Journal of Infection and Public Health 12 (2019) 182–189

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: http://www.elsevier.com/locate/jiph

# Epidemiological trends and therapeutic challenges of malignancies in adult HIV-1-infected patients receiving combination antiretroviral therapy in a tertiary hospital from Romania: An observational retrospective study

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ARTICLE INFO

*Article history:*
Received 2 August 2018
Received in revised form
18 September 2018
Accepted 25 September 2018

*Keywords:*
AIDS
HIV
Cancer
Kaposi sarcoma
Epidemiology
Romania

ABSTRACT

*Background:* Malignancies have become a leading cause of morbidity and mortality in people living with HIV (PLHIV). The primary endpoint of our study was to describe the epidemiology of acquired immunodeficiency syndrome (AIDS)-defining cancers (ADCs) and non-AIDS-defining cancers (NADCs). Epidemiological disparities, mortality predictors and survival analysis within the two groups of patients were key secondary endpoints.
*Methods:* We retrospectively evaluated all adult PLHIV with histopathologically proven cancers registered from 2010 to 2016 in the "Matei Balş" National Institute for Infectious Diseases, Bucharest, Romania.
*Results:* 110 eligible patients have been included in the study. The incidence of ADCs decreased from 1.6% in 2010 to 0.3% in 2016, unlike NADCs which remained fairly stable over time (0.3%). The higher CD4 count and lower HIV-RNA level at the cancer diagnosis were associated with prolonged survival in ADCs group, but not in NADCs group. The mean CD4 count was 449/mm$^3$ to survivors and 92/mm$^3$ to non-survivors ($p = 0.017$). The mean level of HIV-RNA was 64,671 copies/mL to survivors and 1,760,345 copies/mL to non-survivors ($p = 0.002$).
*Conclusions:* A good therapeutic control of HIV infection at the diagnosis of ADCs was associated with better survival, emphasizing the key role of the effective cART in the management of HIV-associated cancers.


## Introduction

Malignancies are a major cause of morbidity and mortality worldwide, accounting for 8.8 million deaths in 2015 [1,2]. Compared with the general population of the same age, human immunodeficiency virus (HIV) infected people have a substantially higher risk of developing some types of cancer [3]. Moreover, people living with HIV (PLHIV) are diagnosed with more aggressive and advanced diseases and have an increased risk of dying from cancer than HIV-uninfected people [4,5]. Traditionally, the HIV-associated cancers were divided into acquired immunodeficiency syndrome (AIDS)-defining cancers (ADCs) and non-AIDS-defining cancers (NADCs). There are three types of ADCs: Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL) and invasive cervical can-

*Abbreviations:* AIDS, Acquired immunodeficiency syndrome; ADCs, AIDS-defining cancers; cART, Combination antiretroviral therapy; CHTx, Cytotoxic chemotherapy; CMV, Cytomegalovirus; HBsAg, Hepatitis B surface antigen; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HCVAb, Antibodies against hepatitis C virus; HIV, Human immunodeficiency virus; HTX, Heterosexual; HL, Hodgkin lymphoma; KS, Kaposi sarcoma; MSM, Men who have sex with men; NADCs, Non-AIDS-defining cancers; NHL, Non-Hodgkin lymphoma; PLHIV, People living with HIV; PWID, People who inject drugs; RTx, Radiotherapy.

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https://doi.org/10.1016/j.jiph.2018.09.011

cer. The group of NADCs is represented by Hodgkin lymphoma (HL) and the various solid organ cancers including anal cancer and melanoma [6]. Since the introduction of combination antiretroviral therapy (cART) the epidemiology of malignancies in HIV population has been substantially changed. It has been observed a decrease in the incidence of ADCs and an increase in the incidence of NADCs, probably as a consequence of better control of viral replication, immune restoration and higher life expectancy [7]. In addition, there is a strong association between the increased incidence of NADCs and the long-term exposure to other cancer risk factors such as co-infection with oncogenic viruses, smoking and alcohol intake [6,7]. However, the new changes in the epidemiology of HIV-related cancers are not uniformly distributed across a diverse range of geographic settings on HIV infection. Thus, despite improvements in antiretroviral therapy access and availability, the recent data showed that the burden of HIV-associated malignancies remains high, especially due to the disproportionately large number of ADCs in low- and middle-income countries [8].

Romania is a central European middle income country with around 22 million inhabitants in January 2018 [9]. Regarding the HIV population, the number of PLHIV registered in the National HIV/AIDS Data Base at December 31, 2016 was 14,349. In addition, the total number of patients linked to care was 12,196 (85%) out of which 10,994 (90%) patients have benefitted from cART with a rate of undetectable viral load (<50 copies/mL) achieved in 6811 patients (62%) [9,10]. In our country, all HIV-infected individuals are now recommended to receive cART irrespective of CD4 count and treatment is provided free of charge through the national program according to last version of the European AIDS Clinical Society guidelines. From the epidemiological point of view, Romania is unique in Europe from at least two reasons: (1) epidemiological studies have shown that subtype F1 prevailed throughout the HIV-1 epidemic in Romania, with the emergence of other subtypes such as B, C and several circulating recombinant forms in recent years [11,12]; (2) the largest number of pediatric AIDS cases in Europe infected in the late 1980s and early 1990s [13]. Phylogenetic analyses indicate that HIV F subtype originated in the 1950s in the Democratic Republic of Congo and was separately spread by immigration waves to Brazil, Angola and Romania [11]. Overall, subtype F represents less than 1% of all HIV-1 subtypes [14]. Concerning the risk factors for HIV infection in Romania, 62.13% of the new HIV infections reported in 2017 were transmitted by heterosexual route. Another important characteristic of our HIV population is related to delayed diagnosis, considering that about 57% of the new HIV patients had a CD4 count below 350/mm$^3$. Tuberculosis represents the leading AIDS defining illness in Romania [15]. However, the existing information about the epidemiology of HIV-related cancers in Romanian PLHIV is limited.

The primary objective of the study was to describe the incidence and prevalence of ADCs and NADCs in our cohort. The secondary endpoints were: (1) describing epidemiological disparities between the two groups of patients, (2) identifying possible mortality predictors, (3) assessing survival of the patients with AIDS-defining and non-AIDS-defining malignancies, and (4) emphasizing the medical needs of our population with HIV-associated cancers.

## Methods

### *Selection and description of participants*

An observational, longitudinal, retrospective cohort study was conducted over a 7-year period, from January 2010 to December 2016, at the National Institute for Infectious Diseases "Prof Dr Matei Balş", Bucharest, Romania. This institute represents the most important reference center of the nine regional centers for diagnosis, treatment and monitoring of PLHIV in Romania, with more than 2000 patients in care. The eligibility criteria for enrolling in the study were as follows: (1) adult HIV infected patients (over 18 years old), with more than six months of cART, at the first regimen or previously exposed to multiple therapeutic regimens, and (2) histopathological confirmation of neoplasia.

### *Data collection*

The data were extracted from medical records and electronic database of the institute by using the International Classification of Diseases, Tenth Revision (ICD-10) diagnostic code in order to find the eligible patients.

### *Statistical analysis*

Means (standard deviation, SD) and frequencies (%) were used to describe the characteristics of patients and incidence and prevalence of malignancies. Gender, Centers for Disease Control and Prevention (CDC) stages, HIV transmission route, other coexisting infections, hepatitis B virus (HBV) and hepatitis C virus (HCV) confections, and treatment protocols were classified as categorical variables. Age, CD4 counts, plasma HIV-RNA levels, and survival were treated as continuous variables. We used the Mann–Whitney U test to analyze differences between groups for continuous variables and the chi-square or Fisher's exact test for dichotomic variables. Statistical significance threshold for different variables was established at p value < 0.05. Univariate analyses were performed to assess the association between mortality and interesting potential variables. Kaplan–Meier curve analysis was used to estimate the survival of patients with ADCs and NADCs. The statistical analysis was performed using IBM SPSS Statistics software, version 23.0.

## Results

### *Baseline characteristics*

The study involved 110 eligible patients, out of which 69 (62.7%) diagnosed with ADCs (group I) and 41 (37.3%) with NADCs (group II). The mean age of the patients was 43 (13) in ADCs group, and 45 (14) in NADCs group (p = 0.552). Regarding the gender distribution, 42 patients (60.8%) of the ADCs group and 20 patients (48.7%) of the NADCs group were male (p = 0.238, OR[95%CI] = 0.61[0.28–1.33]). In the first group of patients, the mean CD4 counts were 256 (281) cells/mm$^3$ at HIV diagnosis, and 410 (379) cells/mm$^3$ at ADC diagnosis. The mean levels of plasma HIV-RNA were 474,185 (874,974) copies/mL at HIV diagnosis and 341,516 (1,475,239) copies/mL at ADC diagnosis (Figs. 1a and b). At the moment of ADC confirmation 49 patients had HIV-RNA results available, out of which 19 (38.8%) had undetectable viral load (<50 copies/mL). In the second group of patients, the mean CD4 counts were 232 (126) cells/mm$^3$ at HIV diagnosis, and 340 (250) cells/mm$^3$ at NADC diagnosis. The mean levels of plasma HIV-RNA were 435,828 (1,428,066) copies/mL at HIV diagnosis and 137,601 (443,646) copies/mL at NADC diagnosis (Figs. 1c and d).

At the time of NADC diagnosis, 21 patients had HIV-RNA results available, out of which 10 (47.6%) had undetectable viral load. Candidiasis (oropharyngeal, esophageal and traheobronchial) was more prevalent in the group of patients diagnosed with ADC than NADC (79.7% vs 53.7%, p = 0.003) reflecting a more advanced

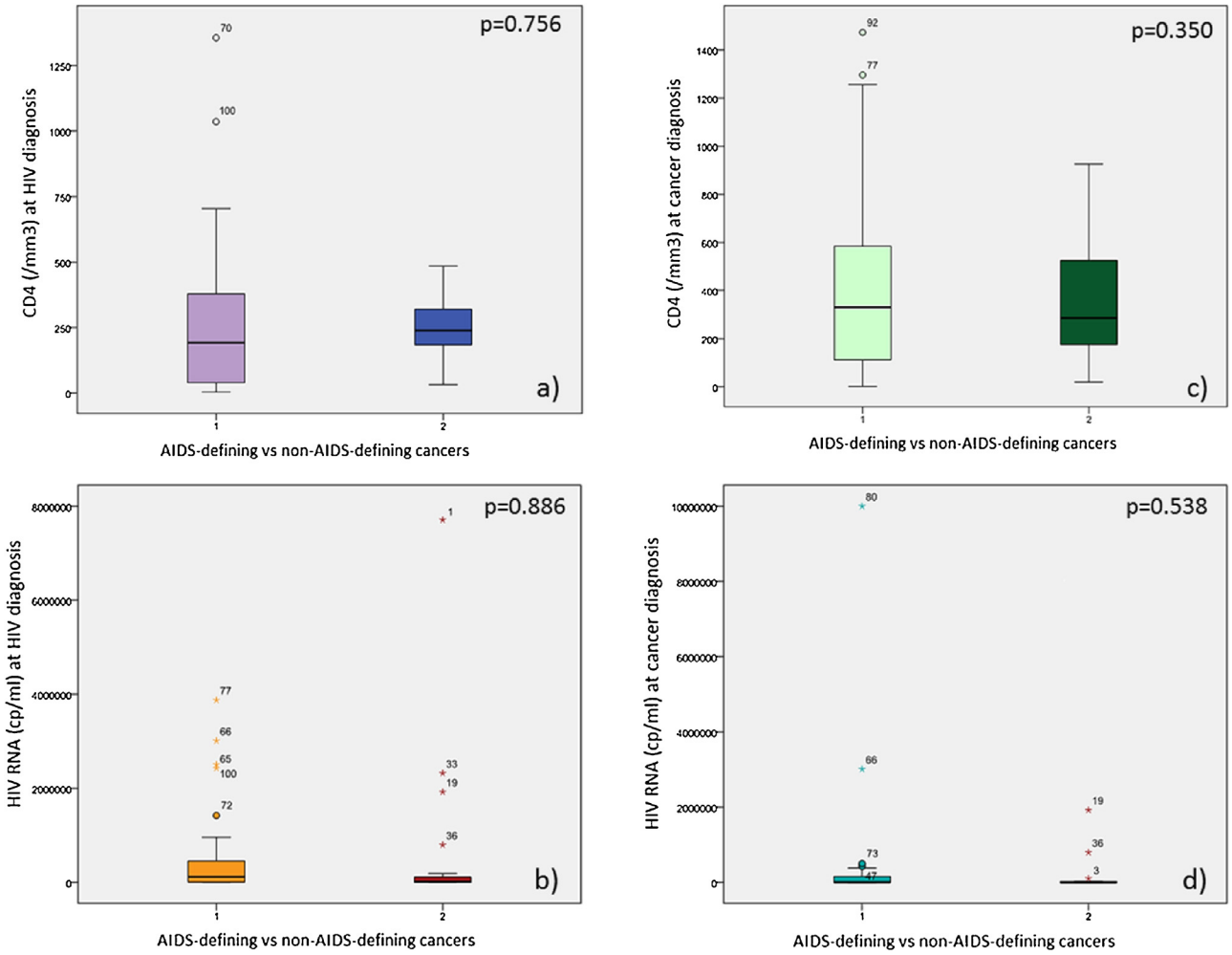


**Fig. 1.** Comparison of mean CD4 count (/mm$^3$) and plasma HIV-RNA levels (copies/mL) at the moment of HIV diagnosis versus cancer diagnosis for patients diagnosed with ADCs and NADCs: (a) comparison of mean CD4 count at HIV diagnosis for patients diagnosed with ADCs and NADCs; (b) comparison of mean HIV-RNA value at HIV diagnosis for patients diagnosed with ADCs and NADCs; (c) comparison of mean CD4 count at cancer diagnosis for patients diagnosed with ADCs and NADCs; (d) comparison of mean HIV-RNA value at cancer diagnosis for patients diagnosed with ADCs and NADCs.

immunosuppression in the first group. Baseline characteristics of the patients from both groups are summarized in Table 1.

*Different subtypes of ADCs and NADCs*

KS was the most diagnosed subtype of ADC (n = 33, 48%), followed by NHL (n = 25, 36%) and invasive cervical cancer (n = 11, 16%). The most common subtype of KS was cutaneous KS (n = 21, 63.7%), followed by mixed or invasive clinical forms: cutaneous and visceral KS (n = 5, 15.2%), cutaneous and mucous KS (n = 4, 12.1%), isolated visceral KS (n = 2, 6%) and combination of cutaneo-mucous and visceral KS (n = 1, 3%). Digestive cancers, including anal carcinoma (n = 11, 26.8%), breast cancer (n = 7, 17%), HL (n = 5, 12.2%) and hepatocellular carcinoma (n = 3, 7.3%) accounted for the majority of NADCs (Fig. 2).

*Prevalence and incidence of ADCs and NADCs*

The prevalence of ADCs and NADCs over the period included in the study was estimated at 3.2% and 1.9%, respectively. The incidence of the ADCs decreased from 1.6% in 2010 to 0.3% in 2016, unlike the NADCs which remained fairly stable over time, around 0.3% (Table 2).

*Treatment protocol*

In terms of treatment protocol it has been observed that cART represented the only treatment provided in the majority of patients (n = 52, 75.4%) with ADCs compared to 21 patients (51.2%) with NADCs (p = 0.009). Combination of cART, surgery and cytotoxic chemotherapy (CHTx) has been used in 7 cases (17.1%) of NADCs and in none of patients with ADCs (p = 0.0007). Complex treatment such as different combination between cART, surgery, radiotherapy (RTx) and CHTx was more commonly used in patients with NADC (Table 3).

*Mortality estimation*

The cumulative mortality rate over 7-years period in ADCs and NADCs group of patients was estimated at 15.9% (n = 11) and 19.5% (n = 8), respectively (p = 0.795, OR [95%CI] = 1.27 [0.46–3.49]). The highest mortality rate in the group of ADCs patients was attributed to NHL (20%, n = 5), followed by KS (15.1%, n = 5) and invasive cervical cancer (9.1%, n = 1). However, due to the low number of cases, we were not able to stratify the mortality rate according to different subtypes of NADCs.

**Table 1**
Baseline characteristics of HIV-infected patients diagnosed with AIDS and non-AIDS defining cancers.

| Baseline characteristics | AIDS-defining malignancies (n = 69) | Non-AIDS-defining malignancies (n = 41) | P value |
|---|---|---|---|
| Age, mean (SD), years | 42 (33–52) | 45 (36–58) | 0.552 |
| Male sex (n, %) | 42 (60.8) | 20 (48.7) | 0.238 |
| HIV transmission route (n, %) | | | |
| Cohort[a] | 7 (10.1) | 6 (14.6) | 0.480 |
| Sexual (HTX + MSM) | 54 (78.2) | 28 (68.3) | 0.265 |
| PWID | 5 (7.2) | 2 (4.9) | 0.622 |
| Unknown | 3 (4.5) | 5 (12.2) | 0.125 |
| CDC stages (n, %) | | | |
| A | 2 (2.9) | 2 (4.9) | 0.591 |
| B | 8 (11.6) | 10 (24.3) | 0.079 |
| C | 49 (71) | 27 (65.9) | 0.571 |
| Unknown | 10 (14.5) | 2 (4.9) | 0.117 |
| Coexisting infections rate (n, %) | | | |
| Candidiasis | 55 (79.7) | 22 (53.7) | 0.003 |
| Tuberculosis | 10 (14.5) | 4 (9.8) | 0.471 |
| CMV reactivation | 5 (7.2) | – | 0.155 |
| Cryptococcosis | 2 (2.9) | – | 0.528 |
| Pelvic inflammatory disease | 4 (5.8) | 1 (2.4) | 0.413 |
| Toxoplasmosis | 3 (4.3) | – | 0.292 |
| Pneumocystosis | 3 (4.3) | – | 0.292 |
| Herpes zoster | – | 2 (4.9) | 0.136 |
| HBsAg positive (n, %) | 7 (11.5) | 4 (10.8) | 1 |
| HCV Ab positive (n, %) | 5 (8.5) | 7 (19.4) | 0.2 |
| CD4 at HIV diagnosis; mean cells/mm$^3$ (SD) | 256 (281) | 232 (126) | 0.756 |
| CD4 at cancer diagnosis; mean cells/mm$^3$ (SD) | 410 (379) | 340 (250) | 0.350 |
| HIV-RNA at HIV diagnosis; mean copies/mL (SD) | 474,185 (874,974) | 435,828 (1,428,066) | 0.886 |
| HIV-RNA at cancer diagnosis; mean copies/mL (SD) | 341,516 (1,475,239) | 137,601 (443,646) | 0.538 |
| HIV-RNA <50 copies/mL at cancer diagnosis (n, %)[b] | 19 (38.8) | 10 (47.6) | 0.491 |

Legend of table: HTX, heterosexual; MSM, men who have sex with men; PWID, people who inject drugs; CMV, cytomegalovirus; HBsAg, hepatitis B surface antigen; HCV Ab, antibodies against hepatitis C virus;

[a] Adults from the cohort of children from orphanages who were horizontally infected in the late 1980s and early 1990s as a result of the particular epidemiological accident in Romania caused by the parenteral transmission of HIV in connection with several healthcare procedures.

[b] Estimation based on available results (49 results available in ADCs group; 21 results available in NADCs group).

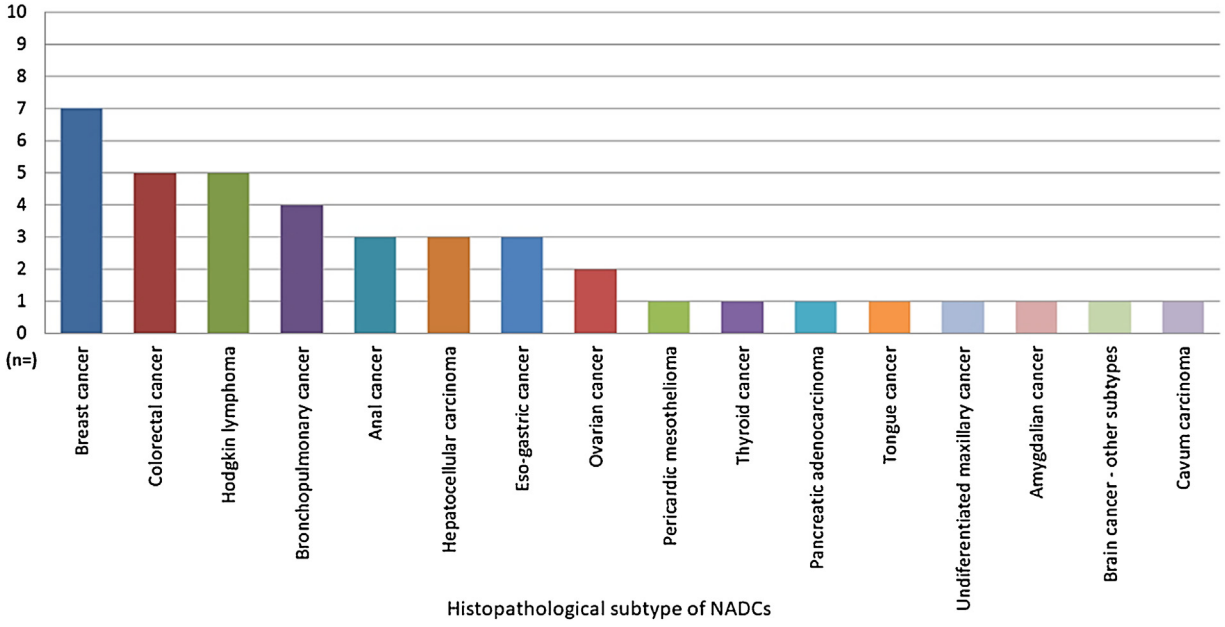


**Fig. 2.** Distribution of different subtypes of NADCs.

**Table 2**
Incidence rate of ADCs and NADCs over a 7-years period (2010–2016).

| Year | Total number of adult PLHIV (n) | ADCs (n) | Incidence (%) | NADCs (n) | Incidence (%) |
|---|---|---|---|---|---|
| 2010 | 1211 | 19 | 1.6 | 4 | 0.3 |
| 2011 | 1268 | 8 | 0.6 | 5 | 0.4 |
| 2012 | 1623 | 6 | 0.5 | 5 | 0.3 |
| 2013 | 1528 | 7 | 0.5 | 5 | 0.3 |
| 2014 | 1655 | 6 | 0.4 | 7 | 0.4 |
| 2015 | 1897 | 9 | 0.5 | 6 | 0.3 |
| 2016 | 2168 | 6 | 0.3 | 3 | 0.1 |

**Table 3**
Different types of therapeutic protocols applied to patients with ADCs and NADCs.

| Treatment protocols (n, %) | AIDS-defining malignancies (n = 69) | Non-AIDS-defining malignancies (n = 41) | P Value |
|---|---|---|---|
| cART only | 52 (75.4) | 21 (51.2) | 0.009 |
| cART + CHTx | 5 (7.2) | 4 (9.8) | 0.642 |
| cART + Surgery | 7 (10.1) | 7 (17.1) | 0.291 |
| cART + RTx | 2 (2.9) | – | 0.528 |
| cART + Surgery + CHTx | – | 7 (17.1) | 0.0007 |
| cART + Surgical + RTx | 2 (2.9) | 1 (2.4) | 0.886 |
| cART + CHTx + RTx | 1 (1.5) | 1 (2.4) | 0.707 |

Legend of table: CHTx, cytotoxic chemotherapy; RTx, radiotherapy.

*Prediction of mortality*

The univariate analysis showed that a higher CD4 count and lower HIV-RNA level at the moment of cancer diagnosis, but not HIV diagnosis, were associated with prolonged survival in ADCs group of patients. The mean CD4 count was 449 (382)/mm$^3$ in survivors, significantly higher than in non-survivors (92 (117)/mm$^3$, p = 0.017). The mean level of HIV-RNA was 64,671 (118,015) copies/mL in survivors, significantly lower compared to 1,760,345 (3,477,680) copies/mL in non-survivors (p = 0.002). Neither CD4 count nor HIV-RNA level at the moment of both HIV and cancer diagnosis were significantly associated with survival of patients with NADCs. However, it has been observed that NADC survivor patients had a higher value of absolute CD4 count and lower levels of HIV-RNA both at HIV and cancer diagnosis. The analysis of possible predictor baseline factors associated with mortality is shown in Table 4.

*Survival rate*

Kaplan–Meier curve analysis was used to estimate the survival of patients diagnosed with ADCs and NADCs followed-up over a period of 7-years (Fig. 3).

There were no statistically significant differences in survival between the two groups of patients (p = 0.249), although a slight downward trend in survival was observed in NADC patients.

## Discussion

We conducted this retrospective study in order to have a better epidemiological overview of malignancies in our HIV population taking into account the peculiarities of the HIV epidemic in Romania: high prevalence of subtype F1 of HIV-1 infections and adult patients from the "old" cohort of HIV infected children by horizontal route, majority during the years 1988–1990. They represent a young population by age but old by length of HIV infection. In addition, we aimed to emphasize the medical needs of our oncologic HIV infected patients for developing an action plan focused on prevention, age-appropriate screening programs and facilitating access to cancer therapy.

Despite the availability of potent and better tolerated antiretroviral drugs in Romania, the results of our study have shown that the percentage of patients diagnosed with AIDS-defining malignancies is still significantly higher compared to those diagnosed with non-AIDS-defining malignancies (62.7% vs 37.3%, p = 0.0001). There are several explanations for this finding such as higher percent of patients diagnosed in advanced stage of HIV infection (71%) and a lower rate of undetectable HIV-RNA under cART (38.8%) compared with viral response rate reported nationwide (62%). The primary route of HIV transmission was associated to sexual exposure both for ADC and NADC patients (78.2% vs 68.3%, p = 0.265). Regarding the CDC classification, the majority of patients in both categories were diagnosed in AIDS stage (71% vs 65.9%, p = 0.571). An important observation of this study was related to the mean age that was similar for the two groups of patients (42 years vs 45 years, p = 0.552). This finding might explain the lower prevalence of non-AIDS-defining neoplasia in a relatively young HIV population. It is well known that aging is one of the main conditions associated with the increased risk of developing the NADCs [4]. In addition, an important risk factor that impacts the incidence of NADCs is the length of HIV infection [16,17]. It is worth mentioning that more than one third of the adult Romanian HIV patients are part of the

**Table 4**
Univariate analysis of CD4 count and HIV-RNA levels as possible predictor baseline factors associated with mortality.

| Analysis of mortality predictive factors | Death | N | Mean | Standard deviation | Standard Error mean | P Value |
|---|---|---|---|---|---|---|
| ADCs | | | | | | |
| CD4 (/mm$^3$) at cancer diagnosis | 0 | 57 | 449 | 382 | 50.563 | 0.017 |
| | 1 | 7 | 92 | 117 | 44.071 | |
| CD4 (/mm$^3$) at HIV diagnosis | 0 | 36 | 293 | 298 | 49.607 | 0.066 |
| | 1 | 8 | 91 | 74 | 26.133 | |
| HIV-RNA (cp/mL) at HIV diagnosis | 0 | 35 | 397,117 | 839,277 | 141,863.661 | 0.231 |
| | 1 | 8 | 811,356 | 1,006,257 | 355,765.661 | |
| HIV-RNA (cp/mL) at cancer diagnosis | 0 | 41 | 64,671 | 118,015 | 18,430.857 | 0.002 |
| | 1 | 8 | 1,760,345 | 3,477,680 | 1,229,545.478 | |
| NADCs | | | | | | |
| CD4 (/mm$^3$) at cancer diagnosis | 0 | 25 | 364 | 253 | 50.619 | 0.330 |
| | 1 | 7 | 257 | 239 | 90.288 | |
| CD4 (/mm$^3$) at HIV diagnosis | 0 | 11 | 251 | 127 | 38.266 | 0.276 |
| | 1 | 3 | 159 | 111 | 64.211 | |
| HIV-RNA (cp/mL) at HIV diagnosis | 0 | 27 | 501,165 | 1,549,940 | 298,286.187 | 0.556 |
| | 1 | 5 | 83,006 | 75,233 | 33,645.410 | |
| HIV-RNA (cp/mL) at cancer diagnosis | 0 | 16 | 172,493 | 506,438 | 126,609.408 | 0.533 |
| | 1 | 5 | 25,946 | 43,089 | 19,269.989 | |

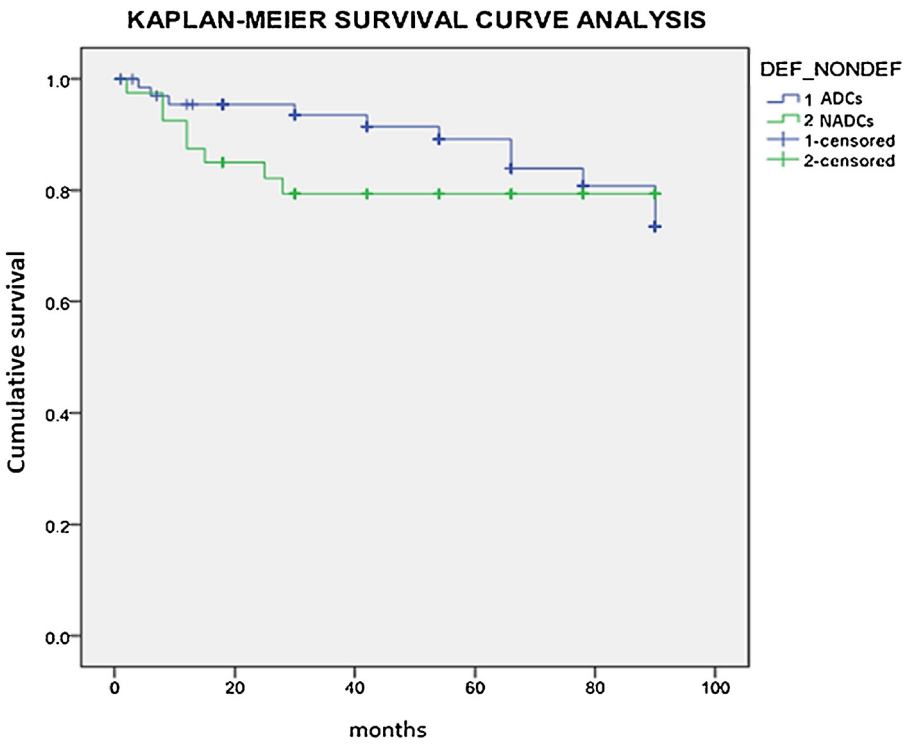


**Fig. 3.** Cumulative survival (months) of the patients diagnosed with ADCs and NADCs over a 7-years period (2010–2016).

cohort of HIV infected children [15]. Nevertheless, only 10.1% of patients diagnosed with ADCs and 14.6% of patients diagnosed with NADCs belong to that cohort.

The incidence of ADCs in our study was decreasing from 1.6% in 2010 to 0.3% in 2016. On the other hand, the incidence of NADCs remained fairly stable over time, between 0.3%–0.4% from 2010 to 2015, with a lower incidence in 2016 (0.1%). KS was the most frequent type of AIDS-defining neoplasia (48%), followed by NHL (36%) and cervical cancer (16%). Cutaneous subtype of KS was found in 63.7% of all patients diagnosed with KS. Digestive cancers, including anal carcinoma (26.8%), breast cancer (17%), HL (12.2%) and hepatocellular carcinoma (7.3%) accounted for the majority of NADCs. One important limit of our study was the absence of a comparative analysis of incidence and prevalence data with the pre-2010 period. The existing data showed that the incidence of all types of cancer diagnosed in HIV population, including both ADCs and NADCs had a favorable trend, with a decrease of 81% in the late cART compared with the pre-cART period. The last two decades have been dominated by the decline in the incidence of KS and NHL. Other studies revealed an increasing of NADCs incidence since the introduction of cART, especially for anal cancer, hepatocellular carcinoma, lung cancer and Hodgkin's lymphoma [18].

In univariate analyses, the higher CD4 count and lower HIV-RNA level at the cancer diagnosis but not HIV diagnosis were associated with improved survival of patients with ADCs. The mean CD4 count was 449/mm$^3$ for survivors compared to 92/mm$^3$ in non-survivors ($p = 0.017$). In addition, the mean level of HIV-RNA was 64,671 copies/mL for survivors compared to 1,760,345 copies/mL in non-survivors ($p = 0.002$). Nevertheless, in the group of NADC patients, the CD4 count and HIV-RNA level were not associated with the survival neither at the HIV diagnosis nor at the cancer diagnosis. The results of another cohort study showed that a higher nadir CD4 count and higher CD4 count at NADC diagnosis were associated with prolonged survival. However, no significant association has been observed with HIV-RNA level at NADC diagnosis [19]. Survival rate of the patients with ADCs and NADCs showed no statistically significant differences between the two groups over a followed-up period of about 7 years ($p = 0.249$). Mortality analyses based on other risk factors such as HBV and HCV co-infections, the histopathological type and cancer stage at the moment of diagnosis were limited due to the relatively small number of patients in each subgroup. Moreover, we were not able to quantify the prevalence of other modifiable risk factors such as smoking and alcohol consumption in our study population.

Regarding the access to cancer treatment, 75.4% of patients diagnosed with ADCs and 51.2% of patients diagnosed with NADCs received only cART ($p = 0.009$). Besides cART, different combination of treatments (surgery, radiotherapy and chemotherapy) have been used in both group of patients, with significantly higher percent of NADC patients (17.1%) who received complex treatment (cART, surgery and CHTx) than none in the ADC patients ($p = 0.0007$). In general, the indication of treatment for cancer is different depending on the stage of cancer and the histopathological type, with decreasing access to curative treatments in favor of palliative treatments in advanced stages of the disease. In our study we were not able to analyze the access to different types of cancer treatments depending on the disease stage and the histopathological type. Although standard treatment should be offered to HIV-infected patients with a newly diagnosis of cancer, mainly NADC, it appears that in clinical practice the access of patients to oncological therapy is lower than in HIV negative patients [20]. From the practical point of view, there are some clinical challenges with potential impact on likelihood of offering cancer treatment such as drug-drug interactions, cumulative toxicity and the additional immunosuppressive effect of chemotherapy [21,22]. Moreover, available data from randomized control trials regarding the outcomes and toxicity of cancer treatments in PLHIV are limited because historically HIV positive patients were excluded from oncological clinical trials [19,22]. Also, among clinicians there are often perceptions that HIV-infected patients with malignancies have lower performance status, higher probability of developing treatment toxicity and thus a limited benefit from cancer treatment [23]. On the other hand,

there are studies which have shown similar toxicity and outcomes in the treatment of various cancers, regardless of the patient's HIV status [22,24]. However, statistical data showed that NADC patients usually have more aggressive and advanced disease at baseline, being a reasonable explanation for the poorer results of cancer treatments in this population [21].

The strengths of this study are reflected by highlighting the epidemiology of HIV-associated malignancies in an Caucasian population with a certain epidemiological background such as the circulating subtype of HIV (predominantly the HIV F1 subtype), the relatively young age of patients, some of them with long-term exposure to both HIV and ARV (pediatric AIDS cohort) and free access to ARV therapy regardless of CD4 value. Concerning the shortcomings of this study we mentioned the absence of a comparative analysis of incidence and prevalence data with the pre-2010 period to define the role of new cART in the changes of the HIV-associated cancers epidemiology. In addition, we did not include in our analysis the type of previous and current ARV regimen and the traditional risk factors like smoking and alcohol intake. Moreover, due to the low number of cases for each subtype of cancers we were not able to perform a multivariate analysis in order to identify possible prognosis predictors.

Regarding the Romanian HIV population belonging to the cohort of horizontally HIV infected children, we ask about the long-term risk of developing NADCs and when should we start age-appropriate screening for cancer in this particular HIV population.

Cancer prevention is a key objective for each clinician dealing with HIV, comprising limiting exposure to modifiable risk factors, active immunization against human papillomavirus (HPV) infection, and prevention and treatment of acute and chronic HBV/HCV infection. One of the major challenges in the near future will be the development of cancer screening programs that need to be validated in HIV infected patients in order to have a cancer diagnosis in early stages. Reducing morbidity and cancer mortality is directly related to improving general and specific HIV management and reducing disparities among certain population risk groups such as people who inject drugs (PWID), men who have sex with men (MSM) and people with very low socio-economic status throughout the cascade of care. An important issue is related to the limited experience of other physicians such as oncologists in the treatment of patients with HIV infection. Thus, the development of centers with experience in treatment of HIV-associated cancers, consisting of oncologists and infectious diseases physicians, can facilitate patients' access to standard protocols for cancer therapy and ultimately can increase confidence among medical staff regarding the outcomes of treatments. In addition, for the future we propose to improve the reporting system of HIV-associated malignancies in a single national registry in order to have a better picture of the epidemiology of different cancers in the HIV population. Moreover, the data collected in this registry might be useful for highlighting the needs of the various HIV populations to act in a specific manner for each target group.

## Conclusions

Although the incidence of ADCs declined progressively over time, the overall burden of ADCs was still higher than NADCs, suggesting that late presenter patients account for a significant fraction of Romanian HIV infected patients. A good therapeutic control of HIV infection at the moment of ADC diagnosis was associated with prolonged survival, reemphasizing the key role of the effective cART in the management of HIV-associated cancers. The main shortcomings identified in our HIV population were limited access to oncology therapy for certain patient subgroups and the absence of a validated cancer screening program addressed to the specificity of our patients.

## Authors' contributions

VG, IFC and AMCR designed the study methods.
IFC, IS, MM collect the data.
VG and IFC analyzed the data.
VG, AMCR, SP, MM, ASC wrote the first draft of the manuscript.
VG, IFC, IS, MM, SP and ASC contributed to the writing of the manuscript.
VG, IS, MM, SP, ASC agreed with the manuscript results and conclusions.
ASC assisted the interpretation of results.

## Funding

No funding Sources.

## Competing interests

None declared.

## Ethical approval

Not required.

## Acknowledgements

We would like to thank all the patients and medical staff of the National Institute for Infectious Diseases "Prof. Dr. Matei Balş", Bucharest, Romania.

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