

Depression in HIV Patients in Sub-Saharan Africa: A pressing Issue that Requires Assistance.

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Abstract: Depression in HIV (Human immunodeficiency Virus) patients has started to become a pressing issue in the current decade. More and more research has shown that the prevalence of depression symptoms among HIV patients is higher than the public. ART (Anti-retroviral Therapy) drugs are the core medications that could slow down the progression of HIV towards the final stage of HIV, AIDS (Acquired Immunodeficiency Syndrome). Still, these drugs are not going to cure the adverse psychological situation among HIV patients. There need to be sufficient epidemiological studies about depression among HIV patients to enable society and physicians to help improve the psychological situation of HIV patients. Some of the ART drugs have psychological side effects, which non-adherence to therapy will cause a worsen side effect, which could lead to depression. In addition, depression could diminish the efficacy of ART drugs by impeding the immune functions, which could start a downward spiral of both physical and psychological conditions of HIV patients. HIV patients would also meet obstacles in society because of lower socioeconomic status and worsening physical condition and experience more social stigma and violence because of their identity as HIV-positive people. Hence, proper interventions are necessary to provide psychiatric support to HIV patients. Since ART drugs play an important part in HIV patients' lives, improving access to ART drugs is fundamental. Because of the lack of professional medical training for psychiatrists in developing countries, it is better to either provide mental health knowledge to existing physicians or establish a system that could use layperson as the bridge between HIV patients and professional psychiatrists. This review paper will include different epidemiological studies to demonstrate the relationship between depression and HIV patients while also including proper interventions to reduce the prevalence of depression. Further investigations about the relationship between depression and HIV patients are needed, and different types of interventions should be tried in various countries to develop the best plan that could be implemented globally.

1. Introduction

HIV has long been a concerning problem in Sub-Saharan Africa, with an extremely high prevalence in the area. Compared with the world, which AIDS (Final stage of HIV) is now the 19th leading cause of death in 2019[1], AIDS is still the fourth leading cause of death in Africa [2], despite the significant improvement in ART (Antiretroviral therapy), which transforms HIV from an inevitably fatal disease into a chronic and manageable disease [3]. The situation in Sub-Saharan Africa is even worse. Among the 6000 new infections that occur globally each day, two-thirds are in Sub-Saharan Africa, with young women being the main infected group [3]. Young women aged 15-24 have been estimated to have an eightfold higher prevalence rate than their male peers [3]. The reason behind this disproportionate rate for females includes lack of access to condoms, contraception, medical services, and violation of human rights such as female genital mutilation or lack of ability to own lands.

It could not be denied that current ART drugs and HIV prevention drugs such as PrEP have successfully decreased the HIV infection rate by 39% between 2005-2013[3]. The government of

South Africa has started to cover the cost of ART average starting at CD4 count 500 cells per microliters, which successfully decreases the mortality and increases the life expectancy of HIV patients by additional ten years [4]. Thus, improving access to drugs to help control HIV infection is the main task for Sub-Saharan countries, as 34% of HIV patients in East and Southern Africa and 60% of HIV patients in West and Central Africa currently are not receiving any treatment [5].

Depression and HIV infection form a vicious cycle that quickly produces a downward spiral of patients' health. The estimation of depression among HIV patients in sub-Saharan Africa ranges from 2 to 56% based on the population studied, while for the general population, it ranges from 1 to 34% [6]. HIV infections could possibly lead to depression with biological and societal factors. Previous reports show that there are regional alterations in the architecture of the white matters of HIV patients with depression compared to the HIV patients without depression [2]. Psychosocial factors also contribute a lot to the depressive symptoms, including alcohol usage, not adhering to HIV medication schedule, and experiencing violence with low social support, all of which are associated with greater depressive symptoms [7]. Conversely, depression would also decrease immune functions and adherence to ART drugs, which would further accelerate the progression towards AIDS. As a result, interventions need to be considered to break this vicious cycle, especially in Sub-Saharan Africa, which is an area that has nearly no professional psychiatric services.

Although there are some researches about this topic from here to there among different countries, there is not sufficient systematic analysis about the relationship between HIV and depression and generally look at all the results. Thus, this paper will systematically summarize the existing literature studying the relationship between HIV and depression epidemiologically, alongside all the methods they took to achieve their conclusion. This review will also include different interventions that have already be taken in Sub-Saharan Countries to reduce the prevalence of depression and how they could potentially benefit HIV patients.

2. Method

2.1 Search Strategy

The search for articles is performed in Google Scholar Database. Articles about the relationship between depression and HIV in Sub-Saharan Africa are searched using the following terms: "Sub-Saharan Africa", "HIV-positive", "Depression", combined with the Boolean operator "And". The articles about interventions are searched using the following keywords: "Sub-Saharan Africa", "HIV", "Depression", "Intervention", combined with the Boolean operator "And". The search was filtered by allowing English Language articles only. All the references are organized by EndNote version 20, while other related articles will be included according to the reference lists of the article. All the articles returned by the search are included based on titles, abstracts, and full text. The study needs to be done using epidemiological methods and correlate HIV patients with depressions using statistical analysis. Moreover, the participant in the study is limited to adult patients to reduce bias caused by age difference. The statistical analysis chart of each paper is also reviewed to ensure that they include a significant amount of factors that correlate with depression to avoid unmeaningful comparisons between studies.

2.2 Measurement of Depression level

Six articles use various measurements of depression levels (Table 1 includes all the details). Two of the studies [6,7] use CESD (Center for Epidemiologic Studies Depression Scale) to assess the depression level. A cutoff of 16 indicates depression, while 16-26 suggests mild depression; scores greater than 27 suggest major depression. One article [8] uses CIS-R (Clinical Interview Schedule-Revised) that studies 14 domains of common mental health problems. Then according to the score, the diagnoses are categorized into the following sections: depression, generalized anxiety disorder, mixed anxiety and depressive disorder, panic disorder, and obsessive-compulsive disorder or phobia. Each section is also separated into different levels, including mild or severe. Another study [9] uses WHOQOL-BREF questionnaires to study the quality of life for HIV patients and uses MINI (Mini

International Neuropsychiatric Interview) to diagnose patients for depression. This study only categorizes HIV patients into "Depression" or "No depression". The other article [10] uses HSCL-D (15-items Hopkins Symptoms Checklist for Depression) to assess the level of depression. Each item is on a 4 point scale (1-4), and an average score of 1.75 or above indicates a diagnosis of depression. In this study, HIV-related stigma is also measured using two surveys: Asking questions on stigmatizing attitudes towards people living with HIV and Asking about whether they will anticipate certain negative attitudes from people if tested positive. For each survey, if one or more replies are yes, they are scored as "Having stigmatizing attitude" from the first survey and "Anticipated HIV stigma" from the second survey. The last study [11] uses PHQ-9(Patient Health Questionnaire-9) to determine the presence and frequency of 9 core depressive symptoms in the DSM-IV. Each symptom is on a 4 point scale (0-3), ranging from not at all to nearly every day. A sum over 10 is an indicator for a possible diagnosis of depression.

3. Epidemiology of Depression in HIV

Table 1. Sample study on incidence rate of HIV by different authors

Author	Year	Sample Size (Response rate)	Assessment	Prevalence of Depression
Marwick K.	2008	220(97%)	Revised CIS-R	15.50%
Adewuya A.O.	2008	87(96.7%)	WHOQOL-BREF with MINI	28.70%
Meffert S.M.	2013- 2017	2307	CESD	18%(Kenya), 25%(Tanzania), 22%(Uganda)
Gupta R. Set P.	2010 2010	1268(89%) 3538	HSCL-D CESD	28% 32.1%(Female), 21.9%(Male)
Cholera R.	2013	1368(82%)	PHQ-9 with MINI	22%

3.1 Characteristics of studies and participants

For all six studies included the epidemiology of depression in Sub-Saharan Africa, five focus on Eastern and Southern Africa, which is the center of the highest prevalence of HIV patients. Another study is implemented in Nigeria, the country with the largest population, which also gives a good pool of participants for studying depression.

All six studies were done after 2008, which is within 15 years of the current date, so it could be estimated that there has been more focus on psychological conditions on HIV patients starting at the end of the last decade [Table 1]. All six studies are either cross-sectional studies or cohort studies that involve questionnaires and surveys for the participants. Among four of the studies that provide a response rate from the participants, all of them exceed 80%, while two show above 90% participation rate [Table 1]. The other two studies recruit participants throughout a period by obtaining the data directly from the participants after they agree to answer the questions. This high participation rate shows a relatively low level of non-response bias.

When correlating depression and HIV, all six studies ask for socioeconomic status, gender, and ART drug usage. For gender, the female percentage in all six studies exceeds 50%, matching the expectations, as females constitute a larger percentage of HIV patients in Sub-Saharan Africa. Socioeconomic status is examined using different factors in different studies. These factors include education, employment status, and household income. Among the four articles [6,8,10,11] that ask for employment status, only in South Africa, the majority of the participants are employed. In contrast, in other Sub-Saharan African countries, the majority of the HIV-patients are not able to find a proper job. As South Africa is among the richest countries in Sub-Saharan Africa, this phenomenon may correlate with the country's economic situation in general. For ART usage, it is found that most of the

participants take proper HIV medications regularly in all the countries except Uganda. Uganda stands out to be an exception, with less than 40% of the participants regularly using ART treatment. This makes Uganda an outlier when correlating ART drugs and depression levels.

3.2 Prevalence of Depression in HIV patients.

Prevalence on depression in HIV patients is a topic that raises concern among physicians and researchers, as the reason behind this high prevalence includes both psychological and biological. At the same time, some of these factors could be mitigated by interventions. Five of the six articles [6,7,8,9,10] studies about the prevalence of depression among HIV patients only. In contrast, the article about South Africa [11] compares the prevalence of depression among HIV-positive participants to HIV non-positive participants. The article about South Africa states that 30.3% of HIV-positive participants are considered to have depression, compared to 19.7% of HIV non-positive participants that have depression. For all six studies, the prevalence of depression in HIV ranges from 15.5% to 30.3%, with rural Tanzania having the lowest prevalence of depression [Table 1]. Gender may play a role in the prevalence of depression, as the study that produces the result for the mean test scores shows a 27% higher depression level among women than men [6]. In the other two studies that consider gender separately [10,11], however, the percentage of women with depression is lower than that of men with depression among HIV patients. So, this shows that gender has a complicated influence on depression among HIV patients. Another unique characteristic that grabs attention is the rural Tanzania study. Only including the rural residents in the study may contribute to the low prevalence of depression. However, the rural residents usually have less access to proper mental health treatment, employment, or education, so the reason behind this low prevalence is still undiscovered.

3.3 Biological reasons of depression in HIV patients

Although the infection of the HIV will not directly cause depression, it is found the neurological injury caused by the HIV virus to the brain tissue will cause secondary depression. HIV virus can enter the central nervous system during acute infection through the trafficking of infected immune cells through the blood-brain barrier [12]. Then the virus will attract inflammatory cytokines and neurotoxins that could possibly induce neurological damage to the brain tissue that the virus arrives. Patients have been seen to have a higher level of CSF (cerebrospinal fluid) neopterin, a biomarker of macrophage activation, which indicates a chronic state of neuroinflammation [12]. Studies have shown that for patients with neurological abnormalities, even with stable ART regimens, the HIV virus may experience CSF escape, which leads to elevated CSF neopterin. Two patients with CSF escape have 76.3nmol/L and 37.6nmol/L of CSF neopterin, compared to the normal level of 10.8nmol/L for HIV patients without CSF escape [13]. This shows that CSF escape is an important mechanism causing potential neurological damages. This injury causes alteration in the structure of white matter, as there are increases of fractional anisotropy in the left thalamus [14], the temporal and frontal area, and the right cingulate, which are all regions that control mood regulation. Therefore, this change leads to the appearance of secondary depression [15]. Another possible biological reason behind the increase in the prevalence of depression is the upregulation of serotonin receptors. It is found that the serotonin protein levels increase by 3.35 fold in the brain samples of mice that are infected with the SIV virus, a similar virus strains as HIV that could infect animals, compared to the brain samples that are not infected [16]. Research about this mechanism has only been done among animals, while this mechanism in humans requires further detailed investigation.

3.4 Correlation between Depression and ART drugs

Adherence to ART drugs is a possible factor that combines psychological and biological reasons why there is an increase in the prevalence of depression among HIV patients. It is considered in four out of five articles [6,7,9,11] and shows a relative correlation with depression in three of them except for the study in South Africa [11]. The study in South Africa does not give a statistically significant result correlating depression and ART drug usage. In the article correlating depression and quality of life of HIV patients in Nigeria [9], it is shown that there is a statistically significant correlation between

physical health and depressive disorder. Physical health could be seen as an indicator for adherence to ART drugs, as proper adherence to ART drugs is positively correlated with better physical health status. For the other two articles [6,7], there is a statistically significant correlation between adherence to ART drugs and depression. Higher adherence to ART drugs leads to a lower level of depression. The article studying HIV-positive patients in Kenya, Namibia, Tanzania [16] shows that there is a worse outcome of depression if the patient takes ART drugs and does not adhere to them than the patient not taking any HIV medications. This is an indication that not properly taking HIV medications may cause serious psychological side effects.

This phenomenon of taking certain ART drugs that may interfere with neurological abilities has been seen in researches. Efavirenz is a drug that is typically used in antiretroviral therapy against the HIV virus in under-developed countries. This drug is reported to have a certain level of neurotoxicity that may influence the neurological abilities of the patients. Patients will experience hallucinations, vivid nightmares, and other adverse neuropsychiatric effects. Efavirenz interacts with GABA-A receptors and acts as a serotonin and dopamine reuptake inhibitor, which could possibly lead to depression. Hence, using efavirenz in HIV treatment is usually combined with anti-depressant drugs to mitigate this effect [17]. However, people who do not properly take HIV medications will even worsen this effect as they may not have access to the anti-depressant drugs that match Efavirenz. Thus, this matches the phenomenon that patients who do not adhere to HIV medications fully have a higher prevalence of depression than patients who adhere 100% of HIV medication and patients who do not take any HIV medications.

3.5 Correlation between Depression and Socioeconomic status

Another essential factor that correlates with depression in HIV patients is socioeconomic status. Socioeconomic factors could be examined by different criteria, including marital status, education level, monthly income, occupation, and location of residence. All five articles study the influence of socioeconomic factors on the level of depression, but the results vary in different study groups. Educational level is studied in three articles [7,9,10], one [9] is shown to correlate with depression. In contrast, one is shown to only correlate with depression for females [10], and another one [7] is shown to not correlate. Marital status is considered in three articles [7,10,16], while separated or widowed is seen to have a worse influence on depression [5,16]. Weekly income is considered but does not statistically correlate with depression among HIV patients [7,10]. Occupation (employed or unemployed) is linked to weekly income, which is also not statistically significantly correlated with depression among HIV patients [10,11]. Living in the rural areas tends to also have a worse outcome of depression for HIV patients [10], but this result contradicts what researchers find in rural Tanzania [8]. All these results show that socioeconomic factors have a certain level of correlation with depression in HIV patients. Still, this correlation is very complicated, and different factors may influence each other and act as confounding variables.

3.6 Correlation between Depression and Psychosocial factors

Psychosocial factors are also vital when considering depression among HIV patients. Alcohol use is one of the factors considered to be important. While consuming some alcohol does not seem to influence depression [10,11,16], HIV patients dependent on alcohol have a much higher chance of experiencing depression [6]. It is shown that there are 6.29 times higher odds for HIV patients dependent on alcohol to develop depression symptoms compared to HIV patients that are non-problem drinkers [6]. Physical and sexual violence is also strongly related to depression, with people experiencing violence have a way higher chance of getting depression [6]. Anticipated HIV stigma and intergenerational relationships also increase the prevalence of depression among HIV patients [10]. This phenomenon shows that social support is essential for the psychological health of HIV patients. In two studies that research the influence of social support, It has been seen that social support could decrease the prevalence of depression by a large amount [9,13]. Hence, it is essential to research for interventions that could support HIV patients so that they will not be scared of communicating with peers about their HIV status and discuss issues with others who have similar experiences [16].

3.7 Bidirectional relationship between Depression and HIV

Depression also reduces immune function by causing steeper declines in CD4, CD8, and NK cells that expedite the progression towards AIDS and death [18]. It is seen that for every 3 point increase in depressive symptoms, the likelihood of progressing to AIDS doubled. Data also shows that HIV patients under the median depression level, there is a 36% fewer probability of developing AIDS than HIV patients above the median depression level [18]. Depression also leads to worse ART treatment adherence, and lack of awareness of depression prevents affected individuals from receiving proper treatment and services due to limited resources [10]. From here, we can see that the relationship between HIV and depression is bidirectional, so it is essential to study the causal relationship from both directions and provide proper interventions.

4. Interventions to decrease the prevalence of depression

4.1 Improving access to ART drugs

One way to help improve the psychological situation of HIV patients is through granting universal access the ART drugs and development in ART drugs. Universal access to ART drugs is essential for adherence to HIV medications. There are already big developments in certain countries, like South Africa, Namibia, and Rwanda which ART drugs had covered 80% or more eligible individuals [3]. However, in countries like Nigeria and the Central African Republic, less than 25% of the population have access to treatment [3]. This huge gap in the access to treatment shows that there is still a large population of under-served people, so reducing the cost, improving the access, and simplifying the treatment is still an important goal to promote the usage of ART drugs.

Advances made in ART treatment could also significantly raise the overall positive attitudes and decrease the related mood disorders like depression. For example, one of the side effects of ART drugs is lipodystrophy, which causes physical disfigurement. This symptom has caused reduced self-esteem and unhealthy mental states to especially in women HIV-positive patients. Recent research has shown that development in ART drugs helps relieve this symptom, which could also reduce the prevalence of depression. The new single-dose ART drugs have notably reduced the occurrence of lipodystrophy: The prevalence of lipodystrophy decreases from 71.4% to 22.2% [19]. This shows that continuous development in new ART drugs is needed and will positively affect the physical condition and the psychological conditions of HIV patients.

4.2 Training physicians about mental health knowledge

Because of the lack of access to physicians in distant areas in Sub-Saharan Africa, it is important to train the existing physicians with proper mental health knowledge so that they can provide thorough services to all the patients. Currently, WHO launched the mhGAP (Mental Health Gap Action Programme), which developed interventions designed for non-psychiatrist medical doctors for the pharmacological treatment of depression and low intensity, non-pharmacological depression interventions delivered by laypeople [20]. In Sub-Saharan Africa, when HIV physicians interact with their patients, these physicians need to know about common mental disorders that are affecting their patients so that proper interventions could be taken earlier to avoid the worsening of the problem. These patients usually do not have the money or resources to go to a mental health specialist for depression problems, so training existing HIV physicians is the best way to recognize depression problems early and decrease the prevalence rate.

4.3 Training layperson to fill the gap in treatment for depression

Lay health workers are an essential part of health delivery person in Sub-Saharan Africa, as professional-trained physicians, especially psychiatrists, are lacking in big numbers. For example, in Zimbabwe, with a population of 13 million people, there are only eight psychiatrists and sixteen clinical psychologists who mainly work in tertiary medical facilities in urban areas [4]. It is impossible to fill this gap of lacking mental health workers by professional training, so properly providing

medications and knowledge to lay health workers and allowing them to approach patients with similar backgrounds is the temporary solution for decreasing the prevalence of depression. Recent research has approached current lay health workers employed by state or city health services to treat mental health problems. Although 92% of the participants recognize there is a need for mental health services for depression among HIV patients, only 7% had received training in mental health, and 83% of them stating that they were too busy to provide structured psychotherapy to patients and they did not have professional knowledge about the usage of anti-depressants [4]. This shows a big margin between the need for mental health services and the competent workforce.

The current approach to address the margin is by peer education among lay health workers and referrals to clinical psychologists through remote connection virtually for severe cases. The professionals designate peer supervisors to provide other lay health workers with knowledge about mental health and recognize seriously ill cases. Then the supervisors will connect with the professional psychiatrists and ask for medical advice to manage these difficult cases [4]. Thus, using new technologies, patients in remote areas can receive proper care by having access to professional medical resources virtually.

This is an important first step in providing HIV patients access to psychiatric services. Still, the final goal is to enable more lay health workers to prescribe medications like anti-depressants without the need to refer to professional psychiatrists every time. Education about mental health will be a long process, but it will eventually be achieved by peer education among health workers and from the help of professionals.

4.4 Integration of depression treatment into HIV care

As there is a relatively high depression rate among HIV patients, integrating depression treatment into HIV care is an option that government could take to reduce the prevalence of depression. The current integration of treatment implements two models when dealing with depression. Both models include routine screening of depression for HIV patients in HIV clinics. When diagnosing depression, one requires primary care provider (usually doctors) to make the final diagnosis and decide the treatment of depression [2]. Another model is through a specific algorithm to calculate the criteria for depression and then prescribe medications through a protocol [2]. This model is completely based on nurses and does not require any professional psychiatrists.

Currently, these two models are in the progress of comparison to decide which model will have a better result on managing depression. The second model is obviously easier to take place, especially in rural areas, and it is more cost-effective. Thus, if the second model is shown to not have a significantly adverse effect on HIV patients, it should be implemented in integrating depression treatment into HIV care.

5. Conclusions

The psychological situation in HIV patients is gaining more and more attention from researchers currently, as physicians and scientists find out that there is a reciprocal relationship between depression level and HIV infection. HIV infection will likely increase the prevalence of depression because of biological alteration in the brain and change in psychosocial behaviors. In contrast, depression will worsen the immune function and pose a risk to adherence to ART drugs. Hence, intervention to control depression among HIV patients is implemented in various countries and cut this reciprocal relationship, especially in developing countries where psychiatric services are extremely limited. This paper summarizes this reciprocal relationship while also categorizing the interventions that could be used. While society and medical services have already done a lot to help improve the psychological situation of HIV patients, the future direction of the research should point towards the efficacy of different implementation and epidemiological research about how these interventions decrease the prevalence of depression. Then, it is possible to recommend these interventions globally and further improve the living condition of HIV patients.

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