



New Day in Medicine
Новый День в Медицине

NDM



TIBBIYOTDA YANGI KUN

Ilmiy referativ, marifiy-ma'naviy jurnal



AVICENNA-MED.UZ



ISSN 2181-712X.
EiSSN 2181-2187

4 (78) 2025

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**ТИББИЁТДА ЯНГИ КУН
НОВЫЙ ДЕНЬ В МЕДИЦИНЕ
NEW DAY IN MEDICINE**

*Илмий-рефератив, маънавий-маърифий журнал
Научно-реферативный,
духовно-просветительский журнал*

УЧРЕДИТЕЛИ:

**БУХАРСКИЙ ГОСУДАРСТВЕННЫЙ
МЕДИЦИНСКИЙ ИНСТИТУТ
ООО «ТИББИЁТДА ЯНГИ КУН»**

Национальный медицинский
исследовательский центр хирургии имени
А.В. Вишневского является генеральным
научно-практическим
консультантом редакции

Журнал был включен в список журнальных
изданий, рецензируемых Высшей
Аттестационной Комиссией
Республики Узбекистан
(Протокол № 201/03 от 30.12.2013 г.)

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4 (78)

2025

апрель

www.bsmi.uz

https://newdaymedicine.com E:

ndmuz@mail.ru

Тел: +99890 8061882

Received: 20.03.2025, Accepted: 06.04.2025, Published: 10.04.2025

UDC 618.3-06:616.98:578.828.6-036

EPIDEMIOLOGY OF HIV- ASSOCIATED DISEASES ACROSS VARYING DEGREES OF IMMUNOSUPPRESSION

Atoyeva Mashhura Abrarovna <https://orcid.org/0000-0001-9906-7595>

E-mail: atoyeva.mashhura@bsmi.uz

Bukhara State Medical Institute named after Abu Ali ibn Sina, Uzbekistan, Bukhara, st. A. Navoi. 1 Tel: +998 (65) 223-00-50 e-mail: info@bsmi.uz

✓ Resume

Patients with HIV/AIDS often experience various respiratory, dermatological, and mucosal diseases, and recently, attention has also been drawn to neurological complications. In this literature review, the prevalence of HIV-associated diseases among patients and their correlation with the level of immunosuppression, determined by CD4 count, were analyzed. Various respiratory tract diseases, dermatological conditions, as well as different infections and neurological disorders were examined. The literature review indicates that irrespective of the degree of immunosuppression, i.e., CD4 levels, HIV-infected patients are prone to associated conditions such as sinusitis, pneumonia, leukoplakia, Kaposi's sarcoma, and meningitis. With a decrease in CD4 count to below 500/mm³, patients also face an increased risk of developing tuberculosis, thrush, herpes, and shingles. At later stages of HIV, when CD4 counts drop below 200/mm³, there is an elevated frequency of pneumocystis pneumonia, coccidioidomycosis, molluscum contagiosum, cryptococcal meningitis, toxoplasmosis, progressive multifocal leukoencephalopathy, Mycobacterium avium complex, as well as non-Hodgkin's lymphoma. In the most advanced stages of HIV, with CD4 counts falling below 50/mm³, they are at risk of pneumonia caused by Pseudomonas aeruginosa, cytomegalovirus retinitis, CNS lymphoma, aspergillosis, and histoplasmosis.

Keywords: HIV; AIDS; associated diseases; immunosuppression.

ВИЧ-АССОЦИИРОВАННЫЕ ЗАБОЛЕВАНИЯ ПРИ РАЗЛИЧНОЙ ВЫРАЖЕННОСТИ ИММУНОСУПРЕССИИ

Атоева М.А. <https://orcid.org/0000-0001-9906-7595>

E-mail: atoyeva.mashhura@bsmi.uz

Бухарский государственный медицинский институт имени Абу Али ибн Сины, Узбекистан, г. Бухара, ул. А. Навои. 1 Тел: +998 (65) 223-00-50 e-mail: info@bsmi.uz

✓ Резюме

У пациентов с ВИЧ и СПИДом часто наблюдаются различные заболевания дыхательной системы, кожи и слизистых оболочек, а в последнее время также стало важным внимание к поражениям нервной системы. В этом обзоре литературы был проанализирован уровень распространенности ВИЧ-ассоциированных заболеваний у пациентов и их связь с уровнем иммуносупрессии, определяемым по уровню CD4. Были рассмотрены различные заболевания дыхательных путей, дерматологические состояния, а также различные инфекции и заболевания нервной системы. Из обзора литературы следует, что независимо от степени иммуносупрессии, то есть уровня CD4, ВИЧ-инфицированные пациенты подвержены ассоциированным заболеваниям, таким как синусит, пневмония, лейкоплакия, саркома Капоши и менингит. При снижении уровня CD4 до 500/мм³ у пациентов также повышается риск развития туберкулеза, молочницы, герпеса и опоясывающего лишая. На более поздних этапах ВИЧ, когда количество CD4 падает ниже 200/мм³, наблюдается увеличение частоты пневмоцистной пневмонии, кокцидиоидомикоза, контагиозного моллюска, криптококкового менингита, токсоплазмоза, прогрессирующей мультифокальной лейкоэнцефалопатии, комплекса Mycobacterium avium, а также неходжкинской лимфомы. На самых поздних стадиях ВИЧ, когда количество CD4 падает ниже 50/мм³, они подвержены риску развития пневмонии, вызванной Pseudomonas aeruginosa, цитомегаловирусного ретинита, лимфомы ЦНС, аспергиллеза и гистоплазмоза.

Ключевые слова: ВИЧ; СПИД; ассоциированные заболевания; иммуносупрессия.

IMMUNOSUPRESSIYANING TURLI TARANGLIGIDAGI OIV BILAN BOG'LIQ KASALLIKLAR

Atoyeva Mashhura Abrarovna <https://orcid.org/0000-0001-9906-7595>

E-mail: atoyeva.mashhura@bsmi.uz

Abu Ali ibn Sino nomidagi Buxoro davlat tibbiyot instituti, O'zbekiston, Buxoro sh.

A. Navoiy kochasi 1 Tel: +998 (65) 223-00-50 e-mail: info@bsmi.uz

✓ Rezyume

OIV va OITS bilan og'rigan bemorlar nafas olish tizimi, teri va shilliq pardalarning turli kasalliklarini tez-tez boshdan kechirishadi va so'nggi paytlarda asab tizimining zararlanishiga e'tibor berish ham muhim ahamiyatga ega. Ushbu adabiyotlarni ko'rib chiqish bemorlarda OIV bilan bog'liq kasalliklarning tarqalishini va ularning CD4 soni bilan o'lchanadigan immunosupressiya darajasi bilan bog'liqligini tahlil qildi. Turli xil nafas olish kasalliklari, dermatologik sharoitlar, shuningdek, turli infeksiyalar va asab tizimining kasalliklari ko'rib chiqildi. Adabiyotlarni o'rganish shuni ko'rsatadiki, immunosupressiya darajasidan, ya'ni CD4 sonidan qat'i nazar, OIV bilan kasallangan bemorlar sinusit, pnevmoniya, leykoplakiya, Kaposi sarkomasi va meningit kabi kasalliklarga moyil. CD4 miqdori 500/mm³ ga tushganda, bemorlarda sil, qo'ziqorin, gerpes va shingillalar rivojlanish xavfi ham ortadi. OIV ning keyingi bosqichlarida, CD4 200/mm³ dan past bo'lsa, pnevmokistik pnevmoniya, koksidioidomikoz, mollyuska infeksiyasi, kriptokokk meningit, toksoplazmoz, progressiv multifokal leykoensefalopatiya, miyokard infarktlari ko'payadi ma . OIVning eng ilg'or bosqichlarida, CD4 miqdori 50/mm³ dan pastga tushganda, ular Pseudomonas aeruginosa pnevmoniyasi, sitomegalovirusli retinit, markaziy asab tizimining limfomasi, aspergilloz va gistoplazmozni rivojlanish xavfi ostida bo'ladi.

Kalit so'zlar: OIV; OITS; bog'liq kasalliklar; immunosupressiya.

Relevance

As it is known, with HIV and AIDS there is a whole range of associated diseases of the respiratory system, skin, mucous membranes, and now lesions of the nervous system have also become of great importance. This literature review analyzed the prevalence of HIV-associated pathology in patients and its relationship with the severity of immunosuppression, which was expressed in CD4 levels. Diseases of the respiratory tract, dermatological diseases, certain infections and diseases of the nervous system have been examined separately.

Respiratory tract diseases. People with HIV infection often experience nonspecific respiratory symptoms, including cough, shortness of breath, and chest pain. In patients with a CD4 count greater than 500/mm³, these symptoms are usually associated with sinusitis, community-acquired pneumonia, and viral infections. Tuberculosis can occur at any CD4 count, but it usually develops when the CD4 count falls below 500/mm³. Once the CD4 count falls below 200/mm³, the incidence of Pneumocystis pneumonia, fungal pneumonia and more severe forms of sinusitis and bacterial pneumonia, including those caused by Pseudomonas aeruginosa, increases significantly [8,10].

Sinusitis. The incidence of sinusitis is higher in HIV-positive individuals than in HIV-negative individuals. Although sinusitis can occur at any CD4 count, its incidence increases as CD4 counts decline. In patients with a CD4 count of less than 200/mm³, sinusitis often involves multiple sinuses, responds poorly to antibiotic therapy, and becomes chronic. Patients often complain of fever, headache, runny nose and facial pain. However, symptoms may be nonspecific or absent, especially in patients with a CD4 count of less than 200/mm³. In one review [10] of 72 cases of sinusitis, 10 patients (14%) had symptoms of fever and headache only. Of the 75 patients with sinusitis, 19 patients (25%) with radiographic evidence of active sinusitis were clinically asymptomatic. If patients do not respond to broad-spectrum antibiotics directed against common pathogens such as Streptococcus pneumoniae, Viridans streptococcus, and Haemophilus influenzae, Pseudomonas aeruginosa should be suspected. Although Pseudomonas aeruginosa rarely causes sinusitis in HIV-negative individuals, it may account for 16–18% of cases of sinusitis in HIV-infected individuals and is associated with a high rate of disease recurrence. When the CD4 count is less than 150/mm³, the presence of fungal pathogens such as Aspergillus should also be considered [11,12].

Pneumonia. As with sinusitis, bacterial pneumonia is more common in people with HIV infection. In a cohort of 1281 patients [2] studied in HIV-infected individuals, an 8-fold increase in the incidence of bacterial pneumonia was reported compared with control groups of HIV-negative subjects. Although bacterial pneumonia can occur with any CD4 count, its incidence and severity are inversely proportional to CD4 count. In one case series, the incidence of bacterial pneumonia in patients with CD4 counts less than $250/\text{mm}^3$ approaches that of Pneumocystis pneumonia. Risk factors include CD4 count less than $200\text{--}250/\text{mm}^3$, smoking and drug use. The most common pathogen is Streptococcus pneumoniae. Among patients with pneumococcal pneumonia, HIV-infected individuals are more likely to develop bacteremia and recurrent disease. However, the clinical presentation and response to therapy are similar to those in HIV-negative individuals. Other pathogens are Staphylococcus aureus and Haemophilus influenzae, as well as, in the stage of advanced AIDS, Pseudomonas aeruginosa. Community-acquired pneumonia due to Pseudomonas aeruginosa occurs with a median CD4 count of $25/\text{mm}^3$, often in patients who do not have traditional risk factors for Pseudomonas aeruginosa infection, such as neutropenia, the presence of intralinear central venous catheters, or long-term steroid use. It may present as cavitary infiltrates on chest x-ray and is associated with a high recurrence rate. Although widespread use of preventive measures has reduced the incidence of Pneumocystis pneumonia, it remains a common complication of HIV infection. Pneumocystis pneumonia often presents with gradually progressive shortness of breath, fever, and cough. It rarely occurs when the CD4 count is more than $250/\text{mm}^3$. One case series found that only 3 (5%) of 61 cases of PCP occurred with a CD4 count greater than $250/\text{mm}^3$. It was found that only 4 (9%) of 43 patients with PCP had a CD4 count greater than $250/\text{mm}^3$, and three of these four had a CD4 count less than $333/\text{mm}^3$. Another series found that only 3 (6%) of 49 patients with PCP had a CD4 count greater than $200/\text{mm}^3$. Risk factors for PCP include CD4 count less than $200/\text{mm}^3$, previous history of PCP, and thrush. These signs, as well as unexplained fever lasting more than 2 weeks, are indications for starting PCP prophylaxis [3,8,10].

Fungal pneumonia develops in advanced stages of AIDS. Patients typically experience nonspecific symptoms, including fever, fatigue, weight loss, cough, and shortness of breath, lasting weeks to months. According to US statistics, coccidioidomycosis is most common in the southwestern states and in patients with a CD4 count of less than $150/\text{mm}^3$. Disseminated histoplasmosis occurs in the Mississippi and Ohio River valleys in patients with a CD4 count of less than $50/\text{mm}^3$. A case series of 980 AIDS patients found that those with disseminated histoplasmosis had a mean CD4 count of $33/\text{mm}^3$. Aspergillosis is a rare complication and occurs in patients with a CD4 count of less than $50/\text{mm}^3$. Risk factors for aspergillosis include neutropenia, corticosteroid use, and the presence of underlying lung disease. Cryptococcus neoformans can cause pneumonia, but more often causes meningitis [8,17].

Tuberculosis. Tuberculosis most often develops when the CD4 count is below $500/\text{mm}^3$. In a case series [4] of 193 HIV-infected patients with tuberculosis, only 4 (2.1%) had a CD4 count above $500/\text{mm}^3$. It is unclear whether the incidence of tuberculosis increases as the CD4 count decreases. Compared with HIV-negative patients, HIV-positive patients have a greater risk of developing disseminated primary tuberculosis, reactivation of latent tuberculosis, extrapulmonary disease, and adverse reactions to antituberculosis drugs. Patients infected with HIV and tuberculosis, especially those with a CD4 count of less than $200/\text{mm}^3$, are also more prone to anergy (failure to respond). In patients with severe immunosuppression, atypical chest radiographs may be detected. Instead of the typical cavitary, upper lobe lesions observed in immunocompetent patients, individuals with AIDS often present with lower lobe infiltrates, pleural effusions, or mediastinal adenopathy [6]. In a case series [8] of 67 HIV-infected patients with tuberculosis, 80% of patients with AIDS had atypical chest radiographs. In one study, 21 of 26 patients with tuberculosis whose CD4 count was below $200/\text{mm}^3$ had abnormal chest radiographs, compared with only 1 (11%) of 9 subjects with a CD4 count above $200/\text{mm}^3$ [22].

Dermatological diseases. Individuals infected with HIV are susceptible to a wide range of dermatological diseases. Candidiasis, seborrheic dermatitis, **leukoplakia of the oral mucosa**, oral and anal herpetic eruptions, herpes zoster, anal warts, and skin cancer are more common in HIV-infected individuals [7].

Candidiasis. Candidiasis can cause oropharyngeal, vaginal, cutaneous and esophageal lesions. Oropharyngeal candidiasis, often the first sign of HIV, is the most common oral lesion in HIV-infected individuals and most often occurs when the CD4 count is less than $500/\text{mm}^3$. Esophageal candidiasis occurs when the CD4 count is less than $100/\text{mm}^3$ and is usually accompanied by acute pain when

swallowing. One study showed that vaginal candidiasis developed with an average CD4 count of 506/mm³, oropharyngeal candidiasis with an average CD4 count of 230/mm³, and esophageal candidiasis with an average CD4 count of 30/mm³ [15,16].

Viral infections. Recurrent viral infection with *H. zoster* virus is an early opportunistic infection that occurs more often in persons with HIV infection than in HIV-negative persons and usually occurs when the CD4 count is less than 400/mm³. The incidence and recurrence of oral and genital herpes virus infections may increase with increasing degrees of immunosuppression. In one study, all 9 cases of anogenital herpes virus infection occurred with a CD4 count of less than 300/mm³. In the later stages of AIDS, perirectal herpes virus infection can manifest as large, confluent, non-healing ulcers resembling bedsores [16,20].

Molluscum contagiosum is a viral skin disease that leads to the formation of characteristic umbilical skin rashes. In HIV-negative adults, the rashes occur in the genital area, while in HIV-positive adults they are more likely to develop on the face and trunk. A series of 10 patients with molluscum contagiosum found that all had CD4 counts below 100/mm³. A study of 27 patients with molluscum contagiosum found a mean CD4 count of 85.7/mm³. An inverse relationship was observed between CD4 levels and the severity of rashes. Three patients developed extensive skin lesions. All of them had severe immunosuppression and CD4 levels below 10/mm³ [7].

The appearance of leukoplakia of the oral mucosa is presumably also associated with CD4 levels, but is a marker of AIDS progression. A retrospective and prospective cohort study of 434 HIV-infected men found that those with leukoplakia had a mean CD4 count of 340/mm³ [19].

Folliculitis. Folliculitis is also common in people with HIV infection. It can occur at any CD4 level and is usually caused by *Staphylococcus aureus*. When CD4 levels are below 300/mm³, patients may develop eosinophilic folliculitis, a clinical syndrome common in HIV-infected individuals, characterized by discrete, pruritic, erythematous follicular eruptions on the trunk or face and associated with eosinophilia and elevated serum IgE levels [14].

Kaposi's sarcoma. Kaposi's sarcoma is the most common tumor and the fourth most common dermatological disease (after candidiasis, seborrheic dermatitis and folliculitis) in people with HIV infection. The suspected etiologic agent is Kaposi's sarcoma-associated virus (Kaposi's virus). An infectious etiology may explain why sarcoma is most common in homosexual and bisexual men, especially those with a history of oral or anal sexual intercourse. In a series of 130 cases, 75% had a CD4 count less than 200/mm³. However, a low CD4 count was not a prerequisite for the development of Kaposi's sarcoma, since 10% of patients in this series had a CD4 count greater than 500/mm³. Painful, purple skin rashes are typical, but they can progress to painful, indurated lesions. In late stages of HIV infection, they can also affect the oral mucosa, gastrointestinal tract and lungs [9,15].

Bacterial angiomatosis. Bacterial angiomatosis causes angiomatous skin lesions that can mimic Kaposi's sarcoma. It occurs when the CD4 count is less than 100/mm³ and is caused by the bacteria *Bartonella henslae* and *B. quintana*. A review of patients with bacterial angiomatosis found that the mean CD4 count was 57/mm³ [20].

Diseases of the central nervous system. Individuals with HIV infection are susceptible to the same viral and bacterial CNS infections as individuals with normal immune function. In addition, people with HIV infection may develop HIV-associated meningitis at any CD4 count. Classically, this occurs during the period of seroconversion. In contrast, most HIV-associated diseases affecting the central nervous system develop in late stages of AIDS. AIDS dementia develops when the CD4 count is below 200/mm³. Cryptococcal meningitis, toxoplasmosis and progressive multifocal leukoencephalopathy develop when the CD4 count is below 100/mm³. Central nervous system lymphoma develops even later, when the CD4 count drops below 50/mm³ [13].

Toxoplasmosis. Toxoplasmosis is the most common infectious disease of the central nervous system in patients with AIDS. It occurs when the CD4 count is less than 100/mm³ and often presents with a subacute onset of focal neurological symptoms with or without signs of general brain damage [16].

Cryptococcal meningitis. Cryptococcal meningitis is caused by *Cryptococcus neoformans*, an encapsulated yeast found ubiquitously, and often occurs when CD4 counts are less than 100/mm³. Symptoms are often latent and nonspecific. Fever is the most common symptom and occurs in 62-88% of patients. The most common non-meningeal organ affected is the lungs. However, dissemination often occurs by the time pulmonary disease is diagnosed, and meningitis is found in 60-70% of patients with primary pulmonary symptoms [18].

Cytomegalovirus retinitis. Cytomegalovirus (CMV) retinitis develops in 7.5-30% of patients with AIDS. It usually occurs when the CD4 count is less than 50/mm³. In one series of 26 patients with cytomegalovirus retinitis, the mean CD4 count was 15.6/mm³. Patients are admitted to the hospital with complaints of visual disturbances, including floaters, blurred vision, decreased visual acuity, and visual field defects. Vision loss progresses rapidly over days or weeks, and retinal detachment may develop as a late complication [1].

Progressive multifocal leukoencephalopathy. Progressive multifocal leukoencephalopathy develops when the CD4 count is less than 100/mm³. In a review of 15 cases, the mean CD4 count was 84/mm³. This disease is caused by the widespread JC virus, which infects myelin-producing oligodendrocytes and causes their lysis and demyelination of nerve fibers. Patients may present to the doctor with focal neurological symptoms or disturbances of consciousness.

Lymphoma of the central nervous system. After toxoplasmosis, central nervous system lymphoma is the second most common cause of intracranial tumors in patients with HIV infection and usually occurs when the CD4 count is less than 50/mm³. Patients complain of headaches, seizures and cranial neuropathy. Diagnosis is based on computed tomography, magnetic resonance imaging and biopsy, since malignant cells are found in the cerebrospinal fluid in only 15-25% of patients [21].

Systemic diseases. Individuals with HIV infection often experience nonspecific symptoms and signs such as fatigue, weakness, anorexia, weight loss, and night sweats. In later stages of immunosuppression they are often caused by debilitating infections and tumors [20].

Non-Hodgkin's lymphoma. People with HIV infection have a 60 times higher risk of developing non-Hodgkin's lymphoma than the general population. Non-Hodgkin's lymphoma usually develops with a CD4 count below 200/mm³ and may present with fever, weight loss and night sweats. Compared with individuals without HIV infection, those with HIV infection have a higher incidence of extranodal involvement, higher disease stages, and a reduced response to chemotherapy [21].

Mycobacterium avium complex. Mycobacterium avium complex is currently one of the most common opportunistic infections associated with AIDS. The incidence of Mycobacterium avium as a first infection has increased from 5.7% of patients from 1985 to 1988 to 28-30% of patients in 2020. Mycobacterium avium complex usually occurs in individuals with a CD4 count less than 75/mm³ and rarely in those with a CD4 count greater than 100/mm³. It usually presents with persistent fever, weight loss, night sweats and diarrhea.

Conclusion

A review of the literature showed that regardless of the severity of immunosuppression, that is, the CD4 level, HIV-infected patients are susceptible to associated pathologies in the form of sinusitis, pneumonia, leukoplakia, Kaposi's sarcoma and meningitis. When CD4 counts fall below 500/mm³, patients are also at greater risk of developing tuberculosis, thrush, herpes and shingles. During the HIV stage, when the CD4 count falls below 200/mm³, the incidence of Pneumocystis pneumonia, coccidioidomycosis, molluscum contagiosum, cryptococcal meningitis, toxoplasmosis, progressive multifocal leukoencephalopathy, Mycobacterium avium complex, and non-Hodgkin's lymphoma increases. In advanced HIV, when the CD4 count falls below 50/mm³, they are at risk of Pseudomonas aeruginosa pneumonia, cytomegalovirus retinitis, CNS lymphoma, aspergillosis and histoplasmosis.

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Entered 20.03.2025