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# Lung Cancer in the Presence of Human Immunodeficiency Virus

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***Abstract***

***Background:*** *People living with human immunodeficiency virus (HIV) have a greater chance of developing malignancies. Success of antiretroviral therapy has led to non-HIV-associated cancers becoming the most common cause of death from acquired immune deficiency syndrome, and the most common of them in developed countries is the lung cancer.*

***Aim:*** *To research nosological characteristics of lung cancer in the context of HIV infection, HIV-associated risk factors during antiretroviral therapy, and compare them with global trends.*

***Materials and Methods:*** *Retrospectively analyzed the medical documentation of 98 patients with lung cancer and HIV-infection, who received specialized treatment in Saint Petersburg from 2008 to 2018.*

***Results:*** *The researched population was dominated by patients of young (18–44 years old) and middle (45–59 years old) age groups, 45.9% and 42.9%, respectively, and 11.2% of elderly patients (60–71 years old), $p < 0.001$. This is in accordance with the global data of earlier incidence of lung cancer in people living with HIV. Adenocarcinomas were the most common histological subtype of lung cancer, as in the general population ($p < 0.001$).*

*There was no statistical significance between high viral load and lung cancer, which can indicate the absence of a direct mechanism of HIV-carcinogenesis (90.8% of patients with low and medium viral load, $p < 0.001$). Nevertheless, the prevalence of 4th stage of HIV infection among lung cancer patients ($p < 0.001$) indicates a history of inflammatory diseases, including pulmonary diseases, as a result of induced immunosuppression due to CD8+-lymphocyte dysfunction and the formation of a tumor microenvironment. It can be a prognostic unfavorable factor in the occurrence of lung cancer in this group of patients, as well as of indirect mechanism of viral carcinogenesis.*

*The presence of elderly patients (11.2%, the eldest patient of 71 years) indirectly indicates an increase of life expectancy among this category of patients in Russia.*

***Conclusion:*** *The mechanisms behind increased risk of lung cancer among HIV-infected people remain largely unclear, and this can be the area for active research. HIV-infected patients with lung cancer are younger than HIV-negative patients, and have more advanced stages of cancer with a prevalence of adenocarcinoma. The lung cancer prognosis of survival in HIV-infected people is much worse than that in patients without HIV-infection, but it is not fully known whether this is due to a more aggressive course of the disease, disparities in treatment, treatment resistance, or a greater risk and toxicity of therapy.*

**Keywords:** Lung Cancer, Human Immunodeficiency Virus, HIV-Non-Associated Cancer, Aids-Non-Associated Cancer

## List of Abbreviations

**MN**-Malignant Neoplasms,
**HIV**-Human Immunodeficiency Virus,
**ART**-Antiretroviral Therapy,
**AIDS**-Immune Deficiency Syndrome,
**NADC**-Non-AIDS-Definig Cancers,
**RR**-Relative Risk,
**CI**-Confidence Interval,
**WIHS**-Women's Interagency HIV Study,
**MACS**-The Multicenter AIDS Cohort Study,
**START**-Strategic Timing of ART,
**FAS** population - Full Analysis Set,
**N**-Non-Missing Indicator Value,
**Mean**-Arithmetic mean,
**Me**-Median,
**IQR**-Interquartile Range as Two Numbers,
**Min**-Minimum,
**Max**-Maximum Values,
**n**-Absolute Number of Observations,
**FWER**-Family-wise Error Rate,

## Introduction

According to the GLOBOCAN database, there have been 19 million cases of malignant neoplasms (MN) recorded in 2019. Among them lung cancer has been the most prevalent in the last few decades. The World Health Organization estimates that more than 2.1 million new cases of lung cancer were reported in 2019, representing about 12% of all MNs.

In 2019, 640,391 new cases of MNs were detected in the Russian Federation (348,894 and 291,497 in male and female patients, respectively). The increase in this indicator compared to 2018 was 2,5% (1,2% in 2017). At the same time the increase of lung cancer in the Russian Federation in 2000-2019 was 6,22%. Lung cancer takes the first place in morbidity among men and the seventh place among women (3,8%) [1].

More than one million people living with the infection caused by human immunodeficiency virus (HIV) were registered in the country in 2019, according to the Federal Scientific and Methodological Center for AIDS Prevention and Control. Russia ranks 3rd after South Africa and Nigeria in speed of new HIV infections rise per unit of time (incidence growth rate). In 2019 there were about 37.9 million people living with HIV.

57.420 cases of HIV infection were registered among St. Petersburg citizens including those who died over the entire period of observation as at 01.01.2019. In 2018 only 2892 cases were detected, of which 2628 were citizens of the Russian Federation: residents of St. Petersburg - 1647, people without a definite place of residence - 79, non-residents - 902 [2].

The widespread use of modern antiretroviral drugs has led to a significant increase in life expectancy, including in the elderly, among people infected with HIV. This became possible primarily because successful antiretroviral therapy (ART) directly leads to a reduction in mortality from causes associated with HIV or acquired immune deficiency syndrome (AIDS). Thus, as the age of the deceased increases, the proportion of MNs among all causes of death in HIV-infected persons also increases [3]. This applies not only to three AIDS-associated cancers (AIDS-defining cancers), such as Kaposi's sarcoma, cervical cancer, and non-Hodgkin's lymphoma, but also to such pathologies as Hodgkin's disease and anal canal cancer. Their manifestation against the background of HIV is so expected that some scientists propose to classify these diseases as AIDS-associated [4, 5]. According to the forecasts of a group of researchers from the National Medical Institute of Maryland, who used the method of statistical modeling, the number of AIDS-associated diseases will sharply decrease in 2030 if the trend in the prevalence of the disease will maintain. At the same time, the number of non-AIDS-associated tumor diseases will increase. Lung cancer, prostate cancer, and liver cancer are expected to be the most common by that time [6].

Consequently, non-AIDS-definig cancers (NADC) can also be attributed to significant mortality factors in HIV-infected patients. Currently, in industrialized countries, they cause more deaths than NADC, hepatitis C or cardiovascular disease. This is the second most frequent (after AIDS) cause of death in HIV-infected patients [7, 8]. There is an obvious connection between the causes of deaths and the number of CD4-cells at the time of death, which is closely related to the level of CD4-cells at the time of ART appointment. The study by N.G. Zakharova et al. showed: when CD4-lymphocyte concentration exceeds 200 cells/μL, the causes of death not related to HIV infection prevail. At the same time, AIDS as a cause of death is associated with CD4-lymphocyte concentration less than 50 cells/μL [9].

The D: A:D 3 study (with 176,775 participants and 880 cases of NADC between 2004 and 2010) showed the three most common NADC: lung cancer (n=140; 0.79/1000 persons/year), non-Hodgkin's lymphoma (n=112; 0.63/1000 persons/year), and anal canal cancer (n=79; 0.45/1000 persons/year) [10].

In 1984, L.E. Irwin et al. were the first to describe a case of metastatic non-small cell lung cancer in an HIV-infected man [11]. Since then, studies conducted before or during the ART era have shown that the risk of developing lung cancer is still higher among HIV-infected patients compared to the general population.

Lung cancer is the most common cause of death from MN worldwide for both men and women; it causes approximately 1.2 million deaths each year. It is also the third most common MN among HIV-infected individuals, second only to Kaposi's sarcoma and non-Hodgkin's lymphoma [12]. There is evidence that the risk of developing non-small cell lung cancer among HIV-infected patients is 3 times higher than among the general population of the same age. At the same time, there is no unambiguous data in the literature on the increased incidence of small cell lung cancer among people living with HIV [13, 14].

Lung cancer is diagnosed on average ten years earlier among HIV-infected patients, even with an adjustment for smoking. In the works of N. Rihana et al. and J. L. Marcus et al. connection was established between the presence of HIV infection and the risk of death (compared to HIV-negative patients) [15, 16].

There are several key questions regarding lung cancer in the setting of HIV infection. HIV-infected patients with lung cancer are younger than HIV-negative patients and have more advanced disease. There is a multifactorial increased risk of lung cancer in HIV-positive patients (these patients are often avid smokers, but even with adjustment for smoking, the risk is still higher). (Relative risk (RR) 2.2 (95% CI 1.3-3.6) to 8.5 (95% CI 4.3-16.7) [17]. Finally, the lungs of patients with HIV are weakened by various diseases such as chronic obstructive pulmonary disease,

emphysema, bronchiectasis, interstitial lung disease, pneumocystosis or other infections that cause chronic inflammation and set the stage for changes in the tumor microenvironment, and thus contribute to an increased risk of lung cancer. Several prognostic factors have been identified. Some are common to lung cancer (functional status and TNM stage) and some are specific to HIV infection: number of CD4, viral load and ART status [18, 19].

Immunodeficiency appears to be an important prognostic risk factor for MN in HIV. Immunosuppression, measured using low number of CD4-lymphocytes as a static indicator, has shown limited association with lung cancer incidence in earlier studies such as Women's Interagency HIV Study (WIHS) and The Multicenter AIDS Cohort Study (MACS) [20, 21]. However, when assessing continued exposure, low number of CD4 appears to have a stronger independent association with lung cancer. In one of the largest studies analyzing immunological risk factors for non-AIDS-related cancers, M. Hleyhel et al. found that HIV-infected individuals whose CD4 concentration did not recover to at least 500 cells/mL during treatment were at increased risk of developing lung cancer [17, 22, 23].

Inflammation, both local and systemic, has also been investigated as an increased risk factor for cancer in HIV infection. In the same early WIHS/MACS studies, prior pneumonia (even with a 5-year lag) was an independent predictor of lung cancer. HIV-related chronic inflammation in the lung may also play a role in the development of pulmonary MN. Various mechanisms have been associated with chronic inflammation in HIV infection, including CD8-lymphocyte infiltration and their dysregulation, viral disruption of epithelial integrity, and alterations in the lung microbiome, although direct correlations between chronic inflammation and subsequent cancer risk in HIV-infected individuals have not been proven. It has also been suggested that HIV and smoking may have synergistic effects favoring inflammation and further alteration, but this has not been proven yet. Systemic inflammation associated with HIV infection has also been implicated as cancer risk. The concentration of pro-inflammatory cytokines has been found to be elevated prior to the diagnosis of lung cancer in HIV-infected individuals [24-27].

Direct viral oncogenesis is also considered as one of the main mechanisms of lung cancer development, particularly in HIV infection. The lung can serve as a kind of compartment where HIV activity may not reflect systemic viral suppression. This theory is supported by the work of S.K. Cribbs et al. who showed that 70% of 23 HIV-infected nonsmoking patients with ART-mediated viral suppression had measurable proviral DNA in alveolar macrophages [28]. However, there is no clear evidence for a direct oncogenic effect [29]. It has been shown that HIV viral proteins may have some direct oncogenic activity, but these data in mouse models did not support a direct tumorigenic effect.

No discernible association between ART exposure and increased risk of lung cancer has been found. However, the international Strategic Timing of ART (START) trial found a significant reduction in overall cancer risk with immediate ART initiation (compared with delayed initiation) and a trend toward a lower risk of HIV-unassociated MN (15% of patients in the study had lung cancer) [30]. In the previously mentioned D:A:D study, researchers evaluated toxic effects on cancer cell formation and found no general or class-specific increased risk associated with ART [8]. M. Bruyand et al. suggested that cytochrome P450 inhibitors (such as protease inhibitors) may affect the metabolism of carcinogens in the lungs and thereby increase the risk of cancer development, but found no statistically significant evidence in the French hospital database [31].

There is evidence that patients with HIV are under-treated for lung cancer, and HIV is also associated with higher mortality from the disease. This is supported by the results of a group of researchers from the United States who analyzed population data from HIV-infected and HIV-uninfected subjects diagnosed with MN from 1996 to 2011 (J.L. Marcus et al. [16]). The baseline cohorts consisted of 24,768 HIV-infected and 257,600 demographically matched HIV-uninfected subjects. There were 80 and 507 cases of lung MN among HIV-infected and HIV-uninfected subjects, respectively. Other HIV-unassociated MNs were also analyzed, but compared with HIV-negative subjects, a statistically significant reduction in five-year survival (10% vs. 19%, p=0.002) was found only for lung cancer.

Despite the fact that HIV infection is a criterion for exclusion from many clinical trials of oncologic diseases, especially in our country, the relevance of treatment of this group of patients continues to increase every year.

The aim is to evaluate the nosologic features of lung cancer in the setting of HIV infection, the influence of HIV-associated risk factors on the background of ART.

## Materials and Methods

### Methods of Outcome Registration

A p value <0.05 was taken as the level of statistical significance. The p value is presented in the report to the nearest hundredth if its value is higher than 0.05, and to the nearest thousandth if p <0.05. Quantitative traits are described using the number of observations with non-missing indicator value (N), arithmetic mean (Mean), standard deviation (SD), 95% CI for the mean, median (Me), interquartile range as two numbers (IQR), minimum (Min) and maximum values (Max). Description of qualitative traits is presented as absolute number of observations (n), percentages (%) and 95% CI for the proportions.

### Statistical Analysis

For statistical analysis, the programming language for statistical calculations R version 4.1.1 (R Core Team, Austria) was used.

The selection of criteria for comparisons of patients by the values of indicators between groups was performed according to the type of indicator. For quantitative indicators, the choice of criteria was based on the results of testing the normality of distribution using the Shapiro-Wilk criterion: in the case of normal distribution, the comparison was performed using Student's t-criterion for unrelated samples; in the case of distribution other than normal - using the Mann-Whitney U-criterion.

Comparisons between patient groups on qualitative measures were performed using the $\chi 2$ criterion (with Yates correction for expected frequencies of measures less than 10 but more than 5) or Fisher's exact test (for expected frequencies of measures $\leq 5$).

Since the FAS population and the patient groups planned for allocation overlapped in all or part of the patient population, the family-wise error rate (FWER), i.e., the probability of making one or more errors of the first kind, was controlled for in the case

of comparisons on indicators in these groups.

The Sidak step-down method was used to correct FWER. Using this method, the corrected first-order error rate for testing each hypothesis is equal to

where α0 is the initially set level of statistical significance, m is the number of hypotheses to be tested, j is the ordinal number of the hypothesis in the ascending ordered series of p levels.

According to J. Stevens et al. Shidak's method controls FWER well even if the tests and samples are dependent (the FAS population and the distinguished groups can be considered related due to their partial or complete overlap) [32].

The search for dependencies of different indicators on each other was performed using conjugacy tables and using correlation and linear regression analysis in identifying relationships of qualitative indicators

## Results

### Objects (Participants) of the Study

For statistical analysis, all patients included in the study (FAS population) were studied. This population was used to describe all patient characteristics.

### Main Results of the Study

The analysis was performed in patient groups. When examining the sex distribution of patients with HIV, it was found that the overall population was predominantly male (69.39% vs. 30.61% female, $p < 0.001$) (see Table 1). Examining the age at the time of lung cancer detection (see Table 2), we found that the FAS population was dominated by young and middle-aged patients (45.9% and 42.9%, respectively, vs. 11.2% of elderly patients, $p < 0.001$). This is consistent with worldwide data on the earlier occurrence of lung cancer in HIV-infected individuals. Moreover, the youngest patient included in the study was 26 years old (MIN) and the oldest (MAX) was 71 years old (see Table 5).

## Tables& Figures

**Table 1: Gender distribution in patients with human immunodeficiency virus**

| Population | Sec | Frequency (fraction);95%CI |
|---|---|---|
| FAS | male | 68/98 (69,4%); 59,1–78,1 |
| | female | 30/98 (30,6%); 21,9–40,9 |

**Note: Criterion χ2, p <0,001.**

**Table 2: Age distribution in patients with human immunodeficiency virus at the time of lung cancer detection**

| Population | Age, years | Frequency (fraction);95%CI |
|---|---|---|
| FAS | Yound (18–44) | 45/98 (45,9%); 35,9–56,3 |
| | Middle (45–59) | 42/98 (42,9%); 33–53,2 |
| | Elderly (60–74) | 11/98 (11,2%); 6,0–19,6 |

**Note: Criterion χ2, p <0,001.**

**Table 3: Viral load distribution in patients with human immunodeficiency virus**

| Population | Viral load | Frequency (fraction);95% CI |
|---|---|---|
| FAS | low ( <10 тыс. copies/ml) | 72/98 (73,5%); 63,4–81,6 |
| | middle (from 10 to 50 thousand copies/ml) | 17/98 (17,3%); 10,7–26,6 |
| | high ( >50 copies/ml) | 9/98 (9,2%); 4,5–17,2 |

Note: Criterion χ2 with Yates's correction; p <0,001.

**Table 4: Tobacco smoking distribution in patients with human immunodeficiency virus**

| Population | Parameter | Frequency (fraction);95%CI |
|---|---|---|
| FAS | Smokers | 79/98 (80,6%); 71,1–87,6 |
| | Nonsmokers | 19/98 (19,4%); 12,4–28,9 |

Note: Criterion χ2, p <0,001.

**Table 5: Age at the time of lung cancer diagnosis in patients with human immunodeficiency virus**

| Parameter | Age at the time of lung cancer diagnosis in patients with human immunodeficiency virus, full years |
|---|---|
| N | 98 |
| M | 46,68 |
| SD | 9,85 |
| 95% CI | 44,73–48,63 |
| Min | 26 |
| Max | 71 |
| Me | 45 |
| IQR | 39; 52 |

Note. N —number of observations; Mean — arithmetic mean; SD standard deviation — 95%; Min —minimal and Max —maximal indicator values; Me —median; IQR — interquartile range.

The FAS population was dominated by patients with low viral load (see Table 3). The proportions of patients with medium and high viral load were not statistically significantly different (17.3% and 9.2%, respectively, p < 0.001), which characterizes the absence of proven direct viral carcinogenesis.

Examination of cancer stage according to TNM classification (see Table 6) revealed that the frequencies of distribution of patients in the FAS population by tumor stages I-IV were statistically significantly different (p <0.001). In the FAS population, patients with locally advanced MN predominated (82.7% vs. 17.3% of patients with stage IV tumors, p <0.001), but few early stages with good prognostic survival were detected, and the most frequent was stage IIIA (32.7%), which indicates late detection and spread of the tumor process of this malignancy in the context of HIV infection.

**Table 6: Lung cancer stages distribution in patients with human immunodeficiency virus, TNM classification**

| Population | Stage (I–IV) | Frequency (fraction);95%CI |
|---|---|---|
| FAS | IA | 5/98 (5,1%); 1,9–12,1 |
| | IA2 | 1/98 (1%); 0,1–6,4 |
| | IB | 6/98 (6,1%); 2,1–3,4 |
| | IIA | 3/98 (3,1%); 0,8–9,3 |
| | IIB | 17/98 (17,3%); 10,7–26,6 |
| | IIIA | 32/98 (32,7%); 23,7–43,0 |
| | IIIB | 17/98 (17,3%); 10,0–25,5 |
| | IV | 1/98 (1%); 0,1–6,4 |
| | IVA | 8/98 (8,2%); 3,8–15,9 |
| | IVB | 8/98 (8,2%); 3,8–15,9 |

Note: Criterion $\chi 2$ with Yates's correction; p <0,001.

The time of manifestation of lung cancer was calculated as the difference between the date of HIV detection and the date of detection of NADC. The median time to manifestation was 81.7 months with 95% CI 72.14-91.26 months, which is typical for HIV-unassociated MN (see Table 7).

**Table 7: Time of manifestation of human immunodeficiency virus unrelated lung cancer in patients with human immunodeficiency virus**

| Parameter | the manifestation time of lung cancer, month |
|---|---|
| N | 96 |
| Mean | 81,7 |
| SD | 48,29 |
| 95% CI | 72,14–91,26 |
| Min | 0 |
| Max | 227 |
| Me | 83,5 |
| IQR | 43,5; 105,25 |

Note. N —number of observations; Mean — arithmetic mean; SD standard deviation — 95%; Min —minimal and Max —maximal indicator values; Me —median; IQR — interquartile range.

The distribution of patients in the FAS population by tumor histologic type (see Table 8) was statistically significantly different (p <0.001). As in the general population, adenocarcinomas predominated among the histologic types of lung cancer. Given the absence of a statistically significant relationship between the degree of tumor differentiation and survival, we did not analyze this indicator in this group of patients. In the available literature, we did not find a sufficient number of cases of small cell lung cancer in HIV infection (probably due to the extremely aggressive course of the malignant process). In this sample, the incidence of small cell cancer was lower than in the general population (5.1%). Some of them were not subject to any specialized antitumor treatment due to the spread of the tumor process and poor functional status.

**Table 8: Histological types of lung cancer distribution in patients with human immunodeficiency virus**

| Population | Histological type | Frequency (fraction);95%CI |
|---|---|---|
| FAS | Adenocarcinoma | 70/98 (71,4%); 61,3–79,9 |
| | Squamous cell carcinoma | 20/98 (20,4%); 13,2–30 |
| | Atypical carcinoid | 2/98 (2%); 0,4–7,9 |
| | Typical carcinoid | 1/98 (1%); 0,1–6,4 |
| | Small cell lung cancer | 5/98 (5,1%); 1,9–12,1 |

Note: Criterion $\chi 2$ with Yates's correction; p <0,001.

When patients were analyzed by number of CD4-cells at the time of cancer detection (see Table 9), the 95% CI was 343.53-409.89 cells/mL from the range of CD4-lymphocyte concentration at the time of lung cancer onset. This range is characteristic of AIDS-unassociated MN, i.e., immunodeficiency is not the cause of lung cancer manifestation in this group of patients.

**Table 9: CD4-cell level distribution in patients with human immunodeficiency virus at the time of lung cancer detection**

| Parameter | CD4-cell level distribution in patients with human immunodeficiency virus at the time of lung cancer detection, cells/mL |
|---|---|
| N | 98 |
| Mean | 376,71 |
| SD | 167,61 |
| 95% CI | 343,53–409,89 |
| Min | 20 |
| Max | 956 |
| Me | 343 |
| IQR | 274,75; 479,75 |

Note. N —number of observations; Mean — arithmetic mean; SD standard deviation — 95%; Min —minimal and Max —maximal indicator values; Me —median; IQR — interquartile range.

In the FAS population, smoking patients predominated over nonsmoking patients (80.6% vs. 19.4%, respectively, $p < 0.001$) (see Table 4).

**Additional Study Results**

In addition, the stages of HIV infection were analyzed (see Table 10). The prevalence of stage 4 (Russian classification of HIV infection) (85.7%, $p < 0.001$) suggests the presence of previous history of inflammatory diseases, including the respiratory system, as a result of immunosuppression, which may be a prognostic factor for the occurrence of lung cancer in this group of patients together with other predictors. Analysis by stage of HIV infection before lung cancer detection in the group by sex (see Table 11) showed no statistically significant differences between patients of different sexes ($p > 0.05$).

**Table 10: Distribution of patients by stage of infection caused by human immunodeficiency virus**

| Population | Study and fase of HIV | Frequency (fraction);95%CI |
|---|---|---|
| FAS | 2A | 2/98 (2%); 0,4–7,9 |
| | 2Б | 1/98 (1%); 0,1–6,4 |
| | 3 | 11/98 (11,2%); 6,0–19,6 |
| | 4A (progression) | 8/98 (8,2%); 3,8–15,9 |
| | 4A (remission) | 33/98 (33,7%); 24,6–44,0 |
| | 4Б (progression) | 1/98 (1%); 0,1–6,4 |
| | 4Б (remission) | 6/98 (6,1%); 2,5–13,4 |
| | 4B (progression) | 19/98 (19,4%); 12,4–28,9 |
| | 4B (remission) | 17/98 (17,3%); 10,7–26,6 |

Note: Criterion $\chi 2$ with Yates's correction; $p < 0,001$.

**Table 11: Human immunodeficiency virus stages distribution at the time of lung cancer diagnosis by gender**

| Group | Study and fase of HIV | Frequency (fraction);95%CI |
|---|---|---|
| Male (n=68) | 2A | 1/68 (1,5%); 0,1–9% |
| | 2Б | 0/68 (0%); 0–6,7% |
| | 3 | 9/68 (13,2%); 6,6–24,1% |
| | 4A (progression) | 7/68 (10,3%); 4,6–20,7% |
| | 4A (remission) | 20/68 (29,4%); 19,3–41,9 |
| | 4Б (progression) | 1/68 (1,5%); 0,1–9,0 |
| | 4Б (remission) | 4/68 (5,9%); 1,9–15,1 |
| | 4B (progression) | 14/68 (20,6%); 12,1–32,5 |
| | 4B (remission) | 12/68 (17,6%); 9,8–29,2 |

| | | |
|---|---|---|
| Female (n=30) | 2A | 1/30 (3,3%); 0,2–19,1 |
| | 2Б | 1/30 (3,3%); 0,2–19,1 |
| | 3 | 2/30 (6,7%); 1,2–23,5 |
| | 4A (progression) | 1/30 (3,3%);0,2–19,1 |
| | 4A (remission) | 13/30 (43,3%); 26,0–62,3 |
| | 4Б (progression) | 0/30 (0%); 0–14,1 |
| | 4Б (remission) | 2/30 (6,7%); 1,2–23,5 |
| | 4B (progression) | 5/30 (16,7%); 6,3–35,5 |
| | 4B (remission) | 5/30 (16,7%); 6,3–35,5 |

Note. Fisher's exact test; p =0,623.

**Adverse Events**

Two patients (2.04% of the FAS population) had HIV after tumor detection; data from these patients were included in the time-to-manifestation analysis. No other adverse events were noted.

## Discussion

**Summary of the Main Result of the Study**

According to the estimates of different authors, lung cancer was reported in HIV-infected patients 1.6-4.0 times more frequently than in the general population. MN is diagnosed among these patients on average ten years earlier, and the extent of tumor spread at the time of MN detection is often higher than in the group of HIV-uninfected patients. Young and middle-aged patients prevailed in the FAS population (45.9% and 42.9%, respectively, vs. 11.2% of elderly patients, $p < 0.001$), which corresponds to the worldwide data on the earlier occurrence of lung cancer in HIV-infected patients. Moreover, the youngest patient included in the study with atypical carcinoid tumor was 26 years old (MIN) and the oldest was 71 years old (MAX). The presence of elderly patients in the FAS population, although in a smaller proportion (11.2%), indicates an increase in life expectancy among this category of patients in Russia, and the predominance of younger patients (88.8%, $p < 0.001$) makes this problem socially and economically significant. In the study, men predominated among HIV-positive patients (69.39% vs. 30.61% of women, $p <0.001$), as in lung cancer without HIV infection, despite the fact that smoking was more prevalent among HIV-positive women.

**Discussion of the Main Result of the Study**

The widespread use of modern antiretroviral drugs has led to a significant increase in life expectancy and including older individuals among people infected with HIV [7]. This is primarily due to the fact that ART successes directly translate into reduced mortality from HIV/AIDS-associated causes.

In 2006, the French ONCOVIH study estimated that the incidence of cancer among HIV-infected people was 14 cases per 1000 people [33]. Today, AIDS-unassociated MNs account for about one third of all MNs in HIV-infected patients. Thus, their incidence is comparable to that of lymphoma and Kaposi's sarcoma.

The increased risk of lung cancer in HIV-positive individuals is multifactorial. As in the general population, smoking serves as a major risk factor for lung cancer. HIV-infected people are often avid smokers, especially in Russia, as confirmed in the work of M.S. Shiels et al. on study groups (80.6%; $p < 0.001$). Some early data from American authors (K.P. Reddy et al.) suggest that HIV-positive smokers get lung cancer more often than HIV-negative smokers, the need for less exposure to smoking through a complex increase in mutational load is suggested [34, 35].

Immunodeficiency, especially number of CD4 lymphocyte, seems to be an important prognostic risk factor for HIV-associated MN, despite the fact that in the analysis population CD4 cell concentration >200 cells/mL is characteristic of AIDS-unassociated MNs. M. Hleyhel et al. found that HIV-infected people whose CD4 concentration did not recover to at least 500 cells/mL during treatment were at increased risk of developing lung cancer, which makes earlier prescription of ART one of the options for secondary prevention in this risk group [23]. The same is true for the CD4/CD8-lymphocyte ratio. Presumably, a ratio level <1 is a predictor of lung cancer occurrence and is inversely proportional to stage at the time of tumor disease detection.

Finally, the lungs of patients with HIV are more prone to various diseases such as chronic obstructive pulmonary disease, emphysema, bronchiectasis, interstitial lung disease, pneumocystosis, or other infections that contribute to an increased risk of lung cancer, and the presence of HIV stage 4 in the study groups is possibly indicative of past respiratory infections (85.7%; $p<0.01$).

ART does not statistically significantly increase the risk of lung cancer. Data from E.A. Engels et al. show that in a study involving 5,238 HIV-infected patients living in urban areas of Baltimore, Maryland, lung cancer was registered 1.6 times more often than in the general population. HIV-infected patients are diagnosed with lung cancer on average ten years earlier, and the degree of tumor spread at the time of MN detection is often higher than in the group of HIV-uninfected patients [13]. As for the histotypes of pulmonary MNs, adenocarcinomas of various degrees of differentiation predominate in this group of patients (71.4%), as in the general population, but the incidence of neuroendocrine tumors is lower. There are limited published data on the prevalence of clinically significant oncogenic mutations in HIV-infected individuals. In a study by P. Crequit et al. the largest cohort to date was described, in which they found 3.3% of EGFR gene mutations and 11.5% of KRAS gene mutations in 63 HIV-infected patients with lung cancer [36]. The presence of KRAS mutation and CD4 concentration <200 cells/mL are poor prognostic factors in survival analysis: hazard ratio (HR): 24.0 [4.1140.2], p =0.0004; HR: 3.1 [1.37.5], p =0.01, respectively.

Mortality from lung cancer remains extremely high in all countries to this day, and it is even higher in patients with HIV. For example, G.D. Kirk et al. studied lung cancer mortality in a cohort of 2,086 injecting drug users and compared the risk in people with and without HIV infection [37]. After adjusting for age, sex, smoking status, and ART, lung cancer mortality was still 250% higher.

## Study Limitations

The study procedure was complicated by working with a large number of primary medical records to select patients with lung MNs among HIV-infected people for the FAS population in St. Petersburg from 2008 to 2018.

The study design did not include the analysis of correlation of CD4/CD8 index indices with the course of lung cancer in the setting of HIV infection, as well as the determination of survival during co-administered antitumor therapy and HIV treatment, which needs further investigation. These results can be used to develop targeted lung cancer prevention measures, determine prognosis and optimize treatment among this group of patients.

## Conclusions

With the progression of ART, the survival of patients with HIV has increased significantly, and as life expectancy has increased, so has the incidence of diseases that are partially associated with aging, including lung cancer. In addition, the prognosis of patients with HIV and lung cancer, which was quite sobering in the era without ART, is now virtually similar to that without HIV with a multidisciplinary approach. The mechanisms of the increased risk of lung cancer among HIV-infected individuals remain largely unclear and require active research. HIV-infected patients with lung cancer are younger than HIV-negative patients and have more advanced stages of cancer with a predominance of glandular type cancers. HIV is also associated with higher mortality from lung cancer. The survival prognosis of HIV-infected individuals with lung cancer is much worse than that of HIV-uninfected individuals, but it is not fully known whether this is due to a more aggressive disease course, disparity in treatment, unresponsiveness to therapy, or greater risk and toxicity of treatment.

The results of the study suggest that screening and prevention of lung cancer in people with HIV infection is becoming an area of increasing clinical interest, and comprehensive treatment should necessarily be multidisciplinary, in collaboration with an infectious disease physician. This group of patients is more and more socially important for our country: in Russia, only recently the diagnosis of HIV infection has ceased to be associated with intravenous drug use or homosexuality

## Ethical Review

The study was approved by the Ethical Committee of the Federal State Budgetary Educational Institution of Higher Education "Pavlov First Saint Petersburg State Medical University" of the Ministry of Health of the Russian Federation, Protocol No. 2 of 21.03.2021.

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