFV-based therapy would cause risk of severe or very severe depression.[13] However, Xiao et al who studied longer duration of treatment until more than 6 years presented that there were no difference in depression experienced by patients who were on treatment for less than 6 years and more than 6 years, in which patients who showed symptoms of the neuropsychiatric disturbance experienced persistence depression.[5] This indicates that studies that focus on longer duration of treatment to give clearer picture on the effects of EFV on long-term depression need to be done. Different social and psychological circumstances throughout the long treatment must also be considered as these highly influence their mental health.[18]

Related to the use of assessment instruments, different tools used to assess the outcome of depression surely affect the study results. All of the five reviewed studies have different scales used, making a lot of variability in the results. Nevertheless, selecting the right tool to do screening and diagnostic assessment is important, as the two different purposes might result in different incidence of depression. For example, Chang et al and Ophinni et al.[14] used screening tools in their study, highlighting the possibility of bias in the assessment since the tools used might be too sensitive.[11,14] Screening is highly recommended for PLHIV as this would help the patients earlier, but we need to be aware of the multiple factors affecting the depression.[14] This reasoning adds up to the motive to conduct more control over the confounding factors and follow-up of longer duration of EFV-based treatment in the future studies.

When compared to the general population, PLHIV on EFV seem to have high physical and mental status but it shows a significant gap when compared to normal people. This was shown in previous study that PLHIV on EFV were found to have prevalent sleep disturbance seven folds higher than general population, experience longer sleep duration and shorter duration of deep sleep in the first weeks of treatment.[19] Nonetheless, this symptom subsides overtime (about 6-8 weeks after treatment initiation).[20] Furthermore, other studies showed that withdrawal from EFV in fact resulted in better sleep quality on self-reported assessment.[21] It has to be taken into account that sleep disturbance cannot easily determined for its independent risk factor, since this might occur at any stage of HIV infection and is highly related to the natural history of the

disease itself.[21] This consideration leads to a recommendation to carefully assess the administration of EFV-based treatment in PLHIV with neuropsychiatric disturbance, especially depression.

Due to the conflicting results regarding the association between EFV and depression, the European AIDS Clinical Society suggests replacing EFV with another ARV drugs for PLHIV with depression or neuropsychiatric adverse events.[5] In Indonesia, most patients with such neuropsychiatric adverse events possibly related to EFV have been suggested to replace the ARV with the new regimen (Tenofovir-Lamivudine-Dolutegravir or TLD), which has been shown to cause less adverse effect.[22] Even so, it is utterly essential for clinicians to pay more attention to the mental or psychiatric health of PLHIV, as this strongly affects the treatment adherence, thus reflecting in patient's health outcome.

CONCLUSION

Depression on EFV-based treatment in PLHIV might be shown in the first few weeks of treatment and its effect in longer period of treatment still requires further studies. Early detection of depression is essential to consider the use of EFV-based treatment in PLHIV with neuropsychiatric disturbance, especially depression. Well management with the right choice of ARV would help improving the patients' treatment adherence, thus resulting in better outcome.

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