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Cancer incidence in HIV patients under HAART therapy in a HIV-1 F1 subtype endemic area

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ABSTRACT
Cancers have been recognized as a major health problem in patients with HIV. The first cases reported, before the existence of the virus was proven, involved patients with immunosuppression and a history of illness characterized by fever, weight loss and/or lymphadenopathy lasting weeks of months. As the population grows older, a consequence of better and largely available treatments, the impact of non-AIDS-defining cancers (NADC) is having a greater impact on the management of HIV infected patients. Studies of different subtypes of HIV-1 in Romania show a very high prevalence of subtype F1, with values between 70% - 90% or the patients being infected with this strain. The study of HIV infected population in Romania is important for identifying particularities of the subtype F1 evolution.
We conducted a prospective study on HIV positive patients under HAART treatment from the Constanta Regional Centre, for a period of eight years, between 2007- 2015. All causes of new discovered cancers were recorded with the occasion of subsequent visits that are done on a regular basis. For comparison we used official data from of new diagnosed cancers from reports on health status for Constanta County for the same time period. The adjusted incidence ratio is 955.18/100000patient-years (95% CI 446.58 – 1463.75/100000 patient-years). As observed in similar studies conducted.
HIV patients that undergo HAART treatment have an increased risk of all cancers significantly higher than what is observed in the general population. Considering this, better screening programs have to be developed and implemented for this population. Also, because of the suspicioned high number of HIV infected patients that are not diagnosed, a screening program for HIV should be implemented for all newly diagnosed patients with any type of malignancy.

Keywords: HIV-1 F1 variants, cancer, neoplasms incidence

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Introduction

Cancers have been recognized as a major health problem in patients with HIV. The first cases reported, before the existence of the virus was proven, involved patients with immunosuppression [1,2] and a history of illness characterized by fever, weight loss and/or lymphadenopathy lasting weeks of months [2].

Starting with 1987 and after the revision from 1993, Kaposi Sarcoma, non-Hodgkin Lymphoma and Cervical Cancer were recognized and categorized as AIDS defining cancers [3,4,5].

Once with the introduction and wide use of highly active antiretroviral therapies (HAART), the life expectancy of people infected with HIV increased [6,7,8]. In this context, the possibility of new outbreaks of non-communicable diseases in patients infected with HIV increases dramatically [9,10,11].

One of the most important groups of non-communicable diseases is represented by neoplastic diseases. In recent years research on this field intensified, with numerous reports on the topic [12,13,14]. As the population grows older, a consequence of better and largely available treatments, the impact of non-AIDS-defining cancers (NADC) is having a greater impact on the management of HIV infected patients [15,16].

Studies of different subtypes of HIV-1 in Romania show a very high prevalence of subtype F1, with values between 70% - 90% or the patients being infected with this strain [17,18,19,20,21]. This fact represents one of the most important particularities of HIV epidemic in Romania. It seems that the strains isolated from Romanian HIV infected patients is related to the ones found in Angola and is different from the F1 strains found in South America [22,23]. Therefore the study of HIV infected population in Romania is important for identifying particularities of the subtype F1 evolution.

Material and Method

We conducted a prospective study on HIV positive patients under HAART treatment from the Constanta Regional Centre, for a period of eight years, between 2007- 2015.

At the first contact we collected sociodemographic characteristics, treatment and complications for patients over 18 years old. All causes of new discovered cancers were recorded with the occasion of subsequent visits that are done on a regular basis. Patients that were already diagnosed with any type of malignancy were excluded from the study and also patients that were lost due to not presenting for regular controls for more than one year. For each participant in the study the relevant time period of person-years starts with the year of enrolment. The end of the time period of follow-up is considered either the year of diagnosis, the year of death of the last visit.

For comparison we used official data from of new diagnosed cancers from reports on health status for Constanta County for the same time period. The population considered for this study is the population at the middle of the year (1st of July) for 2007-2010 and 2012-2015 and for 2011 we considered the population recoded at the National Census conducted in that year.

Incidence rates were calculated by dividing the total number of observed cases of cancers in the study population by the person-years and the standardization method used is direct standardization method [24,25]. The standardization is done for age and the reference population is considered the population of Constanta County as it results from the National Census in 2011 [26]. For standard error calculation and 95% confidence intervals we used Poisson approximation.

Results

We enrolled a number of 566 patients followed for an average of 6.8 years and 3857 person-years. In table I are the baseline characteristics of the patients, for the ones that were discovered with a type of cancer, the ones without one and for all patients.

Table I Baseline characteristics

VARIABLE	LEVEL	Yes (n=21)	NO (N=545)	TOTAL (N=566)	P-VALUE
AGE	mean (sd)	34.5 (13.5)	25.5 (10.6)	25.8 (10.9)	0.0001446
AGE AT DIAGNOSYS	Mean (sd)	36.5 (13.9)			
SEX	Feminin	6 (28.6)	249 (45.7)	255 (45.1)	
	Masculin	15 (71.4)	296 (54.3)	311 (54.9)	0.1856691
BACKGROUND	Rural	6 (28.6)	171 (31.4)	177 (31.3)	
	Urban	15 (71.4)	374 (68.6)	389 (68.7)	0.9743086
PATIENT-YEARS	mean (sd)	3.0 (2.3)	7.0 (1.9)	6.8 (2.1)	< 0.001

More than half of the patients, 54.9% are males. In the case of patients that were diagnosed with a

form of cancer, 71.4% are males. The difference is not statistically significant

(p=0.185). Around two thirds of the patients (68.7%) have an urban background. This proportion is normal for the population of Constanta County were, according to the data from the most recent census, 69% of the population is living in urban areas.

The average age is 25.8 years with a standard deviation of 10.9. In the case of patients that were diagnosed with different forms of cancers, the baseline average age is 34.5 (sd 13.5) statistically significantly higher than in the case of the patients without cancer diagnosis which had an average age of 25.5 (10.6).

Cumulative incidence of cancers calculated for the HIV positive patients from this study over the 8 years study duration is 3.7%. (Figure 1)

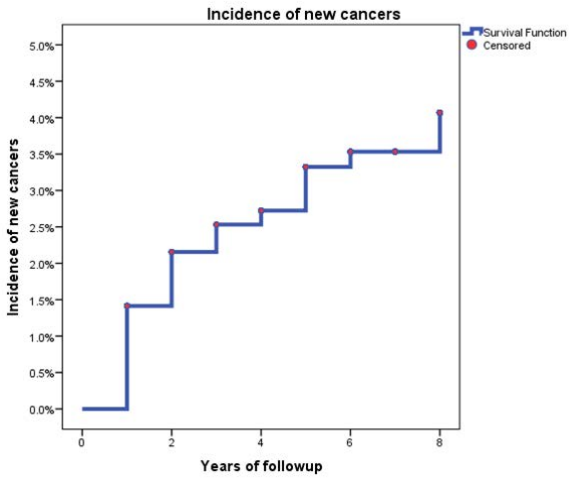

Figure 1 Cummulative incidence ratio

The crude incidence rate calculated is 544.45/100.000 person-years.

In table II we calculated the specific incidence rates by age group. Because the population of the study is at least 18 years old, the first age group is considered from 18 to 29 years in order to avoid very small numbers given by a two years interval.

We observe the fact that none of the patients of 60 years or above was discovered with a type of cancer. This might be explained by the relatively small number of patients at this age. Most of the cases were diagnosed in patients belonging to the 18-29 years group. The highest specific incidence rate was observed, as expected in patients of 50-59 years old, with values of 2515.56/100.000 person-years.

Table II Specific incidence rates for HIV patients under HAART therapy

GRUP	EVENTS	INDEX PT	SPECIFIC INCIDENCE (100000/PERSON-YEAR)
18-29 YEARS	8	2942	271.9238613
30 - 39 YEARS	4	408	980.3921569
40 - 49 YEARS	4	280	1428.571429
50 - 59 YEARS	5	199	2512.562814
60+ YEARS	0	28	0

In table III we calculated the 95% confidence intervals for specific incidence rates, using Poisson approximation.

Table III 95% confidence intervals for specific incidence rates

	INDEX RATE	EXACT 95% CONFIDENCE INTERVAL
18-29 YEARS	271.923861	117.397423 to 535.79841
30 - 39 YEARS	980.392157	267.123866 to 2,510.193303
40 - 49 YEARS	1,428.57	389.237633 to 3,657.710241
50 - 59 YEARS	2,512.56	815.822307 to 5,863.483457
60+ YEARS	0	0 to 13,174.569479

To calculate the standardized incidence ratio using the direct method of standardization we decided to use as reference population the population of Constanta county from the census in 2011. This seemed the best option as it contains recent, quality data. Also the time at which the census was done is at the middle of the study period and considering the slow progress of changes in a population and the large numbers, the variability is neglectable. We considered the use of truncated direct standardization only for subjects older than 18 years.

Table IV Direct Standardization – Calculation of the expected number of events

GRUP	SPECIFIC INCIDENCE (100000/PERSON-YEAR)	REFERENCE POPULATION	EXPECTED NUMBER OF EVENTS (PER YEAR)
18-29 YEARS	271.9238613	111135	302.2025833
30 - 39 YEARS	980.3921569	108035	1059.166667
40 - 49 YEARS	1428.571429	97934	1399.057143
50 - 59 YEARS	2512.562814	101426	2548.39196
60+ YEARS	0	137261	0
TOTAL		555791	5308.818353

Based on this standardization, the adjuster incidence rate ratio is 955.18/100000 person-years. When compared to the general population for which the average incidence rate is 338.85/100000 person-years (calculated using as average population the data from the National Census), the result shows a 2.81 fold increase of risk for the HIV infected population.

For a better understanding we calculated the 95% confidence intervals for the standard error of age-adjusted incidence rates, using the small rates Poisson model as seen in table V

Table V Calculation of standard error for age adjusted incidence rate

GR0UP	SPECIFIC INCIDENCE (100000 PACIENT/YEARS)	REFERENCE POPULATION		
18-29 YEARS	271.9238613	111135	2942	114158001673875
30 - 39 YEARS	980.3921569	108035	408	2804585069444440
40 - 49 YEARS	1428.571429	97934	280	4893402222448980
50 - 59 YEARS	2512.562814	101426	199	12988603161536300
60+ YEARS	0	137261	28	0
TOTAL		555791	3857	20800748455103600

The result shows a standard error r=259.49, thus giving the approximate 95% confidence interval of 446.58 – 1463.75 cases/100000 patients-years. The average incidence ratio calculated for the entire population of Constanta county does not fall inside this interval thus the difference is clearly statistically significant.

Discussion

In this study we followed an index population of HIV positive patients that are under HAART treatment from an endemic area for subtype F1 HIV-1. We found that the cumulative incidence ratio for the study duration is 3.7% for all cancers.

The adjusted incidence ratio is 955.18/100000patient-years (95% CI 446.58 – 1463.75/100000 patient-years). As observed in similar studies conducted, the incidence of all cancers is higher for the HIV infected population with a 2.81 fold risk increase. This is comparable to recently published studies in which most of the patients undergo HAART therapy [12].

The importance of this study is motivated by the lack of information regarding the evolution of patients from areas with this particular type of HIV subtype F1, as the population in this study.

Conclusions

HIV patients from HIV-1 subtype F1 endemic area that undergo HAART treatment have an increased risk of all cancers significantly higher than what is observed in the general population. Considering this, better screening programs have to be developed and implemented for this population. Also, because of the suspicioned high number of HIV infected patients that are not diagnosed, a screening program for HIV should be implemented for all newly diagnosed patients with any type of malignancy.

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