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HIV INFECTION, SECONDARY CONDITIONS AND COMORBIDITIES. PART 2. CONCOMITANT DISEASES

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Comorbid conditions are typical for many chronic pathological processes, especially at a mature and old age. For several reasons, a special place in the formation of these conditions takes HIV infection in combination with non-communicable diseases. The general characteristics of the secondary athologies, which remain one of the leading causes of severe complications and mortality, are presented. Particular attention is focused on possible concomitant somatic pathology, which may affect the quality of life and the prognosis. Among pathological precosses are lesions of the gastrointestinal and urinary tracts, cardiovascular diseases and malignant neoplasms. A method for the integrated assessment of the severity of a patient's condition with a combination of comorbidity and HIV infection is presented. This method allows to improve the prediction of the course and outcome of the main and associated diseases, as well as to influence the nature of the diagnostic and therapeutic processes.

Keywords: HIV infection; comorbidities; concomitant diseases; integral assessment of severity.

ВИЧ-ИНФЕКЦИЯ, ВТОРИЧНЫЕ И КОМОРБИДНЫЕ ЗАБОЛЕВАНИЯ. ЧАСТЬ 2. СОПУТСТВУЮЩИЕ ЗАБОЛЕВАНИЯ

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Коморбидные состояния характерны для пациентов, у которых присутствует несколько хронических патологических процессов, особенно для пациентов зрелого и пожилого возраста. По ряду причин особое место в формировании коморбидных состояний занимает ВИЧ-инфекция в сочетании с неинфекционными заболеваниями. Дана общая характеристика вторичных патологий, которые остаются одной из ведущих причин тяжелых осложнений и смертности пациентов с ВИЧ. Особое внимание уделено возможным сопутствующим соматическим заболеваниям, которые могут повлиять на качество жизни и прогноз, в том числе поражениям желудочно-кишечного тракта, мочевыделительной, сердечно-сосудистой системы и злокачественным новооб-

List of abbreviations

AIDS — acquired immunodeficiency syndrome; ART — antiretroviral therapy; ARVs — antiretrovirals (drug); CHCV — chronic viral hepatitis C; CMV — Cytomegalovirus; CNS — central nervous system; CT — computed tomography; CV — cardiovascular; CVH — Chronic viral hepatitis; EBV — Epstein-Barr virus; ELISA — enzyme-linked immunosorbent assay; HCV — hepatitis C virus; HIV — human immunodeficiency virus; ICD — International Statistical Classification of Diseases; IDU — injecting drug usage; ISI — integral severity index; MNs — malignant neoplasms; MRI — magnetic-resonance imaging; NCDs — neurocognitive disorders; PCP — pneumocystis pneumonia; PCR — polymerase chain reaction; PLHIV — people living with HIV; RF — Russian Federation; RNA — ribonucleic acid; PWID — people who inject drugs.

разованиям. Представлен метод интегральной оценки тяжести состояния пациентов на фоне коморбидности при ВИЧ-инфекции, позволяющий улучшить прогнозирование течения и исходы основного и сопутствующих заболеваний, а также повлиять на характер диагностического и лечебного процессов.

Ключевые слова: ВИЧ-инфекция; коморбидность; сопутствующие заболевания; интегральная оценка тяжести.

Central nervous system impairment

Touching upon somatic diseases that have the most significant impact on human health implies discussing in more details the central nervous system (CNS) impairments and cardiovascular (CV) and liver problems as well as cancers.

Thus, impairments of the central nervous system were diagnosed in 14.3% of patients admitted to the inpatient setting of the AIDS Center during the past decade. Besides, human immunodeficiency virus (HIV) encephalitis, brain lesions due to disseminated toxoplasmosis and/or candidiasis as well as a combination of Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) were encountered most frequently (Table 1).

Also, lesions have been found in the setting of disseminated tuberculosis, neurosyphilis and disseminated herpesvirus infection. The number of patients who survived cerebrovascular accidents caused by a variety of etiologic factors abundantly present in HIV infection goes up every year [1].

A separate subject for fundamental and applied research and developing the unified optimal clinical diagnostic algorithms is an issue of HIV-associated neurocognitive disorders (NCDs) that, according to the literature data, may be found in $^{2}/_{3}$ of patients without CNS organic lesions [2].

Our long-term interdisciplinary study that included the assessment of over 200 patients allows us to conclude that 60–80% of patients have impaired cognitive abilities such as memory, attention and intelligence already at the early stages of the infectious process despite the immunological and virological stability.

In patients with severe HIV infection recrudescence is reported as immunosuppression and viral activity become more profound. Collating clinical and laboratory as well as electrophysiology and neuroimaging studies allowed to reveal the leading role in NCDs of the altered energy structural and functional network of the brain comprising the brainstem reticular formation, nonspecific structures of the midbrain, diencephalic compartments, limbic system, mediobasal parts of the frontal and temporal lobes of the cerebral cortex. As a result the regulation of brain activation gets disrupted ('cortical tone' needed to perform any mental activity, the level of consciousness); the local selective activation processes required for implementing higher mental functions become compromised [2–4].

In the setting of HIV infection, an early involvement of such structures as the cingulate gyrus, medial temporal lobe including the hippocampal region, and putamen may be explained by the proximity of giant circumventricular organs that have the region of permeable capillaries in the lateral ventricles most susceptible to the penetration of HIV viral particles and HIV-infected CD4 lymphocytes.

The results provided by the fundamental research make us hopeful for further improvement of diagnostics, early detection of CNS lesions in HIV infection by virtue of using efficient algorithms and methodological approaches [2–5].

Impairment of the gastrointestinal tract organs

The abnormalities are most frequently (85.5%) represented by chronic gastritis, cholecystitis and cholelithiasis, pancreatitis as well as peptic ulcer disease in the stomach and duodenum. No doubt that a vast majority of patients are diagnosed with

Table 1

Brain impairments as a cause of death in patients with HIV infection

Leading causes of death	Abs	%
Impairment of the brain of various etiologies	45	17.0
Disseminated tuberculosis	24	9.0
Cerebral toxoplasmosis	18	6.8
Cryptococcal meningoencephalitis	18	6.8
Herpetic meningoencephalitis	1	0.4
In total	106	40.0

chronic viral hepatitis (72%), of whom 12% already have cirrhosis [6–9].

Chronic viral hepatitis (CVH), chiefly chronic hepatitis C, is the most common HIV co-infection due to similar modes of transmission. HIV and hepatitis C virus (HCV) co-infection is characterized by rapid progression of CVH towards cirrhosis, which occurs over 10–15 years in 15–25% of HIV-infected patients versus 2–6% in HIV-negative patients during the same period.

5.4% of patients who received antiretroviral therapy (ART) and had a stabilized underlying condition, died of decompensated liver cirrhosis and hepatocellular carcinoma. Among the causes of death clinically unrelated to HIV infection, liver malfunction along with cardiovascular disease and external causes (drug overdose, violent death, suicide, vehicle crashes, etc.) hold the leading place (22.6%). The survival analysis in patients receiving ART (continuous treatment) showed that death of the patients with the maximum lifespan (17.5 years) was caused by viral liver disease (90%) [10–12].

Viral hepatitis, especially HIV/HCV co-infection, is associated with severe extrahepatic manifestations. Among these essential mixed cryoglobulinemia (with multiple symptoms), malignant non-Hodgkin's lymphomas (B-cell), thyroid disorders, idiopathic thrombocytopenic purpura, late cutaneous porphyria, diabetes mellitus, glomerulonephritis and some other conditions are most frequently reported. In HIV/HCV co-infection, arthralgia and myalgia as well as the presence of anticardiolipin antibodies are not uncommon. With this regard patients are recommended a more frequent screening for thyroid and kidney diseases, and also planning and undergoing the additional examinations, once specific symptoms are found. The high rate of HIV/HCV co-infection determines the need for optimizing the approaches to the treatment of patients, involving a broad range of trained professionals in patient management.

Malignancies

A combination of HIV infection and malignant neoplasms (MNs) found in 1.6% of patients admitted to the AIDS Center is the most dreadful scenario from the standpoint of a patient's clinical status [6, 13]. The most common MNs in patients with HIV infection are malignant lymphomas (58%), including non-Hodgkin's lymphomas and lymphogranulomatosis. Kaposi's sarcoma, invasive cervical cancer, lung cancer, colon cancer, breast cancer and some other malignancies can also be considered as the most common tumors. The majority of neoplasms are detected in advanced stages (80%); this factor determines the severity of a patient's somatic symptoms. As a rule, HIV infection is found before a MN is diagnosed; however, less than 10% of patients receive ART by that time. We have analyzed the 5-year overall survival in patients with HIV infection after they were diagnosed with a MN: this indicator amounted only to 39%. In our opinion, prescription of ART upon MN diagnosis is the only factor that significantly improves the overall 5-year survival of patients, as judged by a statistical analysis [14, 15].

The results obtained within the framework of our clinical and epidemiological study of HIV/MN comorbidity vividly illustrated the international experience which indicates that in the population of HIV-infected patients, the size of a cohort of individuals with persistent and profound immune system disorders associated with disease progression and aging will be increasing. Accordingly, the number of MNs will grow steadily. In view of such a high rate of cancers, the mandatory screening among patients with HIV infection at a younger age (under 40 years) along with counseling aimed at the MN risk reduction is a matter of paramount importance. To design the strategic approaches and efficient programs of HIV-associated MN prevention, the prospective epidemiological and clinical studies must be accomplished to ensure the comprehensive treatment of such patients [15].

Severe forms of HIV infection

From the mid-2000s, the physicians working in specialized centers started noticing an apparent increase in a number of patients with severe HIV infection, including those newly diagnosed and those who were already followed up.

Depending on geographical location, there are various reasons for the occurrence of severe HIV infection in patients. The ranking of these causes changes over time as the epidemic proceeds, and their continuous assessment aimed at minimizing the occurrence of severe forms of the disease is required [10, 16].

The causes of severe forms of HIV infection

1. A delayed diagnosis
2. Consequences of an insufficient follow-up
3. Poor ART outcomes:

— prescribing incorrect drug regimens;
— lack of a patient's adherence to treatment;
— unjustified switch therapy;
— HIV drug resistance;
— untimely substitution of non-efficacious drugs;
— drug intolerance or incompatibility with other pharmacies used for treatment of comorbidities;
— opportunistic infections, viral hepatitis, tumors, etc.

Table 2

Distribution of the major causes of death in patients who died with advanced HIV disease in 2010–2014 (*n* = 265)

Leading causes of death	ICD 10	Absolute number (*n* = 265)	Mortality (%)
Impairment of the brain of various etiologies: HIV encephalitis, multifocal brain lesions of unknown etiology, meningoencephalitis of unknown origin, leukoencephalopathy, herpetic leptomeningitis, serous meningitis, cryptococcal meningitis	20.7	80	30.2
Bronchopneumonia	118.0	68	25.6
Pneumocystis pneumonia (PCP)	20.6	30	11.4
HIV-associated cancers Lymphomas, cervical cancer, Kaposi sarcoma	21.0–21.9	24	9.0
Disseminated tuberculosis	20.0	24	9.0
Cerebral toxoplasmosis	20.8	18	6.8
Cytomegalovirus infection	20.2	13	5.0
Atypical mycobacteriosis	20.0	8	3.0

Table 3

Deceased patients diagnosed with chronic viral hepatitis as a co-infection (*n* = 265)

Years	2010	2011	2012	2013	2014	Total
Patients with CVH	47	48	26	22	48	191
of who						
Cirrhotic stage CVH	22	20	15	11	20	88
%	46.8	41.7	57.7	50.0	41.7	46.1

We have performed a retrospective analysis of 265 medical records of the deceased patients treated in the inpatient setting of the St. Petersburg AIDS Center during the period from 2010 to 2014. An average age of these individuals was 37.7 ± 0.6 years (ranging from 21 years [the youngest patient who died] to 78 years [the oldest one]). Among those passed away, men prevailed (68.0%); an average duration of the infection was 10.5 years; the follow-up lasted for 8.3 ± 2.4 years. Forty two patients (16.0%) did not know about their HIV status and were not followed up at the AIDS Center.

Prior to hospital admission 193 patients out of 265 were receiving ART; 86% of them independently discontinued this therapy or were taking antiretrovirals (ARVs) inconsistently, which caused the disease progression and the emergence of opportunistic infections. On an average, ART duration was 6.1 ± 2.3 months.

Both identifying the primary cause of death and making post-mortem diagnosis were difficult because 72% of patients had multiple comorbidities (Table 2).

Among those who died (265 individuals), 191 patients (72%) were diagnosed with CVH; 88 of those (46.0%) had cirrhosis (Table 3).

Of all patients diagnosed with CVH, this disease was the primary cause of death in 55 cases (20.7%). It is noteworthy that the causes of death of patients with HIV infection have been changing over time; in particular, a number of deaths related to the conditions caused by immunosuppression increased since 2010. This might happen due to the natural course of the disease and its progression in patients who acquired HIV infection a few years earlier. The obtained results confirm the importance of timely and early finding of people infected with HIV, their regular follow-up and promotion of adherence to a high-quality ART [10, 17].

The leading causes of the lethal outcome for patients with comorbidities were opportunistic infections (OIs) (76.6%); other patients died of concurrent non-communicable conditions (23.4%). Judging by the autopsy data, the impairment of cerebral functions played the leading role among other opportunistic infections that caused death of patients with HIV beginning from 2010 (40%). Among those are disseminated tuberculosis (9.0%), cerebral toxoplasmosis (6.8%), cryptococcal meningoencephalitis (6.8%) and disseminated Herpes simplex virus infection (0.4%). Cerebral impairments of various etiologies, such as HIV encephalitis, meningoencephalitis of unknown origin, multifocal brain lesions of unknown etiology and other conditions, accounted for 17%. These data support the results reported previously [10, 11, 18].

The number of patients who died of various HIV manifestations differed from one year to another, which was related to peculiarities of both underlying and concomitant pathologic processes [10, 19, 20]. Thus, in 87.4% of patients of the group under study the advanced stages of the disease were recognized with profound immunosuppression and severe manifestations of comorbidities. The loss of other patients with HIV in the subpopulation of people who consume injection drugs were caused by severe disseminated infections and concurrent diseases. Another leading cause of primary mortality was CVH with liver cirrhosis — 20.7%. Among the comorbidities diseases of the digestive system such as pancreatitis (21.3%), cholelithiasis (18.4%), chronic gastritis and peptic ulcer disease of the stomach (65.7%), and community-acquired pneumonia (18.6%) played a significant role. Such an abnormality of the urinary system as exacerbations of chronic pyelonephritis was diagnosed in 17.8% of those deceased. Comorbidities aggravated any underlying medical condition. Purulent-septic complications as the cause of death amounted to 2.0%. Cardiovascular disease was found in older patients (51.5 years). Besides, the leading causes of death included the following comorbidities: impairment of the cardiovascular system (2.6%); cancers unrelated to HIV infection (lung cancers, laryngeal cancer, malignancies of the gastrointestinal tract) (2.2%); sepsis accompanied by infective endocarditis (2%); psychoactive drugs overdose (0.7%).

Data analysis showed that 16.0% of patients did not know about their HIV infection; they were transferred to the AIDS Center inpatient setting from other multidisciplinary clinics in critical condition. It should be noted that in the past some patients were more than once seeking doctor's attention for various reasons, but had not been offered HIV testing, which is quite typical in the RF and causes severe comorbidities [17].

Altered working ability and disability

For several years we kept assessing the permanent disability of HIV-infected patients recognized as disabled. The analysis showed that the number of such patients of employable age among whom men were invariably prevailing, had been steadily increasing since 2008. Moreover, the signs of disability consistent with Disability Group 1–2 were identified in most cases at the initial assessment; in other words, these individuals had significant physical or mental handicaps already upon presentation [6]. For certain reasons, it is more difficult for such patients to get a job even to perform easy

Table 4

Evaluation of permanent disability of HIV-infected patients recognized as disabled, by year

Indicators	2008	2010	2012	2014	2015
Adults (in total), individuals	53	145	112	180	238
Men, abs/%	26/49.0	85/59.0	73/65.2	104/58.0	140/59.0
Women, abs/%	27/51.0	60/41.0	39/34.8	76/42.0	98/41.0
Recognized as disabled for the first time, of who: Group 1 + 2, %	79.2	78.6	60,7	50.6	41.3
Are not employed, abs/%	No data	125/86.0	108/96.0	162/90.0	210/88.0
HIV 4A, abs/%	19/35.8	31/21.0	12/10.7	16/9.0	14/6.0
HIV 4B, abs/%	17/32.1	31/21.0	11/9.8	29/16.0	36/15.0
HIV 4C, abs/%	17/32.1	83/57.0	89/79.5	135/75.0	188/79.0

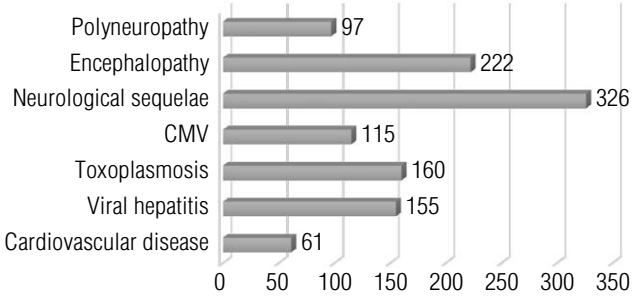

Fig. 1. Causes of disabilities among HIV-infected patients in St. Petersburg (2008–2015)

tasks as opposed to people with no HIV infection. Generally we see the predominance of HIV at advanced stages. The population of such patients significantly grows year after year (2008 — 32.1%, 2015 — 79%) (Table 4).

It is of utmost importance to understand the main reasons for early and irreversible incapacitation of people of employable age, including those with HIV infection. Audit of the charts of 1,065 HIV-infected patients at the AIDS Center showed the distribution of various diseases and pathologic conditions as contributors to disability. The majority of patients who survived the disseminated forms of neural infections like toxoplasmosis and CMV had neurological sequelae, such as paralysis and paresis of varying severity. Besides, the patients demonstrated a gradually increased incidence of polyneuropathy and encephalopathy of mixed (infectious and toxic) etiology, which is explained by the high prevalence of substance dependence, the occurrence of severe OIs, the natural degenerative processes and a variety of other reasons [21].

The serious condition of patients with viral hepatitis was called forth by a combined impact of HIV infection and hepatitis *per se* i.e. by its advanced stage with cirrhosis); the patients were recognized as disabled because of both severe infections. Incapacitation occurred due to the concurrent HIV infection and cardiovascular insufficiency that manifested itself after infective (bacterial) endocarditis damaging the heart valves. In some cases the call for referring to medical and social disability assessment was rooted in the consequences of coronary heart disease, high blood pressure and its complications (Figure 1).

The role of illicit drugs in comorbidities

Drug abuse plays a pivotal role in all stages of the HIV epidemic. Using contaminated equipment or solutions for drug injections exposes patients to both HIV and viral hepatitis. Over the second half of the 1990s these two viruses simultaneously penetrated into the injection drug usage (IDU) environment in the Russian Federation (RF); by now HIV/CVH remains the most common co-infection among the drug users. Thus, a steady triad has formed, comprising drug addiction, HIV infection, chronic hepatitis [6, 20]. Drug administration route associated with infection acquisition has accelerated several-fold the spread of HIV within a short period in the late 1980s.

Parenteral transmission that replaced sexual transmission heralded the transition from the HIV subtype B as the major pathogen to the HIV subtype A to become its marker [4, 22]. Considering the substance abuse disorder as a comorbidity, it is advisable to assess the role and influence of drugs on behavioral characteristics of people living with HIV (PLHIV) and the HIV trajectory. According to reports, the size of this population (IDU and HIV) varies from 15 to 25% depending on a region [19, 23]. Sentinel surveillance accomplished during the past decade indicates that dual diagnosis i.e. drug addiction and HIV, is prevalent in 20 to 70% [24].

The results of monitoring of the second wave of HIV infection in the North-West of the RF also confirms the role of drug addiction in those areas where parenteral transmission used to prevail due to significant representation of people who inject drugs (PWID) [24].

The substance abuse as a form of deviant behavior affects in several ways the trajectory and the outcomes of HIV disease and its comorbidities [6, 25]. Those are:

— impairments of organs and systems (CNS, heart, kidneys and other) due to the effects of illicit drugs aggravating the progression of immunosuppression;
— a person's social withdrawal: deterioration of the living conditions, the changing environment and job loss;
— the probability of imprisonment (changes in the living conditions and therapy);
— the changes in behavioral priorities with poorer adherence to follow-up and ART;
— an increase in sexual activity associated with certain stages of substance abuse and the probability of acquiring sexually transmitted infections.

With this regard the drug addiction holds the first place among comorbidities causing high mortality in PLHIV initially by poisoning, injuries and suicides (up to $^{1}/_{4}$) and subsequently by infections ($^{2}/_{3}$) and somatic disorders ($^{1}/_{10}$) [6, 11].

Since there is no cure for drug addiction, cohort of drug users will remain a source of fueling and expanding the epidemic of HIV infection and of chronic viral hepatitis for a long period of time.

Table 5

Comorbidity scoring system to estimate the integral severity index (ISI) in HIV infection

Disease and condition	Score	IDC-10
Multiple organ failure	10	R00-R99
Miliary tuberculosis	6	A19, B20.0
Liver cirrhosis as an outcome of any liver impairment, primarily, viral hepatitis	5	B18.0-B18.2, B18.8, B22.7, K77.0, K74
Sepsis	5	A40, A41, B20.1-B20.5, R57.2
Heart failure; acute heart failure; congestive heart failure, functional classes 3–4	5	R09, I39, I40, I49, I50, I98
Severe pneumonias; acute respiratory failure; chronic respiratory failure, severe	5	B20.1-B20.3, B20.5, B20.6, J13-J18, J80, J98.9, J96, R09.2
Acute renal failure; chronic renal failure, advanced stages; chronic kidney disease	5	A00-B99, B23.8, B24, N08.2, N08.8, N10-N16, N17, N18, N29.1, N29.8, R30-R39
CNS impairments of various etiologies; with brain involvement, with spinal cord involvement; severe neurological symptoms; severe neurocognitive disorder; dementia	4	A85-A88, B22.0
Chronic liver disease, including viral hepatitis, end-stage liver disease	4	B22.7
Tuberculosis with visceral organ involvement	3	B20.0
Opportunistic infections diagnosed with the use of conventional examination techniques (ELISA, PCR, CT, MRI) by studying blood and other body fluids	3	B20.2, B20.3, B20.4, B20.9
Cancers	3	B21, C00-C97
Lymphadenopathy (clinically significant, extended peripheral and visceral)	3	B23.1, R59
Compensated somatic, hematological and other conditions	2	B22.7, B23.2, B23.8
Psychiatric disorders, including IDU, that are to be referred to specialty care	2	B22.7, F10-F19
Neurocognitive deficit	2	B22.0
Wasting syndrome, cachexy	2	B22.2
Alcoholism	1	B22.7, F10
Fever, longer than 3 months, from low-grade to hectic, of various etiologies	1	B22.7, B23, R50
Pain	1	R52

Note. CNS — central nervous system; ELISA — enzyme-linked immunosorbent assay; PCR — polymerase chain reaction; CT — computed tomography; MRI — magnetic-resonance imaging; PWID — people who inject drugs.

Integral assessment of the disease severity in a HIV-infected patient with comorbidities

Most patients with HIV have multiple infectious and non-infectious diseases that potentiate each other in their manifestations and effects on organs and systems, shaping a patient's condition entailing dubious prognosis. Only $^{1}/_{4}$ of patients die of immunosuppression sequelae, i.e. secondary infections; the remaining $^{3}/_{4}$ of patients pass away due to a complex of various conditions that constitute severe comorbid disorders [10, 11].

All these factors determine the need to search for and implement the methods of assessing the severity of a HIV-infected patient's condition and comorbidities, which will allow to adequately evaluate a patient's clinical status and choose the appropriate treatment sites (an outpatient clinic, an inpatient setting), to prescribe an efficacious antiretroviral therapy regimen for HIV infection, to prevent possible secondary conditions and initiate the treatment of present comorbidities considering the immediate prognosis and averting the threat of the immune reconstitution inflammatory syndrome [9, 13, 18].

Both clinical and integrated approaches to an assessment of a patient's condition and the prognosis for HIV infection have been described previously. The immunity parameters, a typical history, the indicators of a delayed physical development, weight loss as well as the presence of multiple conditions like disseminated lymphadenopathy, hepatomegaly, splenomegaly, HIV encephalopathy, cardiomyopathy, nephropathy, prolonged fever of unknown origin, anemia, localized forms of bacterial infections, a localized form of *Herpes simplex* virus infection, a localized form of candidiasis, etc. were considered to lay the foundation of this methodology [26, 27].

The disadvantage of most calculation formulas ever proposed is a lack of possibilities to consider not only comorbid conditions as a separate category of the severity of a patient's condition, but also the viral activity, the immunity and other characteristics. Nonetheless, most clinicians are looking for options that would permit an integral assessment of a patient's condition. The first versions proposed the classifications of HIV infection stages, some of which implied immunological and virologic abnormalities as well as the presence of co-infections [6].

The previous experience of various clinics made it possible to assess a threat of comorbid conditions and to lay the foundation for the proposed methodology. This experience permitted a chronological evaluation of the clinical significance and the role of secondary and concurrent diseases in the HIV epidemic trajectory. However, the segregation of individual syndromes and diseases dispersed them throughout various sections of the International Statistical Classification of Diseases (ICD) and Related Health Problem, 10th revision (ICD-10) (A, B, J, N, R, and other), which further complicated the clinical assessment of a specific patient with comorbidities among those with HIV infection [11, 19].

The proposed integral assessment of a patient's condition is likely to provide reliable results in case of HIV infection, since it takes into account the comorbidities, viral activity and the immune status [28].

To evaluate a patient's condition the primary assessment is carried out. It is followed by in-depth examination that includes an evaluation of individual organs and systems, identification of comorbidities and diseases and then measuring HIV RNA in the blood as an indicator of viral activity and CD4 counts that characterize the immune status. At the same time, making a diagnosis and reporting clinically significant syndromes as well as tracing the history of alcohol and drug abuse are feasible.

At this stage the first estimate can be made using the formula indicated below to calculate the integral indicator of patient's condition. This is followed by a more profound examination carried out to rule out or confirm tuberculosis and chronic hepatitis with assessment of liver fibrosis as the most significant diseases that determine the severity of a patient's condition. A comprehensive work-up comprises the neuropsychological testing to detect impairments of the central nervous system, psychiatric and neurocognitive disorders; it includes cardiovascular studies, pulmonary function tests as well as an examination of the urinary tract. As a result, each identified concomitant or secondary disease (comorbidity) is scored according to the developed scale (Table 5).

The scoring system takes into account our previous studies of the causes of the lethal outcome in patients with HIV infection based on the clinical observations as well as the results of autopsy in patients from other institutions [6, 10, 11]. For objectivity the materials obtained by the authors were compared with those published by other researchers, and the scores presented in Table 5 were calculated with an input from the experts. Selective assessment of manifestations in individual patients with HIV infection has been done to be compared with the comorbidity severity score presented in Table 6. The severity of a patient's condition has been evaluated in accord with the five major criteria ranging from fair (satisfactory), sufficiently stable to critical with a probable unfavorable outcome.

Table 6

Comorbidity severity score in patients with HIV infection, by ISI

Condition of the patient	Score
Fair (satisfactory), sufficiently stable	to 100
Serious with destabilization phenomena	to 300
Very serious with a possible unfavorable outcome	to 500
Critical with a probable unfavorable outcome	from 500 to 700
Terminal	from 700

To estimate the integral severity index (ISI) of a patient's condition the following formula is proposed:

$$\text{ISI} = \frac{(1 + N_n) \cdot (1 + \log_{10} \text{HIV RNA})}{\text{CD4 T lymphocytes} \cdot 0.001},$$

where N_n is grand total as a sum of scores of all comorbid conditions and syndromes; $\lg_{10}$ HIV RNA is the viral load converted to decimal logarithm; CD4 is cell count in μL; 0.001 is adaptive coefficient.

The proposed formula is designed in such a way that the condition severity is directly proportional to the overall score of comorbid syndromes and conditions (N_n) and viral activity ($\lg_{10}$ HIV RNA) and inversely proportional to the CD4 cell count in the blood as a surrogate marker of the immune status.

This is what makes it different from previously published methods of assessing the condition of a patient with HIV infection and from the conventional classifications that take into account a stage of the pathologic process, the resulting syndrome of which is human immunodeficiency [6, 10, 11]. The presented methodology considers, in addition to the AIDS-defining illnesses, all the identified comorbidities as well as the viral activity and the parameters of the immune function.

In accord with the scale in Table 6, the severity of comorbidities is assessed using ISI and categorized as fair, sufficiently stable; serious with destabilization phenomena; very serious with possible unfavorable outcome; critical with probable unfavorable outcome; terminal.

Clinical illustration of the method

Patient A. aged 37 was admitted to the AIDS Center for treatment. Presenting complaints: fever during past several weeks; weight loss is approximate 10 kg; white lesions of mucous membranes in the month, palate and pharynx; indigestion with tendency to loose stools. On examination: body temperature 38 C; 12% of weight loss; HIV RNA in the blood — 700 thousand copies/mL ($\lg_{10}$ 5.84); CD4 cell count in the blood — 150 cell/μL; hepatic enlargement + 2 cm below the costal margin; chronic viral hepatitis C; liver enzymes (alanine aminotransferase — 145 U/L, aspartate aminotransferase — 178 U/L). Diagnosis formed: 'HIV infection, C3 (CDC), chronic viral hepatitis C (CVHC), wasting syndrome; oral candidiasis' is made.

Two years ago this patient has interrupted the prescribed therapy; estimated duration of the disease is 5 years; possible transmission mode — injecting drugs — through casual psychoactive substance abuse; currently does not use substances. The patient was hospitalized whereas ART was initiated. Upon hospital admission, ISI has been estimated by use of the formula.

$$\text{II} = \frac{(1 + 3\,(\text{CVHC}) + 1\,(\text{mucosal candidiasis}) + 2\,(\text{cachexy})}{150\,(\text{CD4 T lymphocytes})\,0.001} \times$$

$$\times \frac{(1 + 5.84\ \text{HIV RNA})}{150\,(\text{CD4 T lymphocytes})\,0.001} = 319.2.$$

In accord with Table 7, this patient's condition is recognized as a severe one, which is likely have an unfavorable outcome. Half a year after initiating ART and carrying it out first in the hospital and then on an outpatient basis, the fever and candidiasis of mucous membranes and the wasting syndrome have subsided; the patient gained 3 kg. His ISI that had been calculated again amounted to 162.2 points; his condition can be recognized as serious with destabilizing phenomena with a tendency to become fair and sufficiently stable by virtue of ART. The patient's viral load got reduced to 100 thousand copies/mL ($\lg_{10}$ 5); CD4 cell count in the blood was 185 cell/μL. After one year of successful therapy, the patient's condition improved to fair and sufficiently stable.

Thus, the essence of the developed method is as follows:

— the severity of a patient's condition is determined based on comprehensive analysis of identified comorbidities assessed by use of the scoring system with consideration of immune status and HIV activity;
— the suggested technique minimizes subjective evaluation of the severity of a patient's condition by various doctors; it assures common

interpretation and is subject to analyzing and formalizing;
— the subjective evaluation of comorbidities with consideration of immune status and viral activity connected by a mathematical relation allows the integral assessment of a patient's condition with consideration the concurrent and secondary diseases (comorbidities) providing the proofs of the efficacy of given therapy.

Conclusion

After one-and-a-half decades since the first wave of the HIV epidemic, the clinical manifestations of HIV disease in PLHIV have changed significantly. Initial comorbidity — HIV/drug abuse got complemented by new categories; a large group of patients with multiple morbidity (tuberculosis, viral hepatitis, secondary and concurrent infections, somatic and psychiatric and neurological disorders) has been revealed. During this period, the epidemic has embarked on a new stage to become the epidemic of comorbid and severe forms of HIV infection accompanied by the sustained high mortality despite ART.

Identification of a high proportion of patients with comorbidities requires the new approaches to elaboration of health and social care for patients with HIV infection as well as expanding pharmaceutical coverage of outpatients to treat their comorbid conditions. It also requires a qualitatively new type of training and involvement in the service delivery of allied professionals in addition to infectionists.

The suggested method of integral assessment of the severity of patients suffering from HIV infection and various concurrent illnesses and pathologic conditions that is available and easy to use in real clinical practice will improve forecasting of both the course and outcome of the disease. It will significantly affect the nature of diagnostic and therapeutic procedures.

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