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The most frequent clinical symptoms in newly diagnosed HIV-1 patients with high and low HIV-1 viral load

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Abstract

Introduction: Globally, an estimated 39 million people were living with human immunodeficiency virus (HIV) and 40 million had died of acquired immune deficiency syndrome (AIDS) in 2022. Early HIV/AIDS diagnosis is essential for immediate life-saving antiretroviral treatment (ART), but HIV symptoms are non-specific, which make difficult to diagnose. The main objective of this study was to describe the frequency of clinical symptoms among recently HIV-diagnosed individuals.

Material and methods: A cross-sectional study was conducted between 2019 and 2020 among HIV-infected persons admitted to the Department of Infectious Diseases at the Medical University Hospital in Warsaw, Poland. Patient data were collected by physicians from various sources, including patients' registers, lab test records, and electronic medical files. Checklists for data collection were employed, and patients with chronic, non-infectious co-morbidities were excluded. High viral load was defined as a value of > 1,000,000 RNA copies/ml. Data were analyzed using Python version 3.7 software.

Results: A total of 86 newly diagnosed HIV-positive patients were included in the study. The mean age was 38 years, and 75 (87.2%) were males. Half (n = 43, 50%) of the patients had a high HIV-1 viral load and showed severe symptoms, including fever 23 (53%), splenomegaly 16 (37%), rash 11 (25%), and hepatomegaly 11 (25%). However, patients with high HIV-1 viral load had significantly lower platelet counts.

Conclusions: Early detection of HIV is crucial for effective treatment and prevention of complications. Symptoms, such as fever, fatigue, splenomegaly, frequent infections, lymphadenopathy, and mouth sores should induce HIV testing. A comprehensive evaluation of patients' subtle symptoms is important for timely intervention and improved outcomes of HIV-positive individuals.

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Key words: HIV, symptoms, HIV-1 viral load.

Introduction

In 2022, the reported worldwide prevalence of human immunodeficiency virus (HIV) was approximately 39 million people. Since the beginning of the HIV epidemic until 2022, 40.4 million deaths have been reported with acquired immunodeficiency syndrome (AIDS)-related diseases as their causes [1]. Since the start of testing in 1985 until November 30, 2022, HIV infection has been detected in 29,676

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Polish residents and foreign individuals residing in Poland. A cumulative number of 3,979 AIDS cases has been documented, of which, 1,465 individuals have died due to the disease. Moreover, approximately 20% of HIV infections are being undetected [2].

HIV is a pathogen that impairs human immune system. The virus has various ways of transmission, such as sexual contact, blood transfusion, sharing intravenous needles, vertical, and breastfeeding [3]. In the WHO European Region, the predominant mode of HIV transmission is heterosexual contact (the known route of transmission), responsible for over 60% of new HIV diagnoses in 2022. Other transmission routes include drug injecting (16.1%), man having sex with men (11.3%), and vertical transmission (below 1%) [4].

Disease progression leads to a gradual loss of immune function, which is characterized by a decrease in CD4+ T-lymphocytes level [5]. Untreated HIV infection may progress to AIDS, the most severe form of the disease, leading to the development of opportunistic infections and malignant neoplasms [6]. The mechanism of HIV progression to AIDS has not been fully elucidated. Most people will develop AIDS within 10 years from the initial HIV infection, if left untreated. Several factors that play a critical role in immunological and virological responses have been identified, including immune response decline, replication rate increase, and host immune responses [7].

Clinical picture of an HIV-infected patient may vary. The first clinical manifestation of HIV infection is acute retroviral syndrome (ARS), presenting symptoms in 23% to 92% of primary HIV infection cases [8]. It is typically described as a mononucleosis-like illness, and the most common symptoms are fever, fatigue, pharyngitis, rash, lymphadenopathy, weight loss, headache, diarrhea, etc. [9]. ARS typically occurs within 2 to 4 weeks after HIV contamination, and the symptoms last for 2 to 3 weeks [10]. There are many other symptomatic conditions in HIV-infected individuals, which may follow over time, including diarrhea, oropharyngeal or vulvovaginal candidiasis, recurrent herpes zoster, peripheral neuropathy, listeriosis, pelvic inflammatory disease, cervical dysplasia, thrombocytopenia, and many more [11]. HIV progression to AIDS is associated with the occurrence of opportunistic infections and malignancies. These diseases are caused by bacteria, fungi, viruses, and parasites. The diseases may involve any organ or system, and are potentially lethal [12]. The severity of symptoms varies depending on patient's condition.

HIV-1 viral load (HIV-1 VL) is an important assessment in people living with HIV, and it is essential to support treatment follow-up [13]. Moreover, routine HIV viral load assessment is recommended by the World Health Organization for monitoring patients receiving ART [14]. Viral load may also be useful in the assessment of HIV communicability, since high HIV-1 VL is associated with significantly higher HIV transmission than low HIV-1 VL [15].

This study aimed to compare the prevalence of common clinical symptoms between patients with HIV-1 viral load (VL) higher and lower than 1,000,000 copies/ mL at the time of HIV diagnosis. This was achieved by evaluating the association between the prevalence of specific clinical signs and conditions in patients with HIV-1 VL below and above 1,000,000 copies/ml.

Material and methods

In our study, data from individuals infected with HIV who were admitted to the Department of Infectious and Tropical Diseases and Hepatology at the Medical University of Warsaw, Poland were analyzed. Data of 86 patients residing in Warsaw who were admitted between 2019 and 2020 were collected. No sample calculation was conducted as the study included all patients who presented during the specified period of time and met pre-defined criteria. Inclusion criteria were newly diagnosed HIV infection and age of 18 years or older. Data were extracted from patients' medical records, excluding those with chronic, non-infectious comorbidities. Individuals with chronic diseases were excluded from the study in order to enhance the probability that the observed symptoms were due to HIV infection and viremia rather than chronic conditions.

All patients underwent a comprehensive physical examination conducted by medical professionals, along with necessary laboratory tests and imaging studies. Blood samples were collected within 3 hours of hospital admission. We analyzed the ratio and total count (cells/μl) of CD4+ and CD8+ lymphocytes, HIV-1 viral load (copies/ml), alanine transaminase (ALT), aspartate transaminase (AST), erythrocyte count (T/l), leukocyte count (K/l), and platelet count (PLT) (G/l). Abdominal ultrasound (USG) examinations were performed within the first 12 hours of hospitalization.

HIV-1 viral load was categorized as < 1,000,000 and > 1,000,000 copies/ml. Initially, the European AIDS Clinical Society (EACS) guidelines were followed, with the recommended HIV viremia threshold of 100,000 copies/ml. However, clinical observations indicated that patients with HIV viremia levels below 100,000 copies/ml infrequently exhibited clinical symptoms. Consequently, the threshold was revised to 1 million copies/ml, as this higher viremia level correlated more strongly with the presence of clinical manifestations.

Ethical approval

Ethical approval and written informed consent were waived by the Bioethics Committee of Medical University of Warsaw because of the retrospective nature of the study. Instead, the Bioethics Committee of Medical University of Warsaw approved the use of oral consent, which was documented in patients' medical records. All analyzed patients' data were fully anonymized. The study followed the principles of the Declaration of Helsinki.

Statistical analysis

Shapiro-Wilk test was performed for the verification of normality of distribution in the analyzed variables. Student's *t*-test or Mann-Whitney *U* test were used to evaluate

Table 1. Clinical and socio-demographic characteristics of patients with high versus low viral load on hospital admission, *n* = 86

Parameter	Patients with VL > 1,000,000 copies/ml	Patients with VL < 1,000,000 copies/ml
Age (years), median (range)	41 (24-66)	35 (19-69)
AST (U/l), median (range)	97.5 (16-338)	60 (18-205)
ALT (U/l), median (range)	155.6 (17-3,185)	86.3 (13-711)
PLT (G/l), median (range)	187.7 (40-617)	226 (34-550)
HIV-1 viral load (copies/mL), median (range)	4,159,082.7 (1,064,678-26,600,930)	209,582.7 (5,233-801,080)

AST – aspartate transaminase, ALT – alanine transaminase, PLT – platelet count

Table 2. Clinical symptoms in patients with HIV-1 VL > 1,000,000 copies/ml and < 1,000,000 copies/ml

Symptom	Patients with VL > 1,000,000 copies/ml, *n* (%)	Patients with VL < 1,000,000 copies/ml, *n* (%)	*p*-value*
Fever, *n* = 32	23 (53)	9 (21)	**0.003**
Splenomegaly, *n* = 23	16 (37)	7 (16)	**0.050**
Rash, *n* = 12	11(25)	1 (2)	**0.003**
Hepatomegaly, *n* = 14	11 (25)	3 (7)	**0.038**

P-value was calculated using χ^2 test.

the difference in mean value in continuous variables, and χ^2 or Fisher exact tests were performed for categorical variables. *P*-value at < 0.05 was considered statistically significant. All statistical analyses were performed using Python version 3.7 software.

Results

Patients

Among 86 newly diagnosed HIV-positive patients (80 of Polish and 6 of Ukrainian origins), two distinct groups were identified: patients with HIV-1 viral load (VL) > 1,000,000 copies/ml on the day of diagnosis (43 patients: 38 males and 5 females), and patients with HIV-1 VL < 1,000,000 copies/ml (43 patients: 37 males and 6 females). Demographics, biochemical, immunological, and virological data of these groups are presented in Table 1.

In general, the individuals exhibited reduced levels of whole blood cells (leukocytes, platelets, and erythrocytes), while only platelet counts varied significantly between the two groups. Platelet counts showed a more pronounced decrease in patients with high VL. Significant differences were observed in liver enzyme levels, including AST and ALT. In the sample, two patients had both hepatitis B virus (HBV) and hepatitis C virus (HCV) co-infection, three had only HBV, and one had only HCV. However, liver enzyme levels did not correlate with viral hepatitis.

Parameters related to white blood cells, such as CD4 (cells/µl), CD4 (%), CD8 (cells/µl), CD8 (%), CD4 ratio, erythrocyte count (T/l), and leukocyte count (K/l) did not show significant variance between the two groups.

Symptoms

Table 2 presents the symptoms, which caused the patients to seek medical assistance.

Data on patient symptoms were comprehensively gathered through physical examinations conducted by the attending physician, and included oral inflammation assessments, cachexia, lymphadenopathy as well as patient interviews on fever, previous infections, rash, weight loss, mental disorders, and peripheral neuropathy. Hepatomegaly and splenomegaly in patients were determined based on ultrasound examinations.

Nine patients had an HIV-1 viral load (VL) exceeding 10,000,000 at the time of detection, and their primary symptoms were skin lesions and inflammatory changes in the oral cavity, particularly affecting the tonsils. Additionally, two patients were diagnosed with syphilis concurrently. However, in general, the number of patients diagnosed with both low HIV-1 VL and syphilis was comparable with those with high HIV-1 VL. Conversely, painful changes in the oral cavity and rash were reported predominantly by patients with high viral loads.

In terms of complaints, long-term low-grade fevers (37-38°C) were the most prevalent manifestation among HIV-infected individuals, with only 12% experiencing fevers up to 39-40°C. However, patients with low HIV-1 VL reported fever significantly less frequently. According to our department's data, splenomegaly was observed more often than hepatomegaly, whereas hepatomegaly was more typical for higher HIV-1 VL patients. Upper respiratory tract infections were common, with symptoms, such as cough, sore throat, night sweats, chills, and fluctuating body temperature. Addi-

tionally, some patients with low HIV-1 VL reported abdominal pain, vomiting, fainting, and headache.

Pneumonia was the most severe health condition observed, primarily caused (55-60%) by *Pneumocystis jirovecii* pneumonia (PJP) infection in both the groups. One case of atypical pneumonia was noted in a patient with high HIV-1 VL. Tuberculosis occurred in individuals aged 48 to 53 years, with a viral load of up to two million. When comparing symptoms by age, older patients (> 40 years) tended to exhibit a more severe clinical presentation than younger cases with similar HIV-1 VL status. Mental disorders were observed among patients with viral loads not exceeding five million. Additionally, cerebral atrophy was present in HIV-infected individuals under the age of 40. No significant differences were observed in the prevalence of fatigue, lymphadenopathy, weight loss, cachexia, cough, diarrhea, tachycardia, syphilis, atrophic conditions, cytomegalovirus (CMV), pulmonary tuberculosis, progressive multifocal leukoencephalopathy (PML), lymphogranuloma venereum (LGV), HIV, and toxoplasmosis.

Discussion

The objective of this study was to present and compare the most common clinical consequences of HIV-1 infections among patients with high and low levels of viral load. At the time of admission to the clinic, 12 patients were in the stage of acute retroviral disease. Among the patients included in our study, symptoms consistent with findings of other studies were observed. Most patients presented predominantly non-specific symptoms and conditions. Only a few individuals exhibited severe clinical manifestations.

In the patients with high HIV-1 VL, low-grade fever was the most common symptom, whereas it was less noticeable in patients with low HIV-1 VL. Similarly, fever occurred as the first indication in previous studies done in other cohorts, and was unrelated to viral load [16-18]. Lymphadenopathy was observed less frequently in our patients than among cases of two studies [17, 18]. However, one of them investigating patients from two continents reported interesting results: 94% of patients from Thailand and only 9% of Africans presented enlarged lymph nodes. It is possible that the incidence of enlarged lymph nodes is determined genetically, and therefore differs depending on the origin (e.g., tuberculosis or parasitic infections) [19]. In addition, lymphadenopathy is a symptom associated with various diseases, including infections and tumors.

In the current study, fatigue was the second most frequently reported symptom among the patients with low and high HIV-1 VL. Similar conclusions were reported in Crowell *et al.* [16] and Braun *et al.* [17] studies. One of the symptoms recorded frequently were recurrent infections, with often co-occurring persistent, dry cough, which was observed in 35% of Polish patients with high HIV-1 VL and 33% with low HIV-1 VL. Furthermore, infections were the most common symptom in the group of patients with low HIV-1 VL in our study. Robb *et al.* [18] in their study among patients in Africa and Thailand presented similar percentage of HIV-infected patients who observed feeling of illness. Moreover, in studied populations, conditions, such as pharyngitis, sore throat, and night sweats were reported [16, 17].

One of the most common opportunistic infections among HIV-infected people is PJP, and high viral load is a contributing factor to this infection [20]. However, this type of pneumonia still occurs in the group of patients with HIV-1 VL lower than 1,000,000, with its etiology of many lung infections. Neurological problems were rare among our patients, and included only single cases of cortical and sub-cortical atrophy. In most of other analysis, a significant portion of a studied population observed frequent headache [16, 18]. However, in the present group, isolated cases of eye problems were diagnosed as complications of toxoplasmosis or CMV infections. As for the second pathogen, it caused primarily retinitis (66% patients with CMV/HIV co-infection). In one case, magnetic resonance showed changes in central nervous system. In a study conducted among African cohort, this virus was manifested mainly by inflammation of retina, whereas in our population, it was colitis and pneumonia [21]. Atrophic changes were visualized in brain images of three patients with high HIV-1 VL, and none among patients with low HIV-1 VL. It is worth noting, that 3 patients with low HIV-1 VL and 5 patients with high HIV-1 VL presented symptoms, which were the basis of early diagnosis of psychiatric disorders, such as depression and bipolar disorder. Based on a study among Africans, the higher the HIV-1 RNA viral load, the higher the rate of mental illnesses [22].

Among our patients with high HIV-1 VL, there were many cases with skin lesions and changes on mucous membranes. In Shehu *et al.* [23] research, it was shown that the more advanced HIV infection, the more often dermatological diseases occur. This is in line with the current study; in patients with low HIV-1 VL, these conditions were very rare.

Regarding digestive system disorders, vomiting and diarrhea were reported [16]. Frequently, patients noticed a significant weight loss, which was not triggered by a lifestyle nor diet change [16, 17]. Importantly, these symptoms affected equally both the groups of our patients. Seven cases with high HIV-1 VL and six with low HIV-1 VL were diagnosed with cachexia upon admission to the department. One of them lost 30 kilograms in 8 months.

HIV and syphilis are transmitted by the same route. Four of our subjects with high HIV-1 VL and five with low HIV-1 VL were admitted to our department with a diagnosis of co-infection. However, one study only reported a relationship between syphilis and level of viral load; this venereal disease causes an increased level of virus' copies in the blood [24]. The discrepancy in reporting of symptoms among patients may be due to their subjective opinions about symptoms' severity. It is worth mentioning that acknowledging to experience certain symptoms may cause physiological distress in patients, so they may deliberately choose to avoid reporting.

Based on the conducted analysis, a similarity in clinical manifestation among people with HIV-1 infection from all around the world has been noticed. A majority of symptoms occur in different population with various frequency, and discrepancies in the results may be due to conducting a research among varying number of cohorts. The discrepancy of symptoms' frequency depends on individual notification of disturbing symptoms. Patients usually report what bother them the most. But it is possible that some of the manifestations are intentionally ignored, because they are embarrassing to disclose.

Clinical symptoms play a crucial role in impacting the adherence to HIV treatment. Symptoms' severity, such as fatigue is associated with higher treatment burden and poorer self-management adherence in people living with HIV, highlighting the importance of addressing symptoms' severity along with treatment burden screening [25]. Poor adherence to antiretroviral therapy is associated with worse quality of life and various factors, including age, education level, depression symptoms, and lack of family support [26]. Additionally, individuals with non-adherence to combined antiretroviral therapy exhibit lower quality of life in general health domain, emphasizing the importance of proper support for treatment adherence [26]. Understanding the relationship between clinical symptoms, adherence, and quality of life can guide interventions to enhance treatment outcomes and overall well-being of individuals living with HIV/AIDS.

Conclusions

Early HIV diagnosis is crucial for effective management of patients, thereby preventing severe consequences of HIV infection. Fever, fatigue, splenomegaly, persistent recurrent infections, lymphadenopathy, and painful mouth ulcers can prompt HIV testing. It is important to differentiate HIV diagnosis based on a patient's comprehensive assessment, considering non-specific symptoms. These symptoms occur in both high and low HIV-1 VL cases, while more specific symptoms may appear only with a substantial increase in viremia level.

Disclosures

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4. Conflicts of interest: None.

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