MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
SUMY STATE UNIVERSITY
ACADEMIC AND RESEARCH MEDICAL INSTITUTE

Eastern Ukrainian Medical Journal

116, Kharkivska st., Sumy 40007, Ukraine eumj.med.sumdu.edu.ua
e-mail: eumj@med.sumdu.edu.ua ISSN: 2663-5909 (print)/2664-4231 (online)

How to cite / Як цитувати статтю: Cherevko O, Mudrenko I. Neurobiological, psychological, and sociodemographic predictors of mental disorders in HIV infection (literature review). *East Ukr Med J*. 2024;12(1):11-22

DOI: https://doi.org/10.21272/eumj.2024;12(1):11-22

ABSTRACT

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NEUROBIOLOGICAL, PSYCHOLOGICAL, AND SOCIODEMOGRAPHIC PREDICTORS OF MENTAL DISORDERS IN HIV INFECTION (LITERATURE REVIEW)

Introduction. The prevalence of mental disorders among people living with HIV infection has high frequency. According to a 2022 World Health Organization report, up to 70% of people living with HIV have mental disorders such as depression, anxiety, post-traumatic stress disorder, and others. Mental disorders can reduce susceptibility to antiretroviral therapy, increase the risk of re-infection with HIV, reduce social and professional adaptation, and increase the risk of suicide and overall mortality.

Materials and methods. The literature review was conducted based on published scientific research by ScienceDirect, using information and search systems PubMed and Google Scholar. A review of studies primarily from the last 5 years was conducted.

Results. Depression is the leading cause of disability and is the most common HIV-related mental disorder, accounting for about 30% of people living with HIV. Large-scale meta-analyses estimate this prevalence rate is significantly higher than in the general population. Younger people with newly diagnosed HIV infection have higher anxiety levels than older patients. People living with HIV reports higher levels of mental trauma (e.g., child abuse, sexual abuse, physical abuse). The prevalence of post-traumatic stress disorders among people with HIV throughout life is 50% compared to 7% in the general population. The researchers concluded that HIV progression in HIV-infected people with post-traumatic stress disorder is twice as fast.

Among the leading causes of developing mental disorders with HIV infection are neuroinflammation and neurotoxicity, psychological factors, and sociodemographic factors. HIV can make people living with HIV more susceptible to depression due to neurotoxicity, which may lead to neurotransmitter dysfunction,

metabolic dysfunction, and a chronic increase in inflammatory cytokines.

HIV-related stigma leads to negative consequences for the health of people with HIV. Fear of being judged by others impacts decreasing adherence to antiretroviral therapy and internalized HIV stigma provides for low adherence to antiretroviral therapy.

Discussion. People living with HIV are more susceptible to developing mental disorders than the general population. Identification and research of mental disorders among people with HIV is important for improving adherence to HIV therapy. Dissemination of truthful information and educational measures about HIV can help reduce stigmatization and discrimination and improve the mental health of people living with HIV.

Keywords: HIV; persons living with HIV; antiretroviral therapy; mental disorders; depression; neuroinflammation; psychosocial factors.

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НЕЙРОБІОЛОГІЧНІ, ПСИХОЛОГІЧНІ ТА СОЦІАЛЬНО-ДЕМОГРАФІЧНІ ПРЕДИКТОРИ ПСИХІЧНИХ РОЗЛАДІВ ПРИ ВІЛ-ІНФЕКЦІЇ (ОГЛЯД ЛІТЕРАТУРИ)

Вступ. Поширеність психічних розладів серед людей з ВІЛ-інфекцією дуже висока. Згідно зі звітом Всесвітньої організації охорони здоров'я за 2022 рік до 70 % людей, які живуть з ВІЛ мають психічні розлади, такі як депресія, тривожність, посттравматичний стресовий розлад та інші. Психічні розлади можуть знижувати рівень сприйнятливості до антиретровірусної терапії, збільшувати ризик зворотного зараження ВІЛ, знижувати соціальну та професійну адаптацію, підвищувати ризик самогубства та загальну смертність.

Матеріали та методи. Літературний огляд проведений на основі опублікованих наукових досліджень ScienceDirect, за допомогою інформаційно-пошукових систем PubMed, Google Scholar. Проведений огляд досліджень переважно за останні 5 років.

Результати. Депресія це провідна причина непрацездатності є найпоширенішим психічним розладом, пов'язаним з ВІЛ-інфекцією та становить близько 30 % серед людей, які живуть з ВІЛ, а масштабні мета-аналізи оцінюють, що цей рівень поширеності значною мірою перевищує показник у загальній популяції. Вищі рівні тривожності у молодших людей з нещодавно діагностованою ВІЛ-інфекцією порівняно з старшими пацієнтами. Люди, які живуть з ВІЛ, повідомляють про більш рівень психічних травм (наприклад, жорстоке поводження з дітьми, сексуальне насильство, фізичне насильство). Поширеність посттравматичних стресових розладів протягом життя серед людей, які живуть з ВІЛ, становить 50 % порівняно з 7 % у загальній популяції. Дослідники зробили висновки, що прогресування ВІЛ у

пацієнтів із посттравматичним стресовим розладом відбувається удвічі швидше.

Серед основних причин розвитку психічних розладів при ВІЛ-інфекції є нейрозапалення та нейротоксичність, психологічні фактори, соціально-демографічні фактори. ВІЛ-інфекція може зробити людей, які живуть з ВІЛ, сприйнятливішими до депресії внаслідок нейротоксичності що призводить до дисфункції нейромедіаторів, метаболічної дисфункції та хронічного підвищення рівня запальних цитокінів.

Стигма веде до негативних наслідків для здоров'я людей, які живуть з ВІЛ. Страх бути засудженим іншими впливає на зниження прихильності до антиретровірусної терапії, а інтерналізована стигма щодо ВІЛ передбачає низьку прихильність до терапії.

Висновки. Люди, які живуть з ВІЛ, сприйнятливіші до розвитку психічних розладів, ніж загальна популяція. Виявлення та дослідження психічних розладів серед ЛЖВ має значення для покращення прихильності до терапії ВІЛ-інфекції. Розповсюдження правдивої інформація та освітні заходи щодо ВІЛ-інфекції можуть допомогти зменшити стигматизацію та дискримінацію та покращити психічне здоров'я людей, які живуть з ВІЛ-інфекцією.

Ключові слова: ВІЛ; люди, які живуть з ВІЛ; антиретровірусна терапія; психічні розлади; депресія; нейрозапалення; психосоціальні фактори.

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ABBREVIATIONS

HIV – Human Immunodeficiency Virus
AIDS – Acquired Immune Deficiency Syndrome
ART – Antiretroviral therapy
PLWH – People Living with HIV/AIDS
PTSD – Post-traumatic stress disorder
WHO - The World Health Organization
TSPO – microglial activation marker
EDI – Estimated Duration of HIV Infection
MSM – Men Who Have Sex with Men

INTRODUCTION / ВСТУП

Approximately one in eight people worldwide have a mental disorder [1]. Worldwide, 280 million people suffer from depression [2]. Mental disorders are pathological conditions characterized by a clinically significant disorder of cognitive function, emotional self-regulation or human behaviour and are not expected from the perspective of cultural or religious norms. These disorders can be associated with distress and significantly limit the functioning of a person in the social, family, professional, educational or personal sphere of life [3].

Human immunodeficiency virus (HIV) is a retrovirus that infects a person and causes various clinical conditions, from asymptomatic carriage to severe immunodeficiency with fatal outcomes. Acquired Immunodeficiency Syndrome (AIDS) is the most serious form of HIV infection due to a progressive immune system impairment. The HIV epidemic affects all social groups.

The level of mental health in HIV/AIDS depends both on co-morbid mental disorders, in particular the consequences of abuse of addictive substances, and on mental disorders acquired as a result of the impact of HIV on the central nervous system. HIV infection directly affects the central nervous system and causes neuropsychiatric complications, including encephalopathy, depression, mania, and cognitive disorders, in particular dementia. Some antiretroviral therapy (ART) drugs have psychiatric side effects, in particular, insomnia and mood swings in almost 50% of patients taking Efavirenz [1].

Materials and Methods: usage of online collections of published scientific research ScienceDirect, information retrieval systems PubMed, Google Scholar.

According to the World Health Organization (WHO) "World Mental Health Report" for 2022, mental disorders are one of the leading causes of disability and general unproductivity in the world [1], and their prevalence in people living with HIV (PLWH) is significant. About 50% of PLWH have experienced one or more episodes of mental disorder in their lifetime [4]. According to the Joint United Nations HIV/AIDS UNAIDS Programme, the total number of HIV carriers reached 38.4 million people (in 2020, there were 37.9 million) [5]. At the same time, in 2020, there were also about 1.5 million new HIV infections; in 2019 and 2018 – about 1.7 million [6]. It is estimated that at the end of 2022, 245,000 HIV-positive people were living in Ukraine [7].

With the beginning of a full-scale war in Ukraine in February 2022, there were problems in ensuring HIV surveillance, the logistics of providing services for prevention, testing, treatment of HIV infection, and clinical laboratory monitoring of HIV/AIDS among PLWH, primarily in the south-eastern regions, became more complicated [7]. This problematic situation will contribute to an increase in the level of mental disorders in PLWH due to constant stressful situations during the military conflict, limited access to medical services and social programs necessary for the treatment and support of PLWH, social isolation due to massive destruction of infrastructure and due to forced temporary displacement. This problematic situation will contribute to an increase in the level of mental disorders in PLWH due to constant stressful situations during the military conflict, limited access to medical services and social programs necessary for the treatment and support of PLWH, social isolation due to massive destruction of infrastructure and due to forced temporary displacement. There are significantly more women and children than men among refugees from Ukraine, and this population may experience psychological trauma due to uncertain future instability in terms of housing and income. Refugees living with HIV or at risk of HIV infection are unlikely to seek access to HIV testing and care services as their immediate priority in this context. This can complicate stigma and concerns about the impact of a positive diagnosis on a person's residency status [8–10].

The abundance of mental disorders among people with HIV infection is very high. According to the report of WHO Mental Health and HIV/AIDS for 2022, up to 70% of PLWH have mental disorders such as depression, anxiety, post-traumatic stress disorder (PTSD), and others. Almost half of PLWH experience one or more mental disorders during their lifetime [11]. In addition, mental disorders can occur as immediate consequences of HIV infection and be caused by social, cultural, and other factors associated with living with HIV infection[12]. The research on mental disorders in HIV infection is very relevant since these disorders significantly impact the quality of life and prognosis of the disease in PLWH.

Mental disorders can reduce the level of susceptibility to antiretroviral therapy (ART), increase the risk of re-infection with HIV, reduce social and professional adaptation, and increase the risk of suicide and overall mortality.

In addition, numerous people with HIV infection do not have an established diagnosis of a mental disorder and/or do not receive the necessary support and treatment [13]. Thus, the study of mental disorders in HIV infection is an essential step in improving the diagnostics, treatment, and support of people with HIV infection.

Variants of mental disorders in HIV Infection

Numerous studies indicate a high level of mental disorders among PLWH compared to people without HIV infection. The prevalence of various mental disorders depends on gender and age. Anxiety and depressive disorders are most common among both men and women [14–16].

According to the study 426 PLWH in Cameroon, almost 30% of participants showed symptoms of at least one mental disorder, and 14.6% showed symptoms of two or more mental health disorders. Approximately 20% noted moderate or severe depressive symptoms, 16% had symptoms of probable PTSD, and 13% had moderate or severe anxiety symptoms [17].

In a large-scale study of co-morbid mental illnesses in 2022 conducted in the United States among 4,170 PLWH, it was found that 57.2% had at least one mental disorder, and among PLWH with concomitant hepatitis C, 69.1% [18] – Fig. 1.

Acute reaction to stress and adjustment disorders. Even though patients are introduced to information about HIV infection in the preliminary counselling before testing for HIV antibodies, the patient can not be sufficiently emotionally prepared to perceive the fact of his illness, which leads to severe stress and the formation of a stress reaction, disorganization (overflow of thoughts, ideas, emotions), symptoms of anxiety, depression, anger, the forming of a grief reaction, adaptive or maladaptive response. With the adaptive response, a patient accepts the disease and tries various ways to reduce its impact on his condition and improve his overall health by changing and adapting his lifestyle to the disease. With the maladaptive response option, patients deny the existence of the disease, refuse medical care, and have impulsive or suicidal behaviour or risky behaviour that includes casual sexual contact and the use of psychoactive substances.

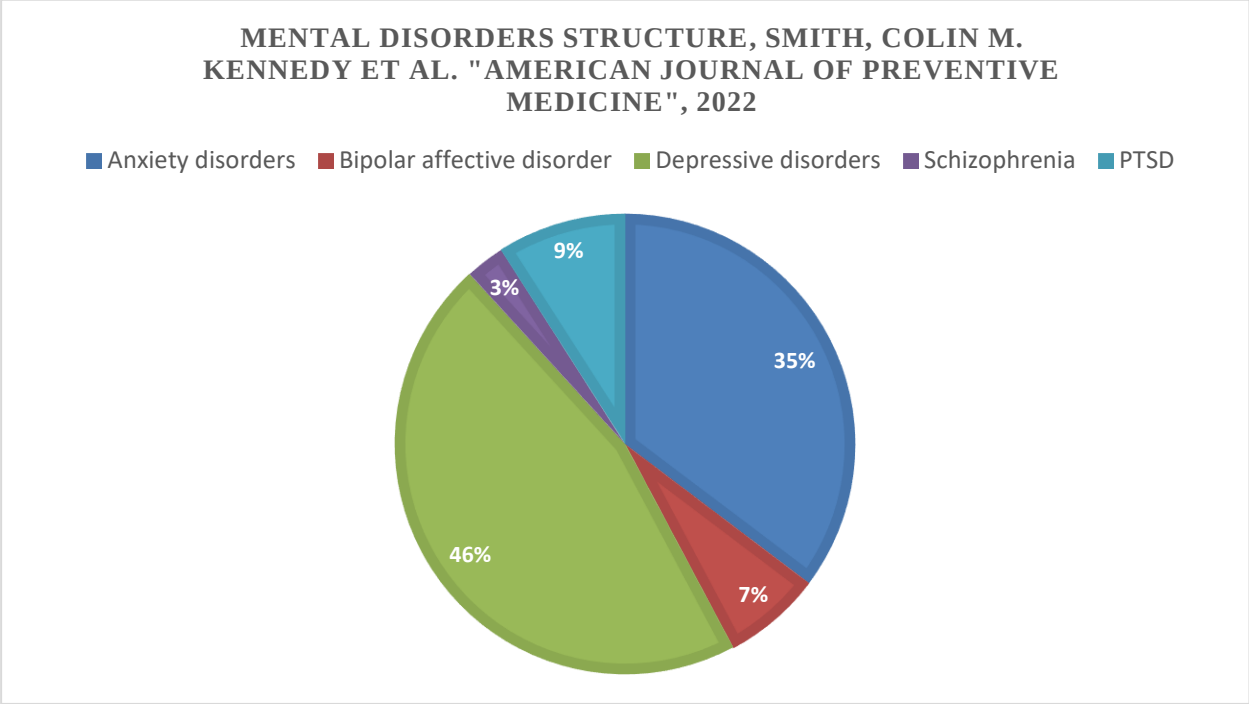

Figure 1 – Mental disorders structure, Smith, Colin M. Kennedy et al. "American Journal of Preventive Medicine", 2022

Biopsychosocial stressors directly related to HIV infection, such as stigma, discrimination and embarrassment, side effects of treatment, symptoms of HIV infection, and disclosure of the diagnosis, impact the deterioration of the mental health of PLWH [19].

Depressive disorders. Depression is the leading cause of disability and is the most common mental disorder connected with HIV infection [15, 17, 20]. It is more common among PLWH than among people without HIV infection [18, 21, 22]. According to the results of studies, the prevalence of depression among PLWH is about 30% [23], and large-scale meta-analyses estimate that this prevalence is significantly higher than in the general population [24]. According to data from WHO for 2023, 3.8% of the population suffers from depression, including 5% of the adult population (4% of men and 6% of women) and 5.7% of people over the age of 60 [1]. Among PLWH, the risk of depression depends to some extent on gender [25], so women have a higher risk of severe or moderate depression. In comparison, men have a higher risk of moderate depression, and people who have recently been diagnosed have a higher risk of developing depression [24]. Among young PLWH, a higher level of depression was found in patients who have recently been diagnosed with HIV infection, compared to those who are chronically infected and people with HIV-negative status. By contrast, among

older PLWH, there is a higher level of depression in people with chronic HIV infection compared to people with HIV-negative status [15, 26].

In the research of 3,996 adults who had recently started ART in Tanzania, the risk of absence of suppression of the virus among women with depression both at the start of ART and six months after ART initiation was 1.94 times higher than in women who did not have depression at any point in time. Similarly, the risk of no suppression of the virus among men with moderate and severe symptoms of depression was 1.58 times higher than the risk among those with mild depressive symptoms [27].

On the other hand, depressive symptoms may, vice versa, increase susceptibility to HIV (due to an increasingly risky behaviour) and worsen the clinical prognosis of PLWH [28].

In addition, prevalence rates depend on geography and are significantly higher in the countries of the "Global South" compared to the countries of the "Global North" [29]. The rate of depression is 40% or higher in countries such as South Africa [5]. Combined with the fact that funding of health care financing and research is focused on the "Global North" [30], this significantly increases the burden of depression among PLWH in the "Global South". Depression itself can significantly reduce the quality of life, worsen the prognosis of the disease, and increase the risk of mortality.

Anxiety disorders. When analyzing data on anxiety disorders in PLWH and the duration of HIV infection (estimated duration of HIV infection – EDI), higher anxiety levels were found in younger people with newly diagnosed HIV infection compared with older patients. However, there was no significant age difference among people with chronic HIV infection. On the contrary, among the studied subjects with HIV-negative status, the level of anxiety increases with increasing age [15, 31].

Among PLWH, **apathy** is also studied, which is considered a neuropsychiatric syndrome characterized by reduced motivation for the initiative, purposeful behaviour, cognitive activity, and blunted affect. Approximately 46% (range 12%-65%) of PLWH demonstrate clinical apathy [32]. Apathy can appear in the early stages of HIV infection, independently of other neuropsychiatric syndromes. Among PLWH, apathy is associated with lower quality of life, cognitive symptoms, functional dependence, and improper treatment [32, 33].

Post-traumatic stress disorder (PTSD). PLWH reports higher rates of trauma (e.g., child abuse, sexual abuse, physical abuse) compared to the general population, with rates ranging from 40 to 90%. Higher rates of the trauma of the incident correspond to higher rates of PTSD among PLWH, with a frequency in the range of 30-74%. 64% of PLWH link PTSD symptoms directly to their HIV diagnosis or other disease-related issues. PTSD is connected with different adverse outcomes, including the use of psychoactive substance disorders and depression. The lifetime prevalence of post-traumatic stress disorders among PLWH is 50% compared to 7% in the general population. Co-morbid post-traumatic stress disorder and psychiatric disorders associated with the use of psychoactive substances lead to an adverse course of the disease, a decrease in overall functioning, and an increase in the risk of suicide, compared to PLWH suffering only from post-traumatic stress disorder or drug pathology. The researchers concluded that HIV progression in PLWH with PTSD is twice as fast [34, 35].

Suicidal behaviour. Suicide is a problem that brings suffering to people in all countries. According to statistics, one completed suicide corresponds to 20 suicide attempts, and suicide is the cause of more than one in every 100 deaths. This is the leading cause of death among young people [1, 36].

In the general population, men outnumber women in the number of suicides in a quantitative ratio of almost 4:1. Among men, the highest suicide rate is observed in adults aged 75 years and older – 37.97 per 100,000. Among women, those aged 40-50 have the highest suicide rate at 7.53 per 100,000. In the past, the suicide rate, in particular for men, has increased linearly with age, but this tendency has been mitigated in recent years [19, 36].

According to the results of a meta-analysis of studies among PLWH from 2000 to 2022, it was found that suicidal risk depends on the patient's family status, which means that married people have a lower suicide rate [13, 37]. Women with sufficient social support have a lower suicide rate compared to men and those who have to cope with the psychological burden of the disease without family support. There is an inversely proportional relationship between the age of the patient and the prevalence of suicide; that is, with increasing patient age, the number of suicides decreases. The article's authors identified *major and low factors of suicidal behaviour among PLWH*. Significant factors included socioeconomic status, mental health of

PLWH, and cultural factors, such as belonging to a single religious culture, as well as stigma connected with HIV infection. The low-risk factors included the level of poverty and unemployment, unfavourable housing conditions, and the level of abuse in the studied regions [38].

Finally, recently published articles report that suicide rates have become relatively lower. A likely cause may be a stigma reduction and increased awareness of mental health issues, which directs the community to take appropriate action to prevent suicide attempts [39]. An analysis of 40 studies of the impact of HIV on suicide also includes factors that reduce suicide rates: access to treatment, art use, and reduction of HIV-related stigma [18].

Causes of Mental Disorders in HIV Infection

Among the leading causes of the development of mental disorders in HIV infection are neurobiological, psychological factors, and sociodemographic factors.

Neurobiological factors

The role of neuroinflammation. Research suggests that the inflammatory process may be essential in developing depression and anxiety in people with HIV infection. HIV is inherently an inflammatory condition. When HIV is first detected in the body, several congenital immune responses are activated to protect the body, including increased levels of circulating cytokines and activation of natural killer (NK) cells. These systemic changes are signs of HIV-induced inflammation. Since HIV is focused on CD4+ T cells, which are crucial for shaping the immune response in humans, the inflammatory response to HIV is paradoxical because the level of immune activation is positively correlated with disease progression [24, 40].

The likely reason why HIV can make PLWH more susceptible to depression is **neurotoxicity,** which leads to neurotransmitter dysfunction, metabolic dysfunction, and chronic increases in inflammatory cytokines. Some studies have found that changes in immunometabolism, such as the tryptophan-kynurenine (KYN/TRP) ratio, are connected with depression among PLWH [41]. This is especially important since the induced effect of art in improving depression symptoms is partly mediated by the reversal of tryptophan catabolism [42]. Tryptophan is an aminoacid that plays a vital role in the biosynthesis of serotonin, a neurotransmitter that influences the regulation of mood and emotional state. There are significant patterns between these different hypothetical mechanisms behind HIV-associated depression. For example, inflammatory cytokines can induce glial cell activation and increase tryptophan metabolism, which can further cause serotonin depletion and overexpression of metabolites such as quinoline acid. Thus, the high risk of depression among PLWH may be derived from a combination of immune metabolism dysfunction, inflammation, and triggering of neurotransmitter cascades [24].

Evidence of a link between the immune system and major depressive disorder has led to a study of the antidepressant properties of anti-inflammatory medications. Among them, minocycline has been identified as a potential new means of treatment for major depressive disorder, in particular, treatment-resistant depression [43, 44]. An essential role of inflammation is confirmed by a study of the use of minocycline, as a result of which there was a decrease in the symptoms of depression [44]; in an experimental model on animals, it was shown that minocycline achieves this by inhibiting the activation of microglia [45, 46]. Indeed, Richards et al. [47] found that the binding of TSPO (a marker of microglia activation) was highest in depressed patients not taking antidepressants. At the same time, drug-treated study participants demonstrated comparable TSPO binding compared to the non-depressed control group. These results confirm the theory that *microglia activation* (a key sign of neuroinflammation) may be aimed at improving the clinical outcome of antidepressant therapy for drug-resistant depression [44, 48, 49]. In conjunction, these conclusions suggest that inflammation, and in particular neuroinflammation, may play a crucial role in the psychopathology of depression.

Psychological and sociodemographic factors

In recent years, it has been found that the development of mood disorders in PLWH largely depends on the person's age and the duration of HIV infection (estimated duration of HIV infection – EDI). Young PLWH with EDI less than three years of age had the highest level of anxiety and depressive disorders, while older PLWH with early infection had low rates of anxiety and depressive disorders. This may indicate a better ability to adapt in aged people and the ability to better cope with acutely stressful situations connected with HIV infection [4, 50, 51]. Elders with PLWH had to survive HIV infection, lose close friends, overcome difficulties during vital life, move from survival to prosperity, and acquire psychological life stability – resilience [52–55]. In the 2019 studies, the resilience and wisdom gained during obsolescence with HIV can help people cope with the diagnosis. It was seen as

an individual psychological characteristic inherent in individual PLWH. In the 2021 study among men who have sex with men (MSM), Canada presented its conclusions on how psychological resilience among MSM is created by resources, protective factors, and personal preferences [56]. Ojukwu researcher and others. (2022) emphasizes the impact of community, political situation, and power on psychological resistance and welfare [57, 58].

Accordingly, the elements of PLWH resilience are formed at the personal and interpersonal level in the society and community where PLWH lives and at the level of state policy regarding PLWH [52, 59].

Stigmatization is a severe problem for people living with HIV and may be one of the causes of mental disorders. The status of an HIV-infected person is still connected with stigma and discrimination. This can lead to a feeling of unacceptability, inferiority, fear, and uncertainty in the person himself, as well as cause rejection by society. Stigmatization and discrimination can prevent timely access to psychiatric care [1, 60].

HIV-related stigma (community, expected, and internalized) is common among PLWH and is *connected with problematic HIV outcomes* (e.g., inappropriate treatment and compliance with the attendance regime). HIV-related stigma is the shame or disgrace connected to HIV and adverse health outcomes for PLWH. Fear of being judged by others impacts decreasing adherence to ART among PLWH and internalized HIV stigma provides for low adherence to ART. While individual treatment does not reduce the harmful tendency of society to stigmatize PLWH and minorities, trauma-focused treatment can combat internal stigma and incorrect perception or over-expectation of perceived stigma, thus preventing additional psychological stress and non-compliance with stigma-related therapies. In particular, trauma-focused treatment provides patients with the opportunity to challenge negative and maladaptive thoughts, including those associated with direct and/or indirect experiences of stigma and discrimination [35, 61].

CONCLUSIONS / ВИСНОВКИ

HIV infection is a factor in the occurrence of mental disorders since the level of mental disorders among PLWH significantly exceeds the level of mental disorders in the general population. Primarily, it concerns anxiety, depressive disorders, and PTSD. According to data obtained by researchers in 2022, 57% of PLWH suffer from at least one mental disorder. Among the mental disorders of PLWH, depressive disorders take the first place and account for 46.4%, anxiety disorders account for 35.6%, and PTSD 9.1%.

The war increased the risk of mental illness in PLWH because of the restriction of access to medical services and social programs necessary for treating and supporting HIV patients, social isolation due to the massive destruction of infrastructure, and forced temporary displacement. This is an additional stressor for this vulnerable segment of the population.

The level of mental health in HIV/AIDS depends on co-morbid mental disorders, the consequences of abuse of psychoactive substances, concomitant hepatitis C, and mental disorders acquired as a result of the impact of HIV on the central nervous system. Both groups of mental disorders likely impact the effectiveness of ART and the quality of life of PLWH. Psychiatric co-morbidity in HIV patients is relatively high, especially for disorders such as depressive disorders, which account for 46.4% of all PLWH mental illnesses and anxiety disorders, 35.6% among PLWH mental illnesses. Diagnosis of PTSD and treatment of the disorder are essential to improve adherence to ART, as well as to mitigate the impact of stigmatization among PLWH.

Recent studies show that stigma is a serious problem that creates barriers to getting help and treatment for HIV. Dissemination of truthful information and educational measures about HIV can help reduce stigmatization and discrimination and improve the mental health of people living with HIV. It is essential to ensure the maintenance and access of medical and psychological assistance to those who need it.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The author(s) declared no potential conflicts of interest to the research, authorship, and/or publication of this article.

FUNDING / ДЖЕРЕЛА ФІНАНСУВАННЯ

None.

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

All authors substantively contributed to the drafting of the initial and revised versions of this paper. They take full responsibility for the integrity of all aspects of the work.

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Received 27.11.2023
Accepted 06.02.2024

Одержано 27.11.2023
Затверджено до друку 06.02.2024