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REZUMATUL TEZEI DE DOCTORAT

Analysis of the relationship between HIV infection and neoplastic diseases

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The doctoral thesis has:

General part consisting of four chapters summing 62pages
Personal part consisting of four chapters summing 129 pages
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90 figures
99 tables

Note: Tables and figures inserted in the summary of the doctoral thesis retain the original numbering from the thesis. abelele și figurile inserate în rezumatul tezei de doctorat păstrează numerotarea originală din teză. The table of contents from the summary retains the structure and page number from the thesis.

Introduction

With an average of two million deaths caused by AIDS complications worldwide in the last 11 years (according to official data from UNAIDS), HIV infection represents a real problem affecting the whole world.

In the last 30 years the HIV infection has become one of the main problem that concern both scientific community and the entire public opinion. The evolution of the treatments and their increasing availability has led to an increased survival ofpatients infected with human imunodeficinecy virus (HIV). This improvement in survival for those infected leads to a higher demand for medical services specific for chronic diseases, services adapted to the special needs of immunodepresed patients.

Since the first cases described in the literature, an increased frequency of certain types of malignancies was observed, which were later recognized as AIDS-defining malignancies. With the availability of highly active antiretroviral treatment (HAART), the incidence and prevalence of these cancers in human immunodeficiency virus-infected patients have undergone significant changes. At the same time, there is a growing proportion of disorders apparently unrelated to HIV, such as cardiovascular disease with slowly progressive organ failure and other chronic conditions. Recent research identifies an increased incidence of non-AIDS defining malignancies in HIV infected patients.

In this paper I intend to analyse the influence HIV infections has on the incidence of malignancies in patients that undergo HAART treatment.

The secondary objectives of this paper are:

- analysis of the incidence of different types of malignancies in general population from Constanta County;
- a descriptive analysis of medical and demographical indicators of HIV infected patients under treatment;
- death risk assessment and calculation of mortality indicators in HIV infected patients under treatment;
- analysis of medical and demographic characteristics of HIV patients diagnosed with malignancies;
- identification of some factors that influence the development of malignancies in HIV positive patients;
- making proposals to improve the legal framework for monitoring and preventions of HIV, according to the results of the research;

- making proposals to improve HIV positive patients' management, according to the results of the research.

Thus, through the objectives and the approach of the theme, the srudy brings new data relating to neoplastic pathology of HIV infected patients.

Another particularity of the study, in an international context results from the specific aspects of HIV infection in the studied area, represented by the circulation of an extremely rare subtype of virus and the typology of the epidemic. The results bring an important contribution to the study of HIV infection and its association with neoplastic diseases, and the correlation with existing data at a global scale offer a better overview.

General Part

The general part is divided into four chapters. Within the chapters I synthesized existing data related to the role that viruses have in the emergence of neoplastic diseases in humans,the way the HIV epidemic has evolved at global and national level, aspects related to the particularities of the evolution and known aspects related to the role the virus plays in the development of malignancies in humans.

Chapter I – The role of the infectious agents in oncogenesis

The chapter is divided into subchapters that analyse aspects of epidemiology, structure and role that some viruses have in the occurrence of malignancies in humans. I analysed data about Epstein-Barr virus, Hepatitis B virus, Hepatitis C Virus, Human Herpes Virus type 8, Human Papillomavirus, Human T-Cell Lymphotropic Virus Type 1.

Chapter II – Epidemiological aspects related to HIV infection

In this chapter I re-evaluated data on HIV infections from the first reports at global and national level. The importance of this reassessment is given by the description of how first HIV infection cases were discovered, case series of rare cancers in young adult, homosexual men.

Next subchapter describes, using the most recend epidemiological data available, the evolution of the HIV infection at global and national level. This information has the purpose of highlighting the spread of the infection,

features related to specific aspects from Romania, namely F1 subtype, subtype globally rare and a large cohort of long term survivors.

At the end of the chapter I highlighted the major role that the introduction of highly actie antiretroviral therapy had by modifying the evolution of the natural course of infection.

Chapter III - Human Immunodeficiency Virus infection

The third chapter is mainly aimed at describing in detail the human immunodeficiency virus, morphology, genetic aspects, mode of transmission, replication cycle. A separate chapter is the natural evolution of the infection and analysis of clinical and immunological classifications used in medical practice now.

Chapter IV - The relationship between malignancies and HIV infection

The last chapter of the general part is an analysis of the known and demonstrated to date aspects on the relationship between neoplastic diseases and HIV infection. In terms of neoplasia analysed, these are considered to be Aids defining respectively non-AIDS defining malignancies.

AIDS-defining malignancies are Kaposi's sarcoma, non-Hodgkin lymphoma and cervical cancer. These were recognised from the beginning of the epidemic as being widespread among HIV positive patients.

Among non-AIDS defining malignancies I analysed anal cancer, genital cancers, skin cancers, pulmonary cancer, hepatic cancer. For these type of malignancies some studies offer evidence of a variable incidence over time, with increases of the incidence following the introduction of HAART therapy, and in some cases a higher incidence in patients that are not taking specific treatment.

Special Part

The special part has four chapters, Material and Method, Results, Discussions and Conclusions.

Material and method

The study of incidence for main types of malignancies in general population

To study the incidence of cancers in Constanta county I did an observational study between 2007-2014. The source of information is the Report of the main health indicators for Constanta county during 2007-2014.

Evaluated indicators are:

- Crude incidence rate – the number of new cases that appear in a population in a certain period of time. In this paper I report the incidence for 100,000 persons and the time frame in 1 year, if not specified otherwise. In the text I used person-year measurement to report incidence rates in general population and patient-year for reportind incidence rates in HIV infected patients. For cancers specific only for specific groups (cancers that appear only for one gender for example), I calculated the incidence considering only population at risk. For breast cancer I approximated that all the cases were registered in females. This decision was taken based on 2013 and 2014 reports where there were no cases of breast cancers recorded in men and data from literature that indicate an incidence smaller thant 1 case/100,000 person-years. Thus the exclusion of men from population at risk offers a better estimate and a better image on the risk to develop breast cancer.
- Specific incidence for urban environment – incidence rate for new cases of cancer in urban population in a certain period of time for people living in urban areas.
- Specific incidence for rural environment – incidence rate for new cases of cancer in rural population in a certain period of time for people living in rural areas.
- Specific gender incidence calculated for 2013 and 2014 represents the number of new cases of neoplastic diseases in male, respectively female population.

To calculate confidence intervals, I used specific statistical methods for Poisson distributions.

The study of the HIV positive population

To calculate malignancies incidence in HIV infected population I used a cohort study. I analysed a lot of 566 HIv positive patients that met the

inclusion and exclusion criteria of the study. New diagnosis of cancer was evaluated at regular intervals.

Information was gathered from medical records of the Infectious Diseases Hospital, respectively Excelence Centre from Constanta within Baylor foundation. I considered the year 2007 as the first year of the study and ended the study in 2014. Thus information from a long period of follow up was obtained.

Inclusion criteria:

- Patient with confirmed HIV infections,
- Patients ues antiretroviral treatment.

Exclusion criteria:

- Previous diagnosis of a malignancy,
- Lack of compliance.

At the inclusion in the study the following information was gathered:

- Age;
- Gender;
- Environment background,
- CD4+ lymphocyte count;
- Clinical and immunological stage of disease.

During subsequent evaluations:

- New diagnosis of malignancies;
- Survival.

To analyse the incidence of neoplastic diseases I use incidence ratio by dividing the number of new identified case to the patient-years unit. This method offers a good estimation because the time factor is integrated in the calculation and, at the same time, allowed me to use all subjects from the study, for each patients the period at risc being calculated individually and by summing all I obtained the total number of patient-years.

To calculate confidence intervals, I used statistical methods specific for Poisson distributions.

Results

Neoplastic diseases incidence in general population

During the studied period of time there was a significant variation of incidence for all malignancies in Constanta County. The highest incidences were in 2008 followed by the one in 2014 with values of 346.66

cases/100,000 person-years, respectively 346,01 cases/100,000 person-years. The lowest incidence was in 2011 with a value of 298,79 cases/100,000 person-years. Looking at figure 12 we can notice the variation of incidence for all malignancies.

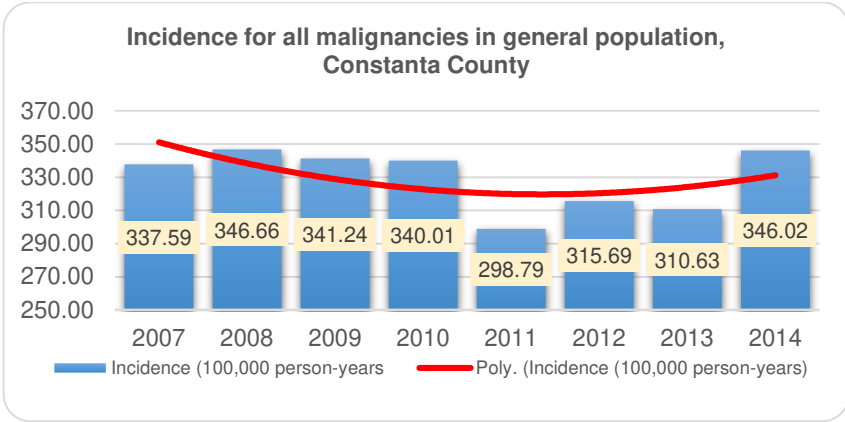

Figura 12 Incidence for all malignancies in general population, Constanta County

A possible explanation for te higher rates seen especially for 207-2010 time frame, followed by a decrease of the incidence can be explained by a better health care during 2007 and 2008 due to the National Program for Assessment of Health Status in Primary Health Care.

In 2014 an important increase of the neoplastic diseases incidence was observed, with a value of over 346 new cases per 100,000 person-years.

In the following table I resumed the average values of incidences for all malignancies represented as crude rate and specific rates based on gender and background. The value of 338.85 cases/100,000 person-years represents the average incidence for all malignancies for the whole period of the study. (Table VI)

Table VI Malignancies incidence for the studied period

	Incidence 100,000 person-years	Confidence Interval 95%
Total	338,85	333,99 – 343,76
Urban	302,89	297,36 – 308,50
Rural	418,31	408,66 – 428,13
Male	407,08	391,19 – 422,69
Female	253,47	241,18 – 265,53

Characteristics of the patients sample

Repartition according to gender

From the total of 566 patients included in this study, 255 were females and 311 males.

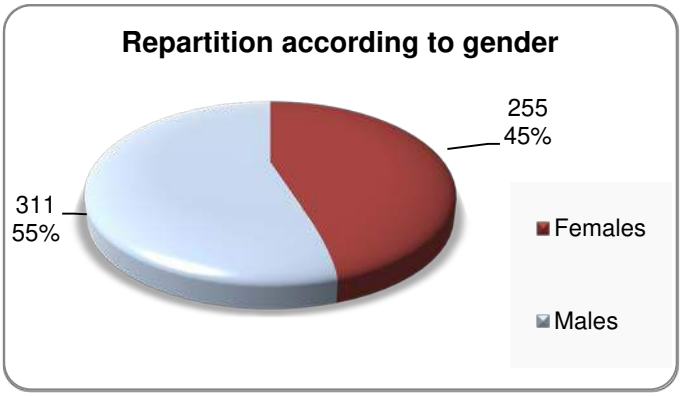

Figura 42 Repartition according to gender

Repartition according to background

Most of the patients have an urban background, total number being 389. Almost one third of the patients live in rural areas.

Although at first sight this aspect seems to indicate a higher infection prevalence for the urban area, if we compare the data with official information from the 2011 census, we notice the fact that this distribution is in concordance with the distribution of the general population for Constanta County, which has a proportion of 68.85% people living in urban areas. In figure 43 I graphically represented the distribution according to background.

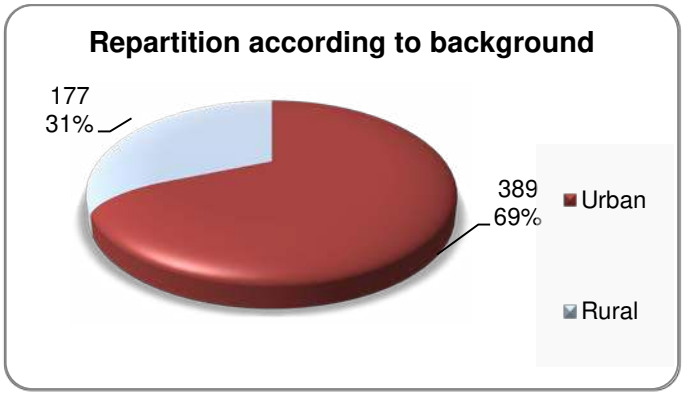

Figura 43 Repartition according to background

Study of the patients according to age

Average age at enrolment is 25.79 years with a standard deviation of 10.86 years. The median is 20 years and the mode is 19 years. This is in concordance with the epidemiological profile of HIV infection in our country, namely with a large cohort of children infected in the last years of the 1980's decade and beginning of the 1990's (Table XXI).

Table XXI Descriptive sttistical analysis of the sample according to age

N	566
Media	25.79
Eroare Standard a Mediei	.456
Mediana	20.00
Modul	19
Valoare Minimă	18
Valoare Maximă	62
Amplitudinea Variației	44
Abaterea Standard	10.860
Varianța	117.940
Asimetria	1.518
Eroarea Standard a Asimetriei	.103
Boltirea	1.100
Eroarea Standard a Boltirii	.205

Analysing the distribution of age groups, at the start of the study, it becomes obvious that most of the patients are young, with ages less than 20

years. These represent approximately 41% of the total number of cases, and patients with an age lower than 30 years represent almost three quarters from the total (Figure 47).

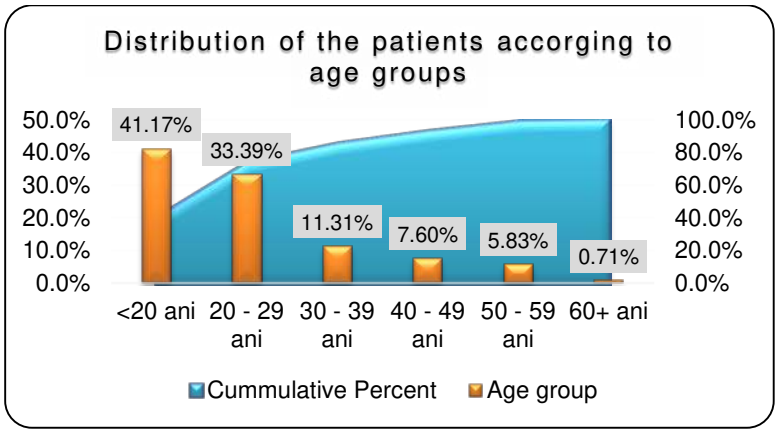

Figura 47 Distribution of the patients accorging to age groups

Over the study period there were 87 recorded deaths within the patients group. These represent 15.37% from the total sample of the study (Figure 55).

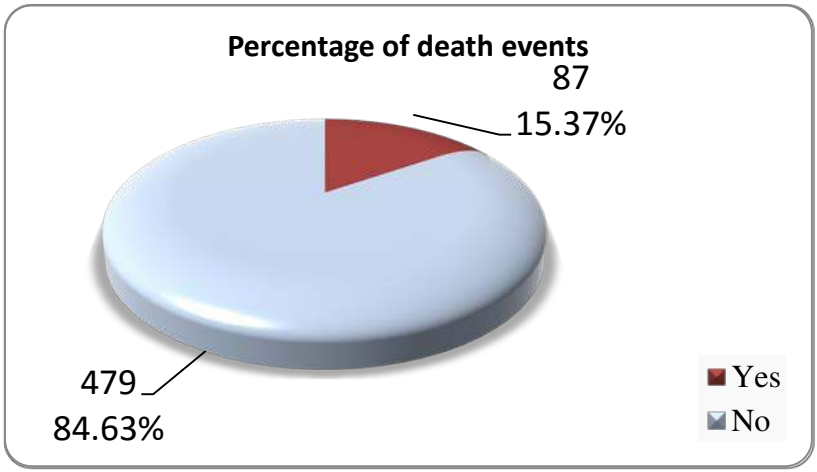

Figura 55 Percentage of death events

Statistical analysis of age at death

Average age of the deceased patients is 31.86years, with a standard deviation of 12.775 years. The descriptive statistical analysis is available in table XXXV.

In the following figure (Figure 57) I analysed, by comparison, the distribution of the patients according to age at the enrolment in the study. Both distributions have a right asymmetry, determined by the predominance of young patients. Significant differences can be seen in the case of patients with an age higher than 25 years, the proportion of these patients being much higher in the group of deceased, 45.99%, than in the group of the survivors, 27.98%.

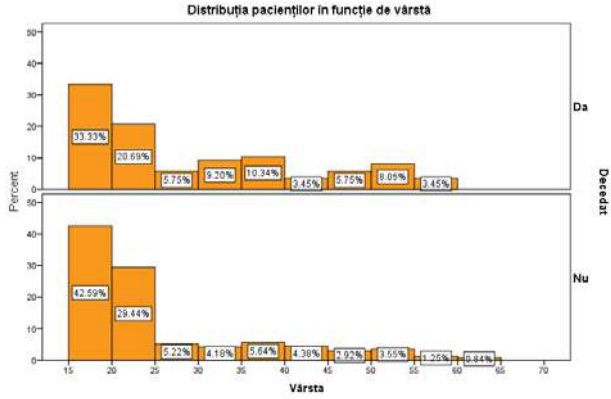

Figura 57 Patients distribution according to age at enrolment

The analysis of the distribution according to immunological status and death

The next analysed aspect is the evaluation of the association between CD4+ lymphocyte counts and death. For almost one quarter of the patients that died a lower than 200 counts were observed, while in the case of patients that survived during the follow-up period of the study this percentage is almost half (Figure 63).

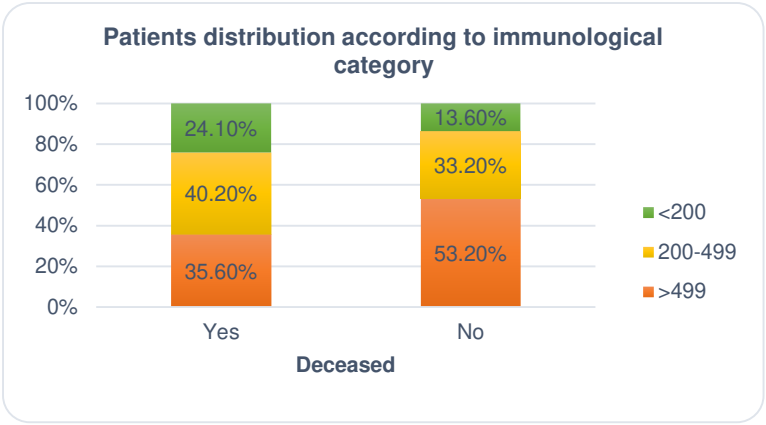

Figura 63 Patients distribution according to immunological category

The result is statistically significant, p=0.004, indicating a statistically significant relation between death event and low CD4+ lymphocyte counts (Table L).

Tabel L Chi-square test for the association between immunological category and death

	Valoare	df	p Estimat (2 cozi)
Testul Chi-Pătrat	10.991	2	.004
Corecția Yates			
Raportul de Verosimilitate	10.705	2	.005
Testul Mantel-Haenszel	10.957	1	.001
Număr cazuri	566		

1. 0 celule (0.0%) au valori așteptate mai mici de 5. Numărul minim așteptat este15.22.

Mortality analysis

The mortality calculated for the entire duration of the study for the patients sample is 22.56 deaths/ 1,000 patient-years, with a 95% confidence interval between 17.76 and 27.36 deaths/1,000 pacient-years (Table LII).

Tabel LII Mortality crude rate (/1,000 pacient-years)

Mortality crude rate	Exact 95% Confidence Interval	
	Lower Limit	Upper Limit
22.56	18.07	27.82

Mortality according to gender

Specific mortality rate for women is 22 deaths/1,000 pacient-years, with a 95% confidence interval 14.90 – 29.11 deaths/1,000 patient-years (Table LIII). For men, the specific mortality rate was 23 deaths/1,000 patients-years.

Tabel LIII Specific mortality rate according to gender (/1,000 patient-years)

		95% Confidence Interval	
Group	Mortality rate	Lower Limit	Upper Limit
Women	22.00	15.57	30.20
Men	23.00	17.02	30.41
Total	22.56	18.07	27.82

Further on, in order to have a comparison between the death rates according to gender, I applied direct standardization methods.

In figure 65 I created a stratified rate ratio plot to compare specific mortalities among genders. No statistically significant differences were observed at any leel or standardized level. A ratio higher than 1 represents higher mortality rates for women.

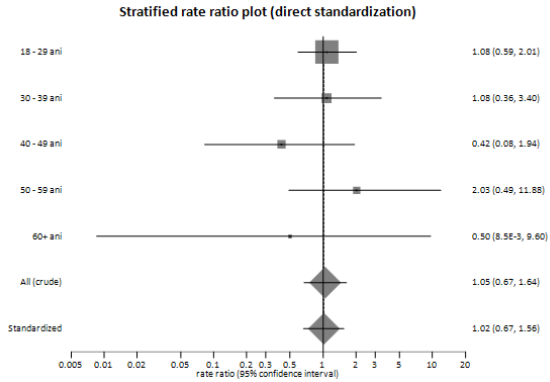

Figura 65 Standardised mortality rates, by gender

Analyssi of the incidence of malignancies

From the total of 566 patients included in this study, 21 were diagnosed with different forms of malignancies. This represents a cumulative incidence of 3.7% (Figure 67).

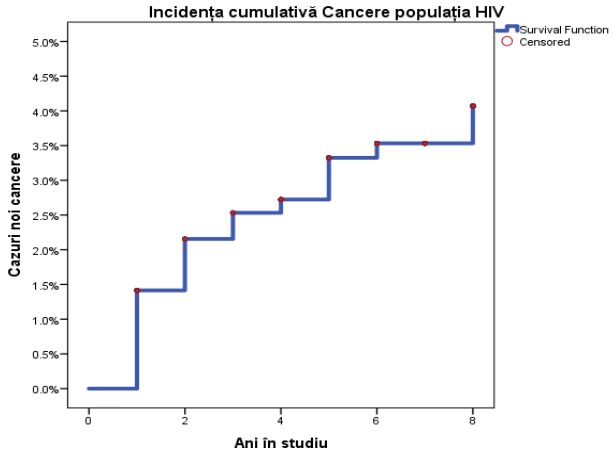

Figura 67 Malignancies cummulative incidence

Distribution according to immunological status

Considering the counts of CD4+ lymphocytes, more than half of the of the patients diagnosed with different malignancies had values between 200 and 499 cells/mm^3. Only 14% of the patients had values of CD4+ lymphocytes higher than 499 cells/mm^3 (Figure 71).

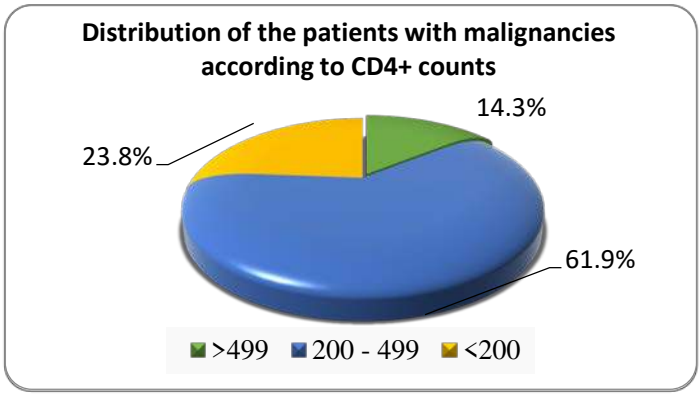

Figura 71 Distribution of the patients with malignancies according to CD4+ counts

Malignancy risk evaluation

Average number of CD4+ lymphocytes in patients that were not diagnosed with malignancies is 527.19, with median of 517 and standard deviation of 276.98. For patients diagnosed with malignancie, average CD4+

lymphocytes number was 347.67 with a median of 315 and a standard deviation of 218.89. It's obvious that ptients without malignanie have significantly higher values of the CD4+ lymphocytes count.

The analysis of the distribution of the number of CD4+ lymphocytes is offering a clear image (Figure 79). Thus it is noted that patients diagnosed with different neoplastic diseases have distribution concentrated in the 200-400 counts interval, around 50% of the patients having values within this interval. Significant percentage of patients are found in the lower part of the chart, almost one quarter of the patients having values less than 200 cells/mm^3.

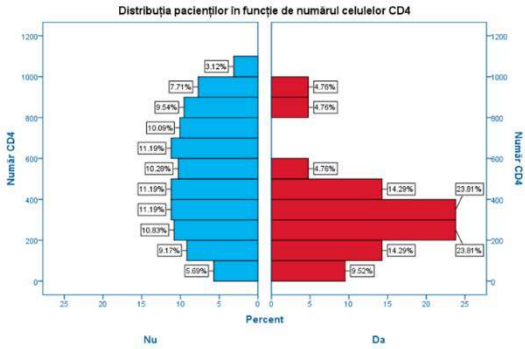

Figura 79 Patients distribution according to CD4+ lymfocytes cout and presence of malignancies

The result of the statistical test used for comparison (Table LXXIV) is statistically significant (U=3547,5, Z=-2,96, p=0,03). This result confirms the results observed in the descriptive statistical analysis where the median number of CD4+ lymphocytes for the patients with malignancies is significantly lower and also confirms the observations from the figure with the distributions of these values.

Tabel LXXIV Mann-Whitney U test to compare the number of CD4+ cells according to malignancies presence

	CD4+ cells
Mann-Whitney U	3547.500
Wilcoxon W	3778.500
Z	-2.958
p (2 tails)	.003

1. Independent variable: Malignancy

Mathematical model for the risk of malignancy incidence in HIV infected patients, according to the demographical features and number of CD4

I developped a mathematical model, by using the logistic regression method, in order to determine the factors associated with the increase of the risk of malignancies in HIV infected patients. In this mathematical model I included the demographical features of age, gender and background, as well as the number of CD4 lymphocytes. The model has a statistical significance. ($X^2(4)=24.69$, $p<0.001$ (Table LXXVII).

Table LXXVII Testing the statistical significance of the mathematical model based on the demographical features and the number of CD4 lymphocytes

Omnibus Tests of Model Coefficients

		Chi-square	df	p
Step 1	**Step**	24.688	4	.000
	Block	24.688	4	.000
	Model	24.688	4	.000

The result has no statistical significance for gender and background ($p=0.078$; $p=0.528$). The model is statistically significant for age and number of CD4 lymphocytes (Table LXXVIII).

Table LXXVIII Variables of the logistic model for the assessment of malignancy risk, according to the demographical indicators and number of CD4 lymphocytes

							IC 95% Raportul Cotelor	
	Coeficient de Regresie	S.E.	Wald	df	p	Raportul Cotelor	Limita Inferioară	
Sex(1)	.891	.506	3.101	1	.078	2.439	.904	6.578
Mediul(1)	.326	.518	.398	1	.528	1.386	.503	3.822
Vârsta	.059	.017	12.765	1	.000	1.061	1.027	1.096
Număr CD4	-.003	.001	9.169	1	.002	.997	.995	.999
Constant	-4.493	.878	26.159	1	.000	.011		

Thus, the risk of malignancies in HIV infected people increases along with age (OR=1.061 (CI 95% 1.027 – 1.096), $p<0.001$), for each additional year the risk having a value with 0.061 higher. In the graphical representation of a function, we can notice how the risk increases along with age (Figure 82).

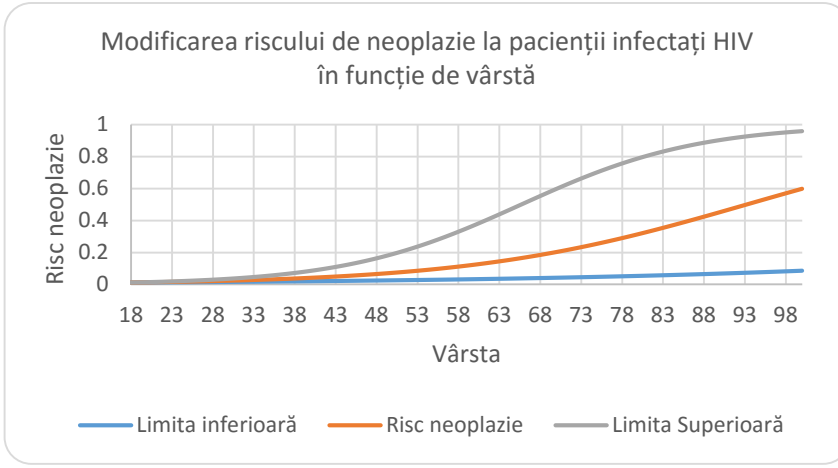

Figure 82 Change of malignancy risk in HIV infected patients according to age

The malignancy risk is also influenced, based on the mathematical model, by the number of CD4 lymphocytes (OR=0.997 (CI 95%; 0.995 – 0.999)). Thus, for every higher unit of CD4 lymphocytes, the malignancy risk decreases with 0.003. For a better representation of this risk, I presented the result in a graph, in which one can notice the change of risk according to the number of CD4 lymphocytes (Figure 83).

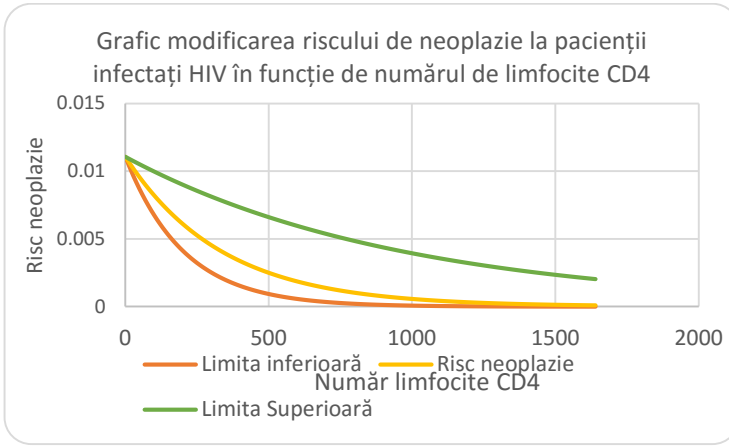

Figure 83 Change of malignancy risk in HIV infected patients, according to the number of CD4 lymphocytes

Incidence of malignancies in HIV infected population

During the study, 21 malignancies were recorded (Figure 87). From the total of the diagnosed malignancies, the most frequent ones were the non-Hodgkin Lymphoma and Kaposi Sarcoma. These two types represent 48% of all malignancies.

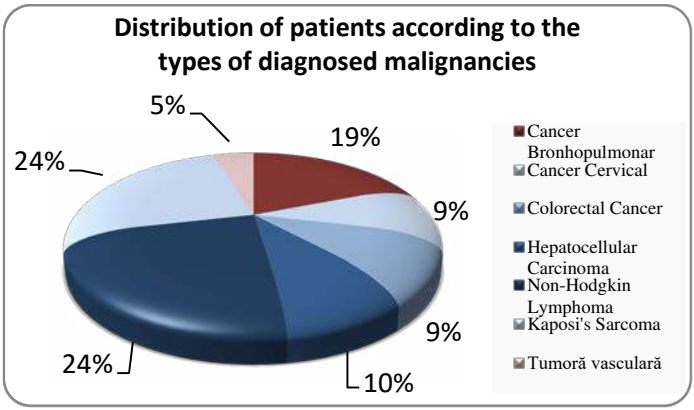

Figure 87 Distribution of patients according to the types of diagnosed malignancies

Taking into account the number of people participating in the study and the follow-up period, I calculated the crude incidence of cancers. This is of 544.47 cases/100,000 patients-year, with a confidence interval of 95% ranging from 337.03 to 832.27 cases/100,000 patients-year (Table LXXXIX).

Table LXXXIX Malignancy incidence in HIV infected patients

Ratio Statistics for Neoplazie / Pacient-an

	Interval Încredere 95%	
Incidența	**Limita Inferioară**	**Limita Superioară**
544,465	337,032	832,272

In order to have a better representation of malignancy incidence in HIV infected population, compared to malignancy incidence in the general population, I applied the direct standardization method. The first step was to calculate the specific incidences for the age groups considered (Table XC). There are four age groups I decided to consider: 18-29 years, 30-39 years, 40-49 years and 50+ years. My decision was based on the fact that, in the

case of 60+ years, the number of HIV infected patients in the study is very low, and there were no recorded malignancies.

Table XC Malignancy Incidence according to age groups

Age Group	Neoplasia	Patient-Years	Specific Ratio
18 - 29 years	8	2942	271,924
30 - 39 years	4	408	980,392
40 - 49 years	4	280	1428,571
50 + years	5	227	2202,643

For each specific incidence I determined the confidence interval of 95%, the result being shown in the following table (Table XCI).

Table XCI Confidence Interval of 95% for the specific incidences according to age groups

Age Group	Index rate	Exact 95% confidence interval
18 - 29 ani	271,924	117,397 to 535,798
30 - 39 ani	980,392	267,124 to 2510,193
40 - 49 ani	1428,571	389,238 to 3657,710
50 + ani	2202,643	715,192 to 5140,234

By applying the specific incidences of HIV infected population to the general population structure, we obtain the expected number of events in the general population, if the incidence of cases were identical to the one noticed in HIV infected patients. Thus, the number of estimated cases is of 8017.85. Therefore, the standardized calculated incidence is of 1442.601 cases/100,000 people-year (Table XCII).

Table XCII Adjusted Malignancy Incidence

Age Group	Standard Population	Specific Ratio	Expected Events
18 - 29 ani	111135	271,924	302,203
30 - 39 ani	108035	980,392	1059,167
40 - 49 ani	97934	1428,571	1399,057
50 + ani	238687	2202,643	5257,423
Total	555791	1442,601	8017,849

By applying the adjusted incidence to an HIV infected population who would have the demographical features (regarding age) of the general population of Constanta County, the estimated number of new malignancies would be of 55.64, over two and a half times more than the number of cases in the studied period.

By applying the formula, using the small rates Poisson distribution, the standard error determined is of 451.939 (Table XCIII).

Table XCIII Determination of standard error of the adjusted incidence

Age Group	Specific Incidence	Standard Population	Patient-years	
18 - 29 ani	271,924	111135	2942	114158001673875
30 - 39 ani	980,392	108035	408	2804585069444440
40 - 49 ani	1428,571	97934	280	4893402222448980
50 -59 ani	2202,643	238687	227	55280991256379900
Total		555791	3857	63093136549947200
Standard Error	451,939			

Thus, after analysing the incidence of all types of malignancies in HIV infected population and standardization using as reference the adult population of Constanta County, I obtained an adjusted incidence of 1,442.601/100,000 patients-year (CI 95% 653.567 – 2537.368).

The standardized incidence, expressed as a ratio between the adjusted incidence of malignancies in HIV infected patients and the malignancy incidence in the general population is 1,442.601 / 338.85 = 4.26.

As the confidence interval of 95% determined for the adjusted incidence ranges from 653.567 to 2537.368, an interval which does not intersect with the confidence interval of malignancy incidence in the general population, ranging from 333.99 to 343.76, we can conclude by saying that the noticed difference is a statistically significant one, the malignancy incidence in HIV infected population being more than four times higher, after adjusting according to age groups, pursuant to the methodology.

Incidence of non AIDS defining malignancies

After analysing the incidence of non AIDS defining malignancies in the HIV infected population, by using the direct standardization method and

using as reference the population of Constanta County, obtained an adjusted incidence of 802.301/100,000 patients-year (CI 95% 238.443 – 1735.57).

The standardized incidence, expressed as a ratio between the adjusted incidence of non AIDS defining malignancies and the malignancy incidence in the general population is 802.301/338.85 = 2.37. Thus, the risk of an HIV infected patient of developing a non AIDS defining malignancy is about two and a half times higher than the risk of a person who does not display an HIV infection.

As the confidence interval of 95% of the standardized incidence of non AIDS defining malignancies ranges from 238.443 to 1735.57, an interval which completely includes the incidence calculated for the cancers of the general population, which is 338.85, with a confidence interval of 95% ranging from 333.99 to 343.76, I cannot assert with a high degree of certainty that the noticed difference is a statistically significant one.

Discussions

In this paper I analysed the incidence of cancers in the general population of Constanta County for an eight-year period, the source of information being the official reports of the Public Health Department, concerning the main markers of health knowledge. The purpose of this analysis was to determine the necessary indicators in order to assess the risk of the HIV infected people undergoing HAART treatment, in the same geographical area. The analysis is exhaustive, covering both incidences calculated for each year, and the general incidence rate calculated for the population of Constanta County. Also, specific incidences were calculated based on the background of the patients and their gender.

In the personal study carried out at the Regional Centre for HIV / AIDS of Constanta, I analysed the data for a total of 566 HIV-infected patients, undergoing HAART treatment, for an average period of 6.81 years, with a standard deviation of 2.06 years and a median of 8 years. Therefore, the observation period of these patients is a significant one.

Besides calculating the incidence of cancers in these patients, I also assessed the risk of cancers according to HIV demographical and evolutional criteria, namely according to the staging suggested by CDC.

The incidence of cancers in the population of Constanta County was estimated at 338.85 cases / 100,000 people-year, with a confidence interval

of 95% between 333.99 and 343.76 new cases / 100,000 people-year. Compared to the existing data about the incidence of cancers at the European level, which indicate, for Romania, an estimated incidence for 2012 of 307.2 cases / 100,000 people-year, we can notice that they are similar, the value calculated for Constanta County being higher than the one estimated for 2012 at the national level.

The study evaluated a group of 566 HIV-infected patients undergoing HAART treatment. In an international context, the particularity of this study is the specifics of HIV in Romania, namely that a percentage between 70% and 90% of the patients are infected with a particular virus subtype, F1. Nevertheless, although the F1 subtype is frequent in Brazil and Angola, genetic studies have shown the fact that there are no direct connections between the main subtype found in Romania and the one in Brazil, the epidemics in the two countries developing separately, although they have distant phylogenetic relationships. Clear phylogenetic links have been found between the subtypes circulating in Romania and Angola.

Romania displays another distinct feature, being recognized by some authors [21] as a special case in the global epidemic of HIV, by the high population of children infected parenterally. These events took place about 25 years ago, these patients currently representing a very large proportion of the total HIV patients, an aspect which is highlighted in this study by the way in which patients are divided by age (Figure 45).

In this study, most patients have young ages, about 41% of them being younger than 20 at the beginning of the study, and over 25% of them being older than 30 (Figure 47). I found neither statistically significant differences regarding gender distribution or backgrounds compared to the general population, nor in terms of age distribution between female and male patients. A statistically significant difference ($p=0.023$) was noticed in the distribution of patients according to backgrounds, the patients from rural areas having a higher average age (Figure 49).

Management of HIV infected patients with cancers

According to the present legislation, namely Government Decision no. 206/2015 on the approval of the national health programmes for 2015 and 2016 and Order no. 386/2015 on the approval of the technical norms of the national public health programmes for 2015 and 2016, the HIV infected

patients are included in the National Programme on Prevention, Surveillance and Control of HIV/AIDS.

This programme includes two major directions, namely HIV/AIDS prevention and surveillance activities, and activities in the field of treatment and monitoring the therapeutic response of patients with HIV/AIDS.

Based on the results obtained by assessing the incidence of cancers in HIV infected population and on the new data from the specialized literature, I demonstrated that these patients have a significantly higher risk of developing neoplastic diseases, compared to the general population.

At the same time, there is a tendency that the number of non AIDS defining malignancies significantly increases, the epidemiological transition from the predominance of AIDS defining malignancies to the predominance of non AIDS defining malignancies requiring a change in attitude, with a preventive objective.

Suggestions to improve the management of HIV infected patients

Taking into account the existing data, prevention, represented by active screening for various neoplastic conditions of HIV infected patients could be an important step forward for the early detection of these diseases. Currently, there are no special screening recommendations for non AIDS defining malignancies for the HIV infected populations, other than the ones for the general population. Another major impediment is the lack of screening methods for some of the main malignancies affecting the HIV infected population, such as Kaposi's Sarcoma and Non-Hodgkin's Lymphoma. The lack of clear guidelines in this area is due to the fact that, for a significant number of malignancies, there are no studies to assess the benefits (mortality, economic etc) or the discomfort of various screening methods.

Regarding the treatment of HIV infected patients suffering from neoplastic diseases, they should benefit from specific oncological treatment of the condition associated with the infection. There are published studies confirming that the patients in this category who undergo optimal treatments, both anti-infective and oncological, display a similar evolution to the non HIV patients. Thus, the development of cooperation agreements between the national health programme responsible for HIV and the National Cancer Program could provide the legal framework to improve management quality of HIV infected patients presenting malignancies and could improve

collaboration between different specialties, with the possibility of significantly better indicators of therapeutic success. This need for an integrated approach of HIV infected patients with malignancies is a goal clearly expressed today, numerous recent studies including this recommendation in their conclusions.

According to the technical norms of the national health programmes for 2015 and 2016 [63] the sums allocated were directed to the treatment of 110,000 patients. According to existing data, the national number of cancer cases in 2012 was 78,760 [1].

According to the information provided by the department for monitoring and evaluating HIV / AIDS in Romania for 2014, 332.422 tests were carried out, of which 207,712 people had a higher risk, and the number of positive tests was 2416, of which 1238 people with a higher risk [64], resulting in a rate of 0.73% positive tests, 0.59% positive tests for people in the risk groups.

Testing all patients with newly detected cancers with unknown HIV status through the national programme of prevention, surveillance and control of HIV / AIDS would add an estimated 80,000 tests annually. In order to comply with the average of detections in populations at risk, the number of positive tests should be of 480, resulting in a positive test proportion of 0.6%. Considering the significantly higher risk of patients infected with HIV to develop various malignancies, the likelihood that this proportion could be achieved is significant, but the data must be validated by a screening pilot project for HIV of all newly diagnosed cancers, with an unknown HIV status.

In terms of cost, based on efficiency indicators mentioned in Order no. 386 of 31 March 2015 on the approval of the technical norms of national public health programmes for 2015 and 2016 [39], the estimated average cost of the rapid HIV testing is 4.70 lei and the cost of ELISA test is 9.50 lei. According to the same document cited above, the total amount allocated for 2015 (state budget + own revenues) is 322.609 million lei.

The estimated budgetary impact of the introduction of the people diagnosed with malignancies into the National Programme for Prevention, Surveillance and Control of HIV / AIDS is, by using rapid tests, of about 376,000 lei / year. To this amount will be added other expenses related to additional testing of persons detected positive, expenditure on treatment of patients who meet the criteria set and other necessary assessments. All this

cannot be estimated; in order to do this, it is necessary to carry out a study to determine the prevalence of HIV infection in the oncological population of Romania, focusing on the prevalence of unknown HIV infection cases

Conclusions

1. Most of the studied malignancies show a decreasing trend of the incidence during 2007-2014, with a higher incidence for people in rural areas
2. More than half of the HIV-infected patients in this study are males, with a similar distribution by background to that observed in the general population.
3. The average age of HIV infected patients at inclusion in the study is 25.79 years, the most common value being 19. They are, in their majority, infected patients in cohort 1987-1990. No statistically significant differences of the age according to gender, and the patients from the rural environment are older.
4. Mortality is of 22.65 deaths / 1,000 patients year (95% CI, 18.07 to 27.82). There is no significant difference between mortality by sex or background. The specific death rates depending on the immunological category of patients differ significantly, the patients in immunological stage 3 showing a mortality of 37.7 / 1,000 patients-year (95% CI, 23.34 to 57.63). Depending on the clinical status of the patients, there are no significant differences between patients in stages B and C. Among patients in stage A, mortality is significantly lower.
5. There are no statistically significant differences in the incidence of malignancies by gender or background.
6. The majority of patients with malignancies have values of CD4 lymphocytes in the range of 200-499 cells / mm3 and the predominant clinical stage is C. Also, the mean values of CD4 lymphocytes are significantly lower in patients with malignancies, while the clinical stage does not show a statistically significant association with the occurrence of malignancies.
7. The adjusted incidence rate of malignancies in HIV infected population indicates a risk more than four times higher than the general population in the same geographical area.

8. The adjusted incidence rate of non AIDS defining malignancies indicates a risk almost two and a half times higher in HIV-infected patients compared to the general population in the same geographical area.
9. According to the results and the data published in the literature, the following measures are necessary:
    a. Screening the HIV infected patients for major malignancies for which there was an increased incidence;
    b. Screening for HIV of all newly diagnosed patients with malignancies.

    To achieve these objectives, we need some legislative changes in the National Health Programmes, by adding the patients diagnosed with cancers in the list of people receiving free HIV testing. It is also necessary to establish the legal framework for monitoring HIV infected patients with oncological screening programmes, where these are defined.
10. With the introduction of HIV testing for people diagnosed with malignancies within the National Programme for Prevention, Surveillance and Control of HIV / AIDS, it will be necessary to introduce the hospitals which have oncology units among the institutions which implement the programme of HIV prevention and surveillance.
11. For a better management and an increased access to testing for detecting HIV screening, it is recommended to amend the legislation on either the existing basic package under the national health insurance or national health programmes and to place free tests for detecting HIV infection in cancer patients on the list of tests that may be recommended by family physicians. Currently, family physicians have the possibility to recommend an HIV test within the health insurance system only to pregnant women.
12. It is also necessary to amend the legislation regarding the treatment of HIV infected patients who have malignancies, so that the access and the way the treatment is conducted, antiretroviral and oncologic, is optimised. A possible solution might be represented by subprograms that will allow an integrated management of these patients of the development of clear and functional protocols that will allow collaboration between existing programs.

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Elements of originality of the doctoral thesis:

Th originality of the study is given by the fact that represents the first study that analyses the relationship between HIV infection and malignancies in South-Eastern Romania

At international level, the study is valuable as it approaches a population with particular characteristics at global level. These add up to the relatively few information available in the specialty literature at the beginning of the research.

Opened perspective by the personal research:

1. As it is proven that malignancies have a significantly higher incidence among HIV positive patients, the next step in research is represented by the investigation of patients diagnosed with malignancies to identify the proportion of HIV positive patients.
2. The perspective of legislation changes to integrate HIV positive patients into existing screening program to identify malignancies.
3. The inclusion of patients with malignancies into HIV/AIDS prevention program.
4. Clear evidence that legislative harmonisation is needed for collaboration protocols between national program responsible with HIV and malignancies treatments or for specific subprogram development.
5. Research related to specific screening procedures for different types of malignancies adapted for HIV positive population are needed
6. Research related to optimal treatment for HIV positive patients with malignancies are needed.