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Lethality among Patients with HIV/AIDS Monitored in the Clinic of Infectious Diseases in St George University Hospital, Plovdiv, 2010–2014

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Background: The introduction of complex antiretroviral therapy has resulted in significant decrease in the mortality rate of HIV positive patients, but it still remains unacceptably high, especially in some groups of patients.

Aim: To investigate the death rate in patients with HIV/AIDS, lethality and mortality in co-infection, and the most common causes and predictors of fatal outcome, focused on early diagnosis and appropriate therapy.

Materials and methods: The study included 53 deceased patients with HIV/AIDS, monitored at the Clinic of Infectious Diseases in St George University Hospital, Plovdiv between 01.01.2010 and 31.12.2014. The methods of research included clinical analysis, laboratory tests, microbiological and serological tests (HCV, HBV, toxoplasmosis), ELISA, PCR. Statistical analysis was performed by descriptive statistics, the Student's t-test, the method of Van der Ward, and regression analysis (logistic regression).

Results: During the study period 316 patients with HIV/AIDS were monitored, 53 of them with lethal outcome. Lethality was 16.7% for the whole group; in intravenous drug users - 13.8%; in co-infected patients: HIV/*M. tuberculosis* - 46%, in HIV/HCV - 17.8%. Lethality and mortality in HIV(+) patients with co-infections in populations of different age, gender, duration since starting cART and degree of immunodeficiency (according to CD4, VL) was compared with the lethality and mortality in patients with these conditions from the general population.

Conclusions: Fatal outcome in patients with HIV/AIDS was most commonly associated with co-infections HIV/*M. tuberculosis* and HIV/HCV. Predictors of a fatal outcome are pulmonary tuberculosis, advanced immunodeficiency with VL > 500 000 c/mL and CD4 < 100/mm³, absence or non-systemic antiretroviral therapy.

BACKGROUND

There is a global trend to restrain AIDS pandemic, but currently 36.9 (34.3 – 41.4) million people worldwide live with HIV/AIDS. According to 2011 UNAIDS data for the countries of Central and Western Europe, the total number of HIV+ persons was 1 million in Central Europe, 1 400 000 in Eastern Europe, and in Bulgaria – 2380. Europe still fails to control HIV infection, and the situation is particularly alarming in the eastern regions. Combined antiretroviral therapy (cART) reduced morbidity and mortality rate in HIV/AIDS.^{1–4} With increasing access

to cART, enhanced efficacy, safety, tolerability and adherence to therapeutic regimens, HIV infection is defined as chronic manageable condition.^{1–5} The introduction of cART resulted in increase of life expectancy of HIV+, but in some groups of patients lethality remains unacceptably high.^{6–8}

HIV infection prevalence is rather low in Bulgaria and yet the number of HIV-infected (HIV+) individuals in the country continues to grow.^{1–3} Contemporary therapeutic regimens are accessible for HIV+ patients in Bulgaria², but there are some factors as late diagnosis ‘late presenters, with ad-

vanced immunodeficiency' late treatment, respectively, and poor adherence to treatment that worsen the prognosis of the disease.

AIM

The aim of the study was to investigate the lethality and mortality rates in patients with HIV/AIDS, the most common causes and predictors of fatal outcome with the purpose of early diagnosis, monitoring and adequate intensive therapy.

MATERIALS AND METHODS

The study included 316 HIV/AIDS patients treated at the Clinic of Infectious Diseases in St George University Hospital, Plovdiv; 53 of them died in the period from 01.01.2010 to 31.12.2014. The methods used include clinical analysis, laboratory, microbiological, and parasitological tests, ELISA, PCR, and instrumental methods such as X-ray, ultrasonography, and endoscopy. Statistical analysis was carried out using descriptive statistics, the Student's t-test, and the method of Van der Waard regression analysis (logistic regression). Data from the records of the Regional Health Inspection on mortality in patients with tuberculosis and hepatitis C in the general population were used.

RESULTS

Figure 1 shows the dynamics of HIV positive patients monitored from 2010 to 2014 at the Clinic of Infectious Diseases in St George University Hospital, Plovdiv.

The gender distribution of patients shows that men were prevalent (81% of the monitored and 80% of the deceased patients).

Analysis of age distribution (**Fig. 2**) showed that the largest proportion of patients was in the age group 25-35 yrs, and it was significantly higher in monitored than in deceased patients ($p < 0.05$, $t = 2.86$). Significantly higher was the share of the deceased against monitored patients in those aged up to 25 (12%, respectively 28% ($p < 0.05$, $t = 2.4$)). The number of patients over 60 years and below 18 years of age was too small in both groups.

The distribution of patients according to the mechanism of HIV transmission (**Fig. 3**) was identical with that of the dead and survivors, the injection drug users being the most commonly affected.

Lethality in our patients in the study period showed minor fluctuations in individual years, but did not show a decreasing trend (**Fig. 4**).

Diseases associated with a fatal outcome were:

hepatitis C (HCV), pneumonia, candidiasis, cachexia and tuberculosis. In other patients the cause of death was meningitis, HSV infection, salmonella spp. infection - sepsis and pyonephrosis.

Immunological and virological indicators CD4 (cells/mm³) and VL (copies/μL) prior to the fatal outcome in the observed 53 patients were as follows: serum levels (mean, SD) of CD4 – 54.23±48; VL – 428 225±62 061. In 22/53 (41.5%) patients with fatal outcome CD4 count was < 50 cells/mm³. There were extremely low values of CD4 (6-25) cells/mm³ in 12 patients.

The number of the deceased until the third month since start of therapy was the highest. By the end of the first year it had dropped three times, but remained high compared to later periods (**Fig. 5**).

A significant difference was found between the lethality of tuberculosis in HIV+ and the general population ($P < 0.01$, $t = 3.4$); the lethality of HBV in HIV+ and the general population ($P < 0.05$, $t = 2.4$), and lethality from HCV in HIV+ and the general population ($P < 0.001$, $t = 4.3$) (**Table 1**).

Using the Student's t-test we found significant difference between the age in deceased from tuberculosis in AIDS patients - an average of 34 years, and the general population - an average of 56 years ($P < 0.05$, $t = 2.0$) (**Table 2**).

Using multi-regression analysis we have studied the effect of CD4, VL, presence of TB, HBV and HCV infections. We found the influence of two independent risk factors on the lethal outcome of patients suffering from HIV infection. These were: CD4 < 100 (odds ratio 8.728; 95% confidence interval 3.994-19.072; $P = 0.000$) and VL > 500 000 (odds ratio 4.169; 95% confidence interval 1.207-14.405; $P = 0.024$).

DISCUSSION

The prevalence of males among all our patients (monitored and dead), repeats the gender distribution in the country. Our data on gender distribution and mechanism of HIV transmission between monitored patients and those with lethal outcome is not fully consistent with data in the literature in other geographical regions. The reasons for the prevalence of the male sex are probably linked to the leading mechanisms of HIV transmission in the region - injection drug users (IDU) and men having sex with men (MSM), where males have a leading position. According to some authors mortality is higher among women and injection drug users (IVDU).¹ Other studies do not find differences by

Figure 1. Patients with HIV/AIDS monitored in the Clinic of Infectious Diseases, Plovdiv

Figure 2. Age distribution of monitored surviving patients (1) and dead patients (2).

Figure 3. Route of HIV transmission in monitored surviving patients (1) and dead patients (2).

gender^{5,7} but are almost unanimous in the opinion that lethality is highest in IDU.⁸⁻¹¹ The reasons for the high incidence of lethal outcome in IDUs are complex: higher frequency of coinfections HBV and HCV, cognitive impairment associated with drugs and poor adherence to therapy, marginalization of these persons and poor living conditions.

The data on differences in age characteristics of the deceased and monitored patients are interesting. In our study, lethality was significantly higher in the age group up to 25 years. A possible explanation is that most of them are IDU, and do not adhere to cART yet.

Survey identified data that lethality is of insignificant fluctuations in the individual years without a trend to decrease, do not correlate with the data of other authors for sustained downward trend in the era of cART.^{1,2,9} What might be the reasons for this inconsistency? Failure to adhere to therapy is crucial. Although the patient could have obtained suitable free cART, lack of adapting to a therapeutic regimen is disastrous.

It is important to define the causes of death - whether they are directly associated with HIV infection or not, since this implies different programs to decrease lethality.

Figure 4. Lethality in patients with HIV/AIDS during study period.

Figure 5. Fatality rate (number of dead patients per month) after starting the cART.

Table 1. Mortality rates (in % and absolute values) from TB, HBV and HCV among HIV (+) patients and among the general population

Condition	2010	2011	2012	2013	2014	Mean
TBC/HIV	28.57 (2/7)	100 (1/1)	4.17 (1/24)	19.23 (5/26)	41.67 (5/12)	20.00 (14/70)
TBC - in the general population	2.40 (5/208)	5.42 (11/203)	4.10 (8/195)	1.29 (2/155)	3.33 (5/150)	3.40 (31/911)
HBV/HIV	25.00 (1/4)	12.50 (1/8)	7.69 (1/13)	10.00 (1/10)	40.00 (2/5)	15.00 6/40
HBV - in the general population	1.92 (1/52)	0 (0/40)	2.78 (1/36)	0 (0/21)	0 (0/16)	1.21 (2/165)
HCV/HIV	22.22 (6/27)	17.39 (4/23)	16.28 (7/43)	14.29 (5/35)	23.81 (5/21)	18.12 (27/149)
HCV - in the general population	0 (0/4)	0 (0/4)	0 (0/15)	0 (0/11)	0 (0/14)	0 (0/49)

Table 2. Mean age at time of death from TB, HBV and HCV among HIV (+) patients and in the general population

Condition	TBC/HIV	TBC in the general population	HBV/HIV	HBV in the general population	HCV/HIV	HCV in the general population
N	14	31	6	2	27	0
x ± SD	34.3±5.8	56.2±9.3	30.2±4.7	56.0±6.9	28.1±6.9	-

According to ARV Cohort Collaboration Study Group, 2010, AIDS related death is assumed in AIDS related infections and neoplasms, CD4 <50 cells/mm³, VL>5 log copies/μL before death, M Hodgkin, while unrelated to AIDS morbidity is assumed in co-infections and neoplasm, non-related to AIDS: HCV, HBV, HSV, M. tuberculosis infection, cardiovascular diseases, hematological conditions.⁴

Differentiation of these two groups is very conditional, since the majority of patients with CD4 <50 cells/mm³ also have tuberculosis, pneumonia or other infections unrelated to AIDS. The global reduction of mortality rate was achieved mainly by reducing AIDS-related mortality, resulting in a larger relative share of the other reasons for the fatal outcome related to comorbidity, co-infection

with HCV, HBV, drug addiction and cardiovascular diseases.

Particularly noteworthy are data on the period in which death occurred since diagnosis, with extremely high mortality in the first three months (76%), three times less patients die in the second quarter while the number drops sharply after the first year.

Our data on early death (till the 6th month since cART) in the vast majority of patients correlates with data of other authors.^{5,6,10-13} A disturbing fact is that 22/53 patients with fatal outcome indeed have just started cART. Unfortunately, the diagnosis is too late, patients have advanced immune deficiency, severe comorbidity (tuberculosis, pneumonia, meningitis) and die shortly after including cART. In cases of TB/HIV cART had to start some weeks

after antituberculosis therapy, due to danger of immune reconstitution inflammatory syndrome (IRIS).

There is disturbingly high prevalence and lethality in patients co-infected with HIV and TB. Tuberculosis was the leading cause of mortality in our patients. The strong synergy between HIV and TB has deadly consequences worldwide, especially among populations with high prevalence of HIV (sub-Saharan Africa, India). HIV pandemic is a huge challenge on TB control at all levels¹⁴⁻¹⁶ - patients are ill with AIDS, but die from tuberculosis!

In patients with HCV co-infection lethality was 26/146 (17.8%), two patients died with signs of hepatic coma. Data of many authors indicate that lethality in patients on cART tends to decrease, but not if they have HIV/HCV co-infection. HCV is defined as a risk factor for adverse outcomes in patients with AIDS.^{5,6,14,15}

Limitations of the study: there are no pathological autopsies, not all patients have died at the Clinic, part of the data on CD4 and VL are not actual, but the latest available, due to the irregular appearance of the patients for monitoring.

CONCLUSION

Fatal outcome occurs most commonly in patients aged up to 35 years, with advanced immunodeficiency and tuberculosis, pneumonia or hepatitis HCV. The most risky period includes the first six and particularly the first three months from start of cART. The causes of death in monitored patients are AIDS-related and the greatest effect on reducing the lethality is early diagnosis and timely cART.

CONFLICT OF INTEREST

All authors declare that they have not conflict of interest.

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Смертность среди ВИЧ/СПИД-инфицированных пациентов, находившихся под наблюдением в Клинике инфекционных заболеваний при Университетской больнице „Св. Георги“ - Пловдив, 2010-2014

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Введение: Введение комплексной антиретровирусной терапии привело к значительному снижению смертности среди ВИЧ(+) – инфицированных пациентов, но она всё ещё продолжает оставаться неприемлемо высокой, особенно среди отдельных групп пациентов.

Целью настоящей статьи является исследование смертности среди ВИЧ/ СПИД – инфицированных пациентов, летального исхода и смертности при коинфекции, а также причин и предикторов летального исхода, которое направлено на возможность раннего диагностирования и на выбор подходящей терапии.

Материалы и методы: Исследование охватывало 53 пациентов, умерших от ВИЧ/ СПИДа, находившихся под наблюдением в клинике инфекционных заболеваний при Университетской больнице „Св. Георги“ – Пловдив в течение периода 01.01.2010 – 31.12.2014. Методы исследования включали в себя клинический анализ, лабораторные исследования, микробиологические и серологические тесты (HCV, HBV, Токсоплазма), ELISA, PCR. Обработка статистических данных была осуществлена с применением дескриптивной статистики, t-теста Стьюдента, метода Ван дер Вардена, регрессионного анализа (логистической регрессии).

Результаты: За время периода наблюдения было прослежено 316 пациентов с ВИЧ/ СПИД-ом, 53 из которых с летальным исходом. Смертность составила 16.7% для всей группы; среди принимавших интравенозные наркотики – 13.8%; среди ВИЧ-инфицированных с коинфекцией M. tuberculosis – 46%, среди ВИЧ/ HCV –инфицированных – 17.8%. Летальный исход и смертность ВИЧ(+)-инфицированных пациентов с коинфекцией среди населения различного возраста, пола, длительности проведения АРТ и степени иммунодефицита (в соответствии с CD4, VL) были сопоставлены с летальным исходом и смертностью пациентов с аналогичными состояниями среди общего населения.

Выводы: Летальный исход среди пациентов с ВИЧ/ СПИДом чаще всего ассоциируется с коинфекцией M. tuberculosis и ВИЧ/ HCV. Предикторами летального исхода являются туберкулёз лёгких, иммунодефицит на продвинутой стадии с VL > 500 000с/μL и CD4 <100/mm³, отсутствие или нерегулярное проведение антиретровирусной терапии.