ORIGINAL ARTICLE

CLINICAL AND LABORATORY MARKERS OF DIGESTIVE SYSTEM DISEASES IN HIV-INFECTED PATIENTS FOR FAMILY MEDICINE PRACTICE

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ABSTRACT

The aim: To identify clinical and laboratory signs of digestive system disease in HIV-infected patients for helping family physicians.

Materials and methods: Research was conducted at five regional HIV / AIDS centers in Ukraine during 2017-2019. Randomly selected 342 adult HIV-infected patients were divided into two groups, with concomitant digestive system diseases and without concomitant digestive system disease. Statistical analysis was performed using the software package EZR 1.41 (Saitama Medical Center, Jichi Medical University, Japan).

Results: The incidence of digestive system disease in patients with HIV clinical stages II, III and IV was significantly higher than in patients with HIV clinical stage I. Gastrointestinal disease was also significantly associated with the incidence of tuberculosis, candidiasis, kidney disease and HIV encephalopathy. Incidence of asthenic-vegetative and dyspeptic syndromes, weight loss, anemia and leukopenia, elevated liver enzymes, low CD4 counts and detectable viral load levels in patients on antiretroviral therapy were significantly more common in HIV-infected patients with gastrointestinal pathologies. HIV patients with digestive system disease significantly more often had changes to their therapy regiment, interruptions in treatment and more often experienced side effects.

Conclusions: Digestive system disease becomes more common with the progression of HIV infection. Comorbidity of HIV infection and digestive system disease is characterized by changes in general clinical, biochemical and immunological blood parameters and patients with digestive system comorbidities more often have a poor virological response to antiretroviral therapy.

KEY WORDS: HIV infections, digestive system diseases, family medicine

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INTRODUCTION

Ukraine has one of the largest HIV epidemics in Eastern Europe and Central Asia by the number of new HIV / AIDS cases. According to the rate of HIV / AIDS spread in Europe and the world, Ukraine is second and fifth, respectively, and ranks 22nd among 123 countries in terms of the estimated number of people living with HIV [1,2].

The key priority of health and social policy in Ukraine is to fight diseases that have the greatest negative socio-demographic and economic impact and together with their associated pathologies form the main burden of infectious diseases in Ukraine and lead to reduced life expectancy, comorbidities and concomitant diseases, disability and premature mortality. With this in mind, the problem of improving the effectiveness of monitoring and treatment of both opportunistic infections and other somatic conditions in HIV-infected patients is a strategic and operational objective of the State Strategy for fighting HIV / AIDS, tuberculosis and viral hepatitis by 2030 and ensuring comprehensive access to HIV treatment [3].

At the same time, the UNAIDS Strategy 2016-2021 On the Fast-Track to end AIDS emphasizes the importance of strengthening and expanding the provision and adherence to antiretroviral therapy (ART) including increasing services aimed at treating co-infections and concomitant pathologies and providing prevention, treatment, care and support services for HIV-infected patients. This requires improving and expanding the integration of care for HIV-infected patients with the treatment of other chronic comorbid conditions, so that the patient-centered clinical monitoring of lifelong ART can provide the best outcome for the patient and help achieve the global goal of ending the HIV epidemic [4].

Digestive system (DS) diseases in Ukraine are the 3rd in prevalence among the whole population (9.8%) and hold the 7th place in causes of morbidity (4.1%). Given that DS diseases affect all age groups, and most patients are of working age, the medical and social relevance of DS diseases is high [5,6]. Given the frequency of comorbidity of HIV infection with diseases of the DS, it is important to study the possibilities of their early diagnosis to prevent the risk of complications, interruptions to continuous antiretroviral therapy (ART) and nonadherence to ART due to DS pathology complications.

International experience of more active involvement of at-risk patients and primary care clinicians in the treatment, spot testing and use of streamlined hepatitis B and C management algorithms has demonstrated improved patient and

community care [7]. It is emphasized that family physicians play a key role in the detection and treatment of many chronic gastrointestinal complications in HIV-infected patients and the monitoring of frequently used drugs [8]. To improve lifelong access to continuous ART, the importance of decentralizing the provision of HIV services to the level of primary care facilities is obvious, including authorize prescription of ART at primary care centers [9]. General practitioners of family medicine are responsible for providing continuous, coordinated and comprehensive integrated health care for all categories of patients and managing the numerous needs of patients, regardless of the nosology of the disease, which is in line with international strategies to combat the HIV epidemic [10-12].

This is especially important in the context of health care system reforms in Ukraine, where family physicians must provide medical care to all patients including those with HIV infection and concomitant pathologies as part of primary care [13,14]. Thereby, the problem of studying the current situation along with the ways to improve and form a modern, comprehensive, patient-oriented approach to help family physicians treat HIV-infected patients with comorbid somatic pathologies of the digestive system becomes especially poignant.

THE AIM

The aim of the study was to identify clinical and laboratory signs of digestive system comorbidities in HIV-infected patients with the end goal of helping family physicians more easily diagnose such patients and provide them with patient-oriented care and support.

MATERIALS AND METHODS

The research was conducted on the clinical bases of the Department of Infectious Diseases and the Educational and Research Center - Ukrainian Family Medicine Training Center of the Bogomolets National Medical University (Kyiv, Ukraine), included the Kyiv City Center for AIDS Prevention and Control at the Kyiv Clinical Hospital №5 and four regional HIV / AIDS centers in Odesa, Kherson, Mykolaiv and Dnipropetrovsk regions during 2017-2019.

Data from medical cards of outpatients, including medical history extracts of inpatient treatment and HIV patient dispensary supervision cards were used. To preserve the anonymity of patients, all medical documents were coded and numbered. Data collection was conducted in compliance with the requirements of existing bioethical norms and scientific standards.

To achieve the objectives of the study, 342 patients who were registered at the HIV / AIDS Centers and had a confirmed diagnosis of HIV infection were selected by randomized sampling from 12680 total patients.

The inclusion criteria were as follows: the patient had a verified diagnosis of HIV infection, male or female, aged 18 years or older. Exclusion criteria: child and adolescent HIV-infected patients.

Medical records were examined for general clinical methods of examination (anamnestic, assessment of general condition, physical examination) used to diagnose gastrointestinal pathology and to establish the clinical picture. Hematological and biochemical studies were used to identify the state of hematopoiesis, indicators of hepatocyte cytolysis, bilirubin metabolism, synthetic liver function and excretory function of the kidneys. Serological tests in dynamics were used to detect antibodies to HIV, hepatitis C virus and hepatitis B virus. Molecular genetic methods were used to confirm diagnoses of HIV infection, chronic viral hepatitis and to monitor the course of the disease and the effectiveness of therapy. Instrumental tests (fibrogastroduodenoscopy, chest radiography, computed tomography of the chest and abdomen, sonography of the abdominal cavity) were used to determine the condition and detect pathological changes in the relevant organs and systems. The diagnosis of HIV infection was established and confirmed on the basis of existing recommendations and protocols.

The assignment of patients into groups was carried out based on the presence or absence of digestive system (DS) disease. The main group (MG) consisted of 252 patients with pathology of the DS. The control group (CG) consisted of 90 patients without signs of damage to the DS. The groups are comparable in age and sex composition. Patients with II, III and IV HIV clinical stage predominated in the MG, in the CG more than half the patients were in stage I (Table 1).

Statistical processing of the data was performed using the EZR 1.41 software package (Saitama Medical Center, Jichi Medical University, Japan).

RESULTS AND DISCUSSION

The nature of concomitant gastrointestinal disease observed in patients in the main group and the control group was analyzed. Tuberculosis ($p < 0.01$), candidiasis ($p < 0.05$), kidney disease ($p < 0.001$) and HIV encephalopathy ($p < 0.01$) were significantly more often observed in the main group. Using the Chi-squared test ($\chi 2$) the relationship between having digestive system disease and other comorbidities as a factor that increases its likelihood was determined. The relationship is considered significant in cases where the confidence interval does not contain the null value of 1. (Table II).

It was found that patients with candidiasis and tuberculosis were twice as likely to have DS disease and in the presence of HIV encephalopathy and kidney disease the chance of having DS disease was 4.5 and 3.7 times more likely, respectively.

The majority of patients in the main group with DS disease, 150 (59.5%) patients, ($p < 0.001$), had two or more organs affected by digestive system pathologies. Hepatitis of various etiologies - viral, toxic or of unknown etiology was the most common DS disease. A total of 220 (87.3%) main group patients were diagnosed with hepatitis ($p < 0.001$). Hepatitis diagnoses included chronic hepatitis C

Table I. Baseline characteristics of patients included in the study

	Main group	Control group
Number of patients	252	90
Male	140 (55,6%)	47 (52,2%)
Female	122 (44,4%)	43 (47,8%)
Average age	42,7±0,6	38,7±1,1
Median age	42	38
HIV clinical stage I	43 (17,1%)	51(56,7%)
HIV clinical stage II	25 (9,9%)	5 (5,6%)
HIV clinical stage III	69 (27,4%)	7 (7,8%)
HIV clinical stage IV	115 (45,6%)	27 (30,0%)

Table II. The odds ratio of patients having DS disease in the presence of other comorbidities

Variables	Odds Ratio	Standard Error	95% Confidence Interval
Candidiasis	2,055	0,262	1,229-3,436
Tuberculosis	1,961	0,302	1,086 - 3,541
HIV encephalopathy	4,471	0,447	1,860-10,747
Kidney disease	3,696	0,489	1,418-9,631

(HCV) - 118 (46.8%), HCV and hepatitis of unknown etiology together - 10 (4.0%), chronic hepatitis B (HBV) - 9 (3.6%) HCV and HBV - 9 (3.6%) and hepatitis of unknown etiology - 74 (29.4%) of the patients. The second most common DS disease was chronic pancreatitis in 116 (46.0%) patients. It is noteworthy that only 4 (3.4%) patients had pancreatitis as a DS monopathology, in the remaining 112 (96.6%) pancreatic disease was combined with other DS diseases. Gastro-duodenal disease was found in 88 (34.9%) patients. Gastroduodenitis was diagnosed in 47 (53.4%), gastritis in 14 (15.9%), and peptic ulcer disease in 4 (4.5%) patients. The remaining 23 (26.1%) patients had multiple gastric pathologies.

Chronic cholecystitis was found in 74 (29.4%) patients, of which 66 (89.2%) was acalculous and 8 (10.8%) was calculous. Of these, 56 (75.7%) patients had cholecystitis combined with pancreatitis 38 (51.4%) and other DS diseases, 8 (10.8%) with chronic hepatitis, 5 (6.8%) with gastroduodenal lesions, 3 (4.1%) with chronic hepatitis, gastroduodenitis or gastritis, and 2 (2.8%) with colitis and chronic hepatitis or gastritis. Only one patient (1.7%) had calculous cholecystitis as a monopathology.

Candidal esophagitis was observed in 13 (5.2%) of the patients. As it is a manifestation of severe immunodeficiency it was observed only in stage IV HIV-infected patients and was combined with chronic hepatitis and gastroduodenitis or gastritis in 6 (46.2%) patients, with chronic hepatitis in 4 (30.8%) patients, with chronic hepatitis, pancreatitis and peptic ulcers in 3 (23.1%) patients. Colitis was observed in 8 (3.2%) patients and only in one case (12.5%) was the only diagnosed gastrointestinal disease.

Distribution of patients with DS diseases by the clinical stage of HIV infection (Fig. 1).

Digestive system pathologies were more frequent as HIV infection progressed. In patients with clinical stages II, III and IV they were observed significantly more often than in patients with clinical stage I. Of patients in HIV clinical stage I 43 (45.7%) had gastrointestinal disease ($p > 0.05$), 30 (83.3%) in clinical stage II ($p < 0.05$), 69 (90.8%) in stage III ($p < 0.05$) and 115 (81.0%) with IV clinical stage ($p < 0,05$).

The frequency DS disease in patients with different clinical stages of HIV infection was compared. It was found that for HCV and HBV infections and for hepatitis of unknown etiology the association with the stage of HIV infection was not significant ($p > 0.05$). There was also no statistical difference in the frequency of detection of cholecystitis ($p > 0.05$). On the contrary, there was a statistically significant relationship between HIV clinical stages and the frequency of gastroduodenitis and pancreatitis ($p < 0.01$ and $p < 0.05$, respectively).

The following symptoms were observed statistically more often in the MG patients then in the CG patients (Table III).

Other symptoms, such as headache, pallor, vomiting, heartburn, diarrhea, bloating, cough, and rashes were observed in MG and CG patients with the same frequency ($p > 0.05$).

Antiretroviral therapy was prescribed in accordance with existing protocols and recommendations. Therapy changes and interruptions in treatment, as well as the frequency of adverse reactions in the main group were significantly more frequent than in the control group, $p < 0.05$. The most common side effects that required therapy correction were lack of immune response, hematotoxic effects manifested by the development of anemia, leukopenia, thrombocytopenia or pancytopenia, lipodystrophy, and severe dyspeptic syndrome in the form of nausea, vomiting

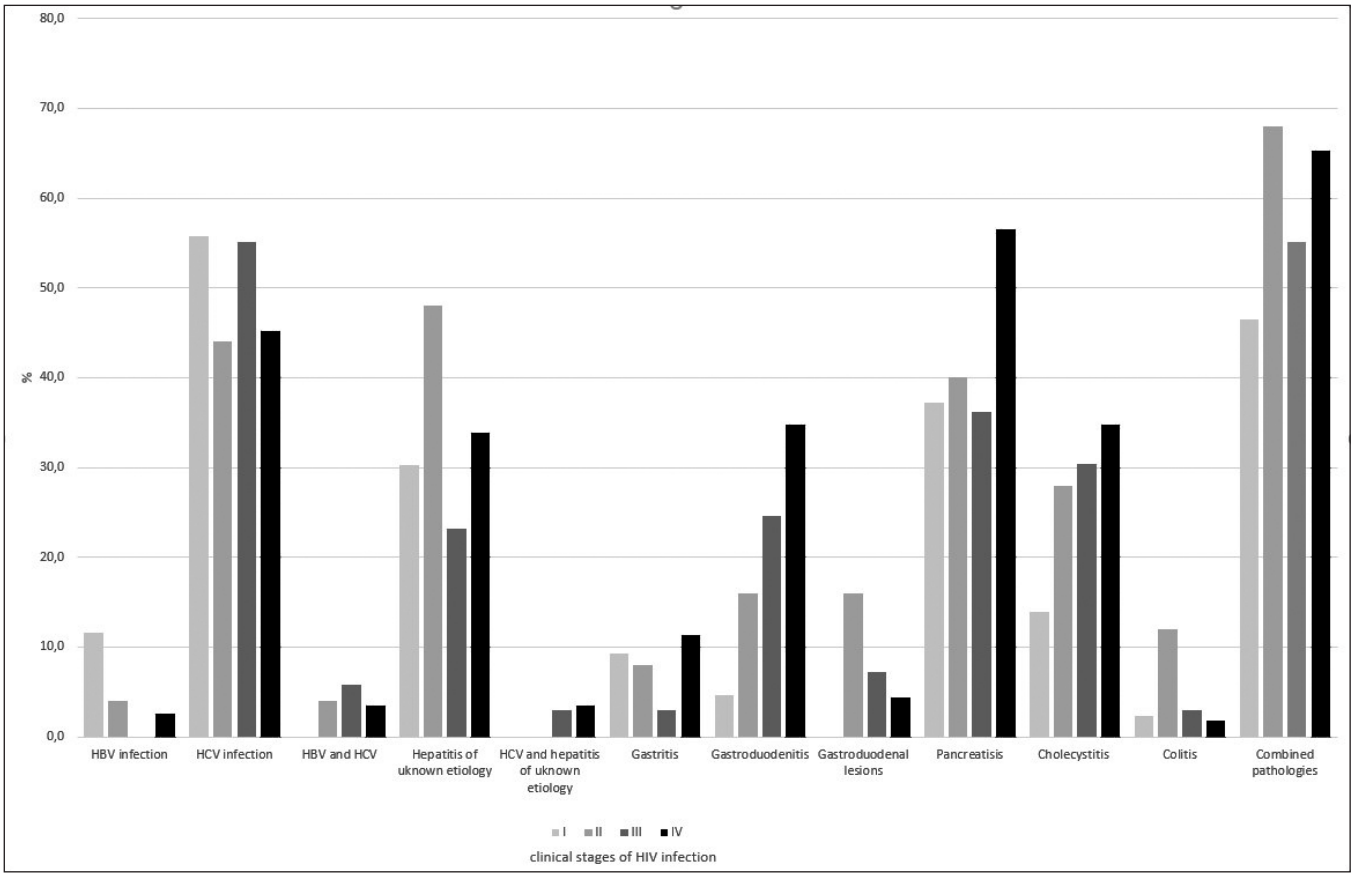

Fig. 1. Distribution of DS diseases in patients with different clinical stages of HIV infection.

Table III. Clinical symptoms in HIV-infected patients in the MG and the CG

Symptoms	Main Group		Control Group		P
	N	%	N	%	
Weakness	123	48,8	17	18,9	<0,001
Weight loss	66	26,2	9	10,0	<0,01
High temperature	63	25,0	8	8,9	<0,01
Cognitive disorders and neurological issues	54	29,0	6	8,9	<0,01
Loss of appetite	67	26,6	7	7,8	<0,001
Nausea	45	17,9	2	2,2	<0,001
Epigastric pain	49	19,4	7	7,8	<0,05
Itchy skin	24	9,5	1	1,1	<0,01

and pain. Significantly more patients in the main group experienced adverse effects of ART: hematotoxicity was experienced by 18 (81.8%) MG patients and 4 (18.2%) CG patients ($p < 0.05$), lack of immunological response by 20 (87%) MG patients and 3 (13%) CG patients ($p < 0.05$), lipodystrophy by 6 (85.7%) MG patients and only 1 (14.3%) CG patient ($p < 0.05$), dyspeptic syndrome by 9 (100%) and 0 CG patients ($p < 0.05$).

The frequency and nature of hematological changes in MG and CG patients were analyzed. Anemia with a decrease in hemoglobin below 120 g/L in women and 130 g/L in men was observed in 94 (48.5%) MG patients and 11 (34.5%) CG patients ($p < 0.05$).

Leukopenia with a leukocyte count below $4.0x10^9$ /L was detected in 59 of 193 MG patients (30.6%) and in 4 of 28 CG patients (14.3%) ($p < 0.05$). Leukocytosis, on the contrary, was significantly more common in CG, 6 of 28 patients (21.4%) compared with 8 of 193 (4.2%) MG patients ($p < 0.05$). An increase in erythrocyte sedimentation rate of more than 10 mm/hour in men and 15 mm/hour in women was found in 95 of 193 (58.6%) MG patients and in 9 of 18 (50.0%) CG patients, the difference was not statistically significant ($p > 0.05$).

There was no statistically significant difference between the mean hemoglobin, erythrocyte count and erythrocyte sedimentation rate ($p > 0.05$) between groups. The average

level of leukocytes in the control group was statistically significantly higher than in the main group ($p < 0.05$).

The biochemical parameters present in all blood profiles were analyzed. Overall biochemical blood profiles were available for 117 of 252 MG patients (46.4%) and 42 of 90 CG patients (46.7%) ($p > 0.05$). Low total protein levels and hypoalbuminemia in patients in both groups were observed with almost equal frequency ($p > 0.05$). Increased alanine aminotransferase (ALT) levels were found in MG patients significantly more often due to the inclusion in this group of patients with viral and toxic liver disease of various etiology ($p < 0.05$). Elevated gamma-glutamyl transferase (GGT) levels were also significantly more common in the main group ($p < 0.05$), which included patients with hepatitis and pancreatitis and significantly more patients with kidney disease than in the control group (17.9% and 5.6% respectively, $p < 0.01$). Probably for the same reason, MG patients were statistically significantly more likely to have elevated levels of urea and creatinine ($p < 0.05$).

When comparing the average values of various biochemical blood tests, no statistically significant differences were found between groups in the average values of total protein, albumin, urea and creatinine levels ($p > 0.05$). However, the average levels of ALT and GGT were statistically higher in the main group ($p < 0.05$).

The results of immunological tests showed that a moderate decrease in the CD4 lymphocyte count was observed in 96 of 234 (41.0%) examined main group patients and in 25 of 71 (35.2%) control group patients. The difference was not statistically significant ($p > 0.05$). However, CD4 lymphocyte counts which correspond to a state of severe immunodeficiency were found in the main group in 63 (26.9%) patients against 9 (12.7%) in the control group, and normal values were 75 (32.1%) patients in the main group and 37 (52.1%) in the control group. That is, MG patients were more likely to have advanced immunodeficiency and lower CD4 counts, with a statistically significant difference, $p <0.05$ and $p <0.01$, respectively. The average CD4 count in the main group was 418.96 ± 18.26 cells/μl (Me = 394, Mo = 190) and was statistically significantly lower than in the control group, 548.7 ± 40.15 cells/μl (Me = 525.5, Mo = 808), ($p <0.01$).

The results of virological testing showed that the vast majority of HIV-infected patients in the study 174 (69.0%) in the main group and 79 (87.8%) in the control group achieved a good virological response to ART with a viral load of less than 40 copies/ml ($p < 0.05$). However, there were 78 (31.0%) patients in the main group whose viral load was above detectable levels, which was statistically significantly higher than in the control group, which had 11 (12.2%) patients ($p < 0.05$).

The presence of untreated comorbid diseases of the digestive system in HIV-infected patients may be a marker of reduced effectiveness of ART. Therefore, the role of primary care physicians, and especially family physicians, in ensuring the timely detection, monitoring and treatment of typical digestive diseases in HIV-infected patients is crucial.

This is especially relevant in primary care facilities, where family physicians are entrusted with the provision of medical care to patients with HIV and treating their concomitant somatic pathologies. Primary care institutions carry out seroepidemiological monitoring of HIV infection spread, including tracing HIV transmission routes, as well as reporting deaths among HIV-infected patients, according to the order № 180 from 05.03.2013 of the Ministry of Health of Ukraine [15].

That is, these above-mentioned activities of the current primary care practice and policies aim to create a modern integrated, patient-oriented approach to the management of these nosologies in family medicine practice, which would be in line with international strategies to counteract the HIV epidemic, which emphasize the importance of expanding and implementing patient-oriented care strategies.

CONCLUSIONS

1. Digestive system disease was found in 73.7% of examined HIV-infected patients. The most common DS diseases found were chronic viral hepatitis, chronic hepatitis of unknown etiology, gastroduodenal disease, chronic and cholecystitis. The majority of patients had multiple organs affected by DS diseases. The incidence of DS diseases increased with the progression of HIV infection and was diagnosed in HIV-patients with clinical stages II, III and IV significantly more often than in patients with stage I.
2. HIV-infected patients with DS diseases were found more likely to complain of asthenic-vegetative syndrome symptoms.
3. ART regimen changes, interruptions in treatment and side effects of ART were found to occur significantly more frequently in patients with DS diseases.
4. Anemia, leukopenia, increased ALT and GGT levels, CD4 and lymphocyte counts below 500 cells/ml and a detectable viral load level while on ART ($p < 0.05$) were significantly more common in HIV patients with DS diseases.
5. Markers of gastrointestinal comorbidities in HIV-infected patients are available for monitoring and control in medical records of primary care practices in Ukraine and can be used for timely detection, monitoring and treatment of typical digestive system diseases by family physicians.

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The Authors declare no conflict of interest.

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