The Spectrum of Malignancies among Adult HIV Cohort in Poland between 1995 and 2012: A Retrospective Analysis of 288 Cases

Jacek Kowalski1, Grażyna Cholewińska1, Karolina Pyziak-Kowalska1, Elżbieta Jablonowska2, Grażyna Baralkiewicz3, Anna Grzeszczuk4, Magdalena Leszczyżn-Pynka5, Anila Olczak6, Maria Jankowska7, Tomasz Mikula8, Monika Bociaga-Jasilk8, Ewa Firląg-Burkacka8, Andrzej Horban9

1Hospital for Infectious Diseases in Warsaw, Warsaw, Poland
2University of Lodz, Lodz, Poland
3Poznan University of Medical Sciences, Poznan, Poland
4Medical University of Bialystok, Bialystok, Poland
5Pomeranian Medical University, Szczecin, Poland
6Nicolaus Copernicus University, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Bydgoszcz, Poland
7Medical University of Gdańsk, Gdańsk, Poland
8Medical University of Warsaw, Warsaw, Poland
9Jagiellonian University Medical College, Krakow, Poland

Introduction

The prevalence and spectrum of malignancies have continued to grow, resulting in high morbidity and mortality. It also concerns, with no exceptions, people living with human immunodeficiency virus (PLHIV) [1–3]. Experience has taught us that several malignancies, such as Acquired Immunodeficiency Syndrome-AIDS-defining malignancies (ADMs), including Kaposi sarcoma (KS), non-Hodgkin’s lymphoma (NHL), and an invasive cervical cancer (ICC) are closely connected with human immunodeficiency virus (HIV) infection and are found more frequently in HIV-infected patients. Since the introduction of combination antiretroviral therapy (cART), the number of ADMs as a whole has decreased significantly. Nevertheless, it remains a significant problem and one of the major causes of death [4–6]. There also exist non-AIDS-defining malignancies (NADMs), the number of which seems still to be rising and the reasons for which may be completely different [7–13]. NADMs appear to have increased prevalence and higher malignancy-related mortality attributable to earlier onset, a more advanced malignancy stage, and a worse prognosis at malignancy diagnosis in HIV-infected patients than in the general population [9–10, 14–17]. Although the introduction of cART has considerably improved HIV positive patients’ prognosis and contributed to a significant decrease of opportunistic infections prevalence and mortality, NADMs have become responsible for a new challenge in HIV-positive patients’ care and cure. It is still unclear whether the number of NADMs has indeed increased or whether their prevalence is the result of both increased surveillance and longevity of HIV-positive patients [18–19]. Furthermore, there are many possible reasons and risk factors of NADMs prevalence in HIV-infected individuals. The rise in survival caused by cART may also result in an increased exposure of the population to oncogenes, including, among others, HIV chronic infection, prolonged immunosuppression, environmental...
were divided into ADMs and NADMs. Additionally, NADMs and virus unrelated (NADMs-VUR). Epidemiological data was analysed according to demographic data, medical history, HIV-related information, ART, and malignancies' outcome, and was collected from all patients at the time of malignancy diagnosis. The contact with HBV was defined as HBV surface antigen positive. The contact with HCV was defined as HCV core antibody positive at baseline or ever in the past. Baseline characteristics of the patients are summarised in Table 1, stratified by separate malignancy types. A standard descriptive analysis was performed, including frequency distributions for categorical data and calculation of medians alongside interquartile ranges (IQR) for continuous variables. The predictors of declining screening were explored using univariate and multivariate logistic regression. The parameters Odds Ratio (OR) and 95% confidence limits (95% CI) were reported in the analysis of the association of chosen attributes in various types of cancers (ADMs vs. NADMs and NADMs-VR vs. NADMs-VUR). The system R and package EpiTools of the function Epitab were used for data calculation. The Fisher’s exact test was used to calculate the p-value. Specific ethical approval for this study was not a requirement, in accordance with Polish national legislation.

Results

In this study, between 1995 and 2012, a total of 288 malignancies were finally confirmed in 285 HIV-infected adult patients and were ultimately included in the analyses. One patient diagnosed with NADM was previously diagnosed with an ADM, and two patients were diagnosed with two malignancies from the same group; however, they occurred at different times. In the vast majority of the cases, the malignancies were confirmed by histological examination (n = 260; 90.3%) and the rest were defined as the probable degree of certainty as mentioned above (n = 28; 9.7%). Table 1 gives the main characteristics of patients included in the present study. The mean age at the malignancy diagnosis was 41 years (IQR, 20–81 years); the youngest for ADMs was 46 years. Patients were mainly male (n = 208; 72.2%) and of white ethnic origin (n = 284; 98.6% Caucasian). Overall, the risk behaviours reported were as follows: 37.8% Injecting Drug Users (IDUs; n = 109), 33.3% Men who have Sex with Men (MSM; n = 96), and 24.3% heterosexual (n = 70), and they were broadly similar to each group of malignancies. Men who have Sex with Men dominated solely in the ADMs group (n = 61; 38.4%) where KS diagnosed patients constituted 75.5% (n = 37). HIV-infected patients diagnosed with malignancies had, in the majority, smoked tobacco at some time (n = 216; 75%) and they had high prevalence of co-infections with HBV (n = 105; median 36.5%) and HCV (n = 116; median 40.3%).

Most of the patients showed advanced HIV disease. In total, 87.2% (n = 250) had an AIDS diagnosis before malignancy diagnosis, and 74.1% (n = 214) had an AIDS diagnosis before malignancy diagnosis. The median age at the time of malignancy diagnosis was 41 years (IQR, 20–81 years); the youngest for ADMs was 38 years and the most advanced for NADMs was 96 years. Five patients were late presenters. Moreover, most of them were previously diagnosed with AIDS – over two third of them (n = 219;
Table 1. Characteristics of the patients at the time of malignancies’ diagnosis, for all malignancies in total and for each group: ADMs, NADMs, NADMs-VR, NADMs-VUR

| Characteristics (n = 288): | Total (n = 288) | ADMs (n = 159) | NADMs (n = 129) | NADMs-VR (n = 58) | NADMs-VUR (n = 71) |
|---------------------------|----------------|---------------|----------------|-------------------|-------------------|
| Age at baseline           |                |               |                |                   |                   |
| median [IQR] (years)      | 41 [20-81]     | 38 [21-66]    | 45 [20-81]     | 44 [22-71]        | 46 [20-81]        |
| Gender                    |                |               |                |                   |                   |
| male                      | 208 (72.2)     | 106 (66.7)    | 102 (79.1)     | 50 (86.2)         | 52 (73.2)         |
| female                    | 80 (27.8)      | 53 (33.3)     | 27 (20.9)      | 8 (13.8)          | 19 (26.8)         |
| Race                      |                |               |                |                   |                   |
| Caucasian                 | 284 (98.6)     | 156 (98.1)    | 129 (100.0)    | 58 (100.0)        | 70 (98.6)         |
| other                     | 4 (1.4)        | 3 (1.9)       | 0 (0.0)        | 0 (0.0)           | 1 (1.4)           |
| Exposure group            |                |               |                |                   |                   |
| homosexual                | 96 (33.3)      | 61 (38.4)     | 35 (27.1)      | 17 (29.3)         | 18 (25.4)         |
| IDU                       | 109 (37.8)     | 54 (34.0)     | 55 (42.6)      | 28 (48.3)         | 27 (38.0)         |
| heterosexual              | 70 (24.3)      | 38 (23.9)     | 32 (24.8)      | 13 (19.0)         | 21 (29.6)         |
| other                     | 13 (4.5)       | 6 (3.8)       | 7 (5.4)        | 2 (3.4)           | 5 (7.0)           |
| Hepatitis B status        |                |               |                |                   |                   |
| negative                  | 182 (63.2)     | 107 (67.3)    | 75 (58.1)      | 36 (62.1)         | 39 (54.9)         |
| positive                  | 105 (36.5)     | 51 (32.1)     | 54 (41.9)      | 22 (37.9)         | 32 (45.1)         |
| unknown                   | 1 (0.3)        | 1 (0.6)       | 0 (0.0)        | 0 (0.0)           | 0 (0.0)           |
| Hepatitis C status        |                |               |                |                   |                   |
| negative                  | 167 (58.0)     | 97 (61.0)     | 70 (54.3)      | 27 (46.6)         | 43 (60.6)         |
| positive                  | 116 (40.3)     | 58 (36.5)     | 58 (45.0)      | 31 (53.4)         | 27 (38.0)         |
| unknown                   | 5 (1.7)        | 4 (2.5)       | 1 (0.8)        | 0 (0.0)           | 1 (1.4)           |
| Ever smoked               |                |               |                |                   |                   |
| yes                       | 216 (75.0)     | 114 (71.7)    | 102 (79.1)     | 46 (79.3)         | 56 (78.9)         |
| no                        | 72 (25.0)      | 45 (28.3)     | 27 (20.9)      | 12 (20.7)         | 15 (21.1)         |
| Ever abused alcohol       |                |               |                |                   |                   |
| yes                       | 129 (44.8)     | 74 (46.5)     | 55 (42.6)      | 31 (53.4)         | 24 (33.8)         |
| no                        | 159 (55.2)     | 85 (53.5)     | 74 (57.4)      | 27 (46.6)         | 47 (66.2)         |
| Ever abused drugs         |                |               |                |                   |                   |
| yes                       | 112 (38.9)     | 57 (35.8)     | 55 (42.6)      | 29 (50.0)         | 26 (36.6)         |
| no                        | 176 (61.1)     | 102 (64.2)    | 74 (57.4)      | 29 (50.0)         | 45 (63.4)         |
| Duration of HIV-infection |                |               |                |                   |                   |
| < 1                       | 90 (31.3)      | 66 (41.5)     | 24 (18.6)      | 10 (17.2)         | 14 (19.7)         |
| 1-5                       | 85 (29.5)      | 46 (28.9)     | 39 (30.2)      | 16 (27.6)         | 23 (32.4)         |
| 6-10                      | 46 (16.0)      | 22 (13.8)     | 24 (18.6)      | 14 (24.1)         | 10 (14.1)         |
| > 10                      | 67 (23.3)      | 25 (15.7)     | 42 (32.6)      | 18 (31.0)         | 24 (33.8)         |
| Prior opportunistic infections |    |               |                |                   |                   |
| yes                       | 127 (44.0)     | 61 (38.4)     | 66 (51.2)      | 35 (60.3)         | 31 (43.7)         |
| no                        | 161 (55.9)     | 98 (61.6)     | 63 (48.8)      | 23 (39.7)         | 40 (56.3)         |
| Nadir CD4 count           |                |               |                |                   |                   |
| median [IQR] (cells/mm³)  | 145 [0-1265]   | 135 [0-1265]  | 157 [2-965]    | 131 [2-426]       | 179 [2-965]       |
| CD4 count at baseline     |                |               |                |                   |                   |
| median [IQR] (cells/mm³)  | 282 [8-1265]   | 232 [3-1265]  | 345 [8-1260]   | 283 [8-1260]      | 395 [18-1242]     |
| VL suppression at baseline|                |               |                |                   |                   |
| (< 50 copies/ml)          |                |               |                |                   |                   |
| yes                       | 89 (30.9)      | 32 (20.1)     | 57 (44.2)      | 25 (43.1)         | 31 (43.7)         |
| no                        | 175 (60.8)     | 109 (68.6)    | 66 (51.2)      | 28 (48.3)         | 39 (54.9)         |
| unknown                   | 24 (8.3)       | 18 (11.3)     | 6 (4.7)        | 5 (8.6)           | 1 (1.4)           |
| Ever started cART before malignancies’ diagnosis | | | | | |
| yes                       | 150 (52.1)     | 70 (44.0)     | 80 (62.0)      | 33 (56.9)         | 47 (66.2)         |
| no                        | 138 (47.9)     | 89 (56.0)     | 49 (38.0)      | 25 (43.1)         | 24 (33.8)         |
| cART at baseline          |                |               |                |                   |                   |
| yes                       | 139 (48.3)     | 63 (39.6)     | 76 (58.9)      | 33 (56.9)         | 43 (60.6)         |
| no                        | 149 (51.7)     | 96 (60.4)     | 53 (41.1)      | 25 (43.1)         | 28 (39.4)         |
| Duration of cART (years)  |                |               |                |                   |                   |
| < 1                       | 138 (47.9)     | 89 (56.0)     | 49 (38.0)      | 25 (43.1)         | 24 (33.8)         |
| 1-2                       | 48 (16.7)      | 33 (20.8)     | 15 (11.6)      | 6 (10.3)          | 9 (12.7)          |
| 3-5                       | 33 (11.5)      | 18 (11.3)     | 15 (11.6)      | 7 (12.1)          | 8 (11.3)          |
| > 5                       | 23 (8.0)       | 8 (5.0)       | 15 (11.6)      | 6 (10.3)          | 9 (12.7)          |
76.0%) had nadir CD4+ cell count < 200 cells/mm³ (Centres for Disease Control and Prevention (CDC) classification system-clinical categories 3) and/or almost half of the patients (n = 127; 44%) had experienced at least one of the opportunistic infections (not including ADMs) before the baseline (CDC classification system – clinical categories C). An average duration of HIV infection before the diagnosis was short, averaging 5.7 years. Attention shall be paid to a longer period of HIV infection among NADMs, particularly among the NADMs-VR. Mean nadir CD4+T cell count was 145 cells/mm³ (the lowest for NADMs-VR 131 cells/mm³ and the highest for NADMs-VUR 179 cells/mm³). The average duration of cART according to accurate diagnosis period, while the highest mortality was registered for NADMs-VR (n = 58). For as much as 92.9% of patients, the opportunistic infections (not including ADMs) before the baseline (CDC classification system – clinical categories A) were not confirmed malignancies from each group is represented by a percentage against the total sum, and they were divided into types of malignancies’ prevalence in certain periods of time, most of malignancies increased,

### Table 1. cont. Characteristics of the patients at the time of malignancies’ diagnosis, for all malignancies in total and for each group: ADMs, NADMs, NADMs-VR, NADMs-VUR

| Characteristics                      | Total (n = 288) | ADMs (n = 159) | NADMs (n = 129) | NADMs-VR (n = 58) | NADMs-VUR (n = 71) |
|--------------------------------------|----------------|---------------|----------------|------------------|--------------------|
|                                      | n (%)          | n (%)         | n (%)          | n (%)            | n (%)              |
| Death during study period            |                |               |                |                  |                    |
| yes                                  | 130 (45.1)     | 66 (41.5)     | 64 (49.6)      | 33 (56.9)        | 31 (43.7)          |
| no                                   | 158 (54.9)     | 93 (58.5)     | 65 (50.4)      | 25 (43.1)        | 40 (56.3)          |
| Overall survival after malignancies’ diagnosis (years) |                |               |                |                  |                    |
| < 1                                  | 99 (34.4)      | 55 (34.6)     | 44 (34.1)      | 27 (46.6)        | 17 (23.9)          |
| 1-2                                  | 66 (22.9)      | 32 (20.1)     | 34 (26.4)      | 7 (12.1)         | 27 (38.0)          |
| 3-5                                  | 56 (19.4)      | 27 (17.0)     | 29 (22.5)      | 11 (19.0)        | 18 (25.4)          |
| 6-10                                 | 46 (16.0)      | 27 (17.0)     | 19 (14.7)      | 10 (17.2)        | 9 (12.7)           |
| > 10                                 | 21 (7.3)       | 18 (11.3)     | 3 (2.3)        | 3 (5.2)          | 0 (0.0)            |

ADMs – AIDS-defining malignancies; NADMs – non-AIDS-defining malignancies; NADMs-VR – non-AIDS-defining malignancies virus related; NADMs-VUR – non-AIDS-defining malignancies virus unrelated

The most frequent malignancies classified by sex were as follows: non-Hodgkin lymphoma (NHL) (n = 76; 26.4%), Kaposi sarcoma (KS) (n = 49; 17.0%), invasive cervical cancer (ICC) (n = 34; 11.8%), Hodgkin’s disease (HD) (n = 23; 8.0%), lung cancer (n = 18; 6.3%), and hepatocellular carcinoma (HCC) (n = 14; 4.9%). The spectrum of confirmed malignancies from each group is represented by a percentage against the total sum, and they were divided into sexes (Table 2). Taking into consideration the frequency of particular types of malignancies’ prevalence in certain periods of time, most of malignancies increased,

![Fig. 1. Estimated prevalence of AIDS-defining malignancies (ADMs) and non-AIDS-defining malignancies (NADMs). The latter are divided into virus related (NADMs-VR) and virus unrelated (NADMs-VUR) over the presented periods of time.](image)
especially among NADMs – lung, skin, and anal cancer as well as among HD and HCC. The only types of malignancies which showed a tendency to decrease were ICCs and PCNSLs.

On closer inspection of the ADMs and NADMs, multivariate statistical analysis eventually revealed that patients diagnosed with NADM were more often male ($p = 0.024$) and of advanced age: 50–60 years ($p = 0.01$) and $\geq 60$ years ($p < 0.001$). Also, the probability of NADMs prevalence among patients who had been diagnosed with prior opportunistic infections other than ADM is statistically significant and is associated with an increased NADMs risk ($p = 0.032$). Besides, a longer history of HIV-infection (1–5 years: $p = 0.009$; 5–10 years: $p = 0.004$; > 10 years: $p < 0.001$) and successfully received cART currently ($p = 0.003$) alongside HIV-1 viral load suppression ($p < 0.001$) and with higher levels of CD4+T cell count (CD4+ > 501 cells/mm$^3$ vs. $\leq 500$ cells/mm$^3$: $p < 0.001$) at baseline were independent predictors of NADMs, respectively. Comparing NADMs-VR and NADMs-VUR, fewer factors remained statistically significant, namely: nadir CD4+ count > 500 cells/mm$^3$ ($p = 0.03$) and previous or current alcohol abuse ($p = 0.032$) were independent predictors of NADMs-VUR. Moreover, for patients diagnosed with NADM-VUR there is

| Type of malignancies (288 evaluable data sets from 285 patients) | Total, n | Total, % | Men, n | Women, n |
|---------------------------------------------------------------|----------|----------|--------|----------|
| Grand total                                                   | 288      | 100.0    | 208    | 80       |
| **AIDS-Defining Malignancies (ADM) – subtotal:**               |          |          |        |          |
| Non-Hodgkin’s Lymphoma (NHL)                                  | 76       | 26.4     | 57     | 19       |
| Diffuse large B-cell lymphoma (DLBCL):                         |          |          |        |          |
| DLBCLs                                                        | 55       | 19.1     | 40     | 15       |
| Primary central nervous system lymphoma (PCNSL)                | 9        | 3.1      | 3      | 6        |
| Centroblastic lymphoma                                         | 4        | 1.4      | 3      | 1        |
| Burkitt lymphoma                                               | 18       | 6.3      | 15     | 3        |
| Plasmablastic lymphoma (PBL)                                   | 3        | 1.0      | 2      | 1        |
| Kaposi Sarcoma (KS)                                            | 49       | 17.0     | 49     | 0        |
| Invasive Cervical Cancer (ICC)                                 | 34       | 11.8     | 0      | 34       |
| **Non-AIDS-Defining Malignancies (NADM) – subtotal:**          | 129      | 44.8     | 102    | 27       |
| Non-AIDS-Defining Malignancies-Virus Related (NADM-VR):        |          |          |        |          |
| EBV-related:                                                   | 28       | 9.7      | 24     | 4        |
| Hodgkin’s disease (HD)                                         | 23       | 8.0      | 19     | 4        |
| T-cell non-Hodgkin’s lymphoma                                  | 3        | 1.0      | 3.0    | 0        |
| Not classified                                                 | 2        | 0.7      | 2.0    | 0        |
| HPV-related:                                                   | 16       | 5.6      | 13     | 3        |
| Anal                                                           | 9        | 3.1      | 8      | 1        |
| Larynx                                                        | 5        | 1.7      | 4      | 1        |
| Tonsil                                                         | 2        | 0.7      | 1      | 1        |
| HBV and HCV-related                                            | 14       | 4.9      | 13     | 1        |
| Hepatocellular carcinoma (HCC)                                 | 14       | 4.9      | 13     | 1        |
| **Non-AIDS-Defining Malignancies-Virus Unrelated (NADM-VUR):   |          |          |        |          |
| Lung                                                           | 18       | 6.3      | 17     | 1        |
| Skin cancer                                                    | 13       | 4.5      | 9      | 4        |
| Germ cell tumor                                                | 7        | 2.4      | 7      | 0        |
| Colon                                                          | 5        | 1.7      | 3      | 2        |
| Prostate                                                       | 5        | 1.7      | 5      | 0        |
| Thyroid                                                        | 5        | 1.7      | 3      | 2        |
| Acute promyelocytic leukemia                                   | 3        | 1.0      | 1      | 2        |
| Central nervous system                                         | 3        | 1.0      | 2      | 1        |
| Ovary                                                          | 3        | 1.0      | 0      | 3        |
| Breast                                                         | 2        | 0.7      | 0      | 2        |
| Uterus                                                         | 2        | 0.7      | 0      | 2        |
| B-cell chronic lymphocytic leukemia                            | 1        | 0.3      | 1      | 0        |
| Gallbladder                                                    | 1        | 0.3      | 1      | 0        |
| Multiple myeloma                                               | 1        | 0.3      | 1      | 0        |
| Stomach                                                        | 1        | 0.3      | 1      | 0        |
| Suprarenal gland                                               | 1        | 0.3      | 1      | 0        |
a statistical tendency to a shorter life expectancy over a 1-2 year-long period of time ($p = 0.003$) and 2-5 years ($p = 0.004$) after a malignancy diagnosis. All characteristics of the patients at the time of malignancies' diagnosis as well as their statistical relations for ADMs vs. NADMs and for NADMs-VR vs. NADMs-VUR are presented in Tables 3 and 4.

### Table 3. Characteristics of the patients at the time of malignancies’ diagnosis for AIDS-defining malignancies (ADMs) versus non-AIDS-defining malignancies (NADMs). Factors statistically associated with NADMs in bold

| Characteristic | ADMs | NADMs | OR  | 95% CI         | p value |
|---------------|------|-------|-----|----------------|---------|
|               | n    | %     | n   | %             |         |
| Sex           |      |       |     |               |         |
| female        | 53   | 33.3  | 27  | 20.9          | 1       |
| male          | 106  | 66.7  | 102 | 79.1          | 1.889   |
|               |      |       |     |               | 1.104–3.233 | 0.024    |
| Age at the malignancies’ diagnosis (years) |      |       |     |               |         |
| [20; 30)      | 34   | 21.4  | 18  | 14.0          | 1       |
| [30; 40)      | 65   | 40.9  | 22  | 17.1          | 0.639   |
| [40; 50)      | 38   | 23.9  | 41  | 31.8          | 2.038   |
| [50; 60)      | 20   | 12.6  | 32  | 24.8          | 3.022   |
| [60; 81)      | 2    | 0.13  | 16  | 12.4          | 0.1111  |
|               |      |       |     |               | 3.122–73.151 | 0     |
| Duration of HIV-infection at the malignancies’ diagnosis (years) |      |       |     |               |         |
| (0; 1)        | 66   | 41.5  | 24  | 18.6          | 1       |
| (1; 5)        | 39   | 24.5  | 35  | 27.1          | 1.468   |
| [5; 10)       | 26   | 16.4  | 27  | 20.9          | 2.856   |
| [10; 34)      | 28   | 17.6  | 43  | 33.3          | 4.223   |
|               |      |       |     |               | 2.168–8.228 | 0     |
| Opportunistic infections before malignacies’ diagnosis |      |       |     |               |         |
| no            | 98   | 61.6  | 63  | 48.8          | 1       |
| yes           | 61   | 38.4  | 66  | 51.2          | 1.683   |
|               |      |       |     |               | 1.051–2.694 | 0.032   |
| Nadir CD4 count (cells/mm$^3$) |      |       |     |               |         |
| (0; 200)      | 126  | 79.2  | 93  | 72.1          | 1       |
| [200; 350)    | 21   | 13.2  | 24  | 18.6          | 1.548   |
| [350; 500)    | 8    | 0.50  | 6   | 0.47          | 1.016   |
| (＞500)        | 4    | 0.25  | 6   | 0.47          | 2.032   |
| Smoking status |      |       |     |               | 0.558–7.407 | 0.336   |
| no            | 45   | 28.3  | 27  | 20.9          | 1       |
| yes           | 114  | 71.7  | 102 | 79.1          | 1.491   |
|               |      |       |     |               | 0.863–2.576 | 0.172   |
| Alcohol status |      |       |     |               |         |
| no            | 85   | 53.5  | 74  | 57.4          | 1       |
| yes           | 74   | 46.5  | 55  | 42.6          | 0.854   |
|               |      |       |     |               | 0.535–1.363 | 0.552   |
| Drugs status  |      |       |     |               |         |
| no            | 102  | 64.2  | 74  | 57.4          | 1       |
| yes           | 57   | 35.8  | 55  | 42.6          | 1.33    |
|               |      |       |     |               | 0.826–2.141 | 0.274   |
| Hepatitis C status |      |       |     |               |         |
| negative      | 97   | 61.0  | 70  | 54.3          | 1       |
| positive      | 58   | 36.5  | 58  | 45.0          | 1.386   |
| unknown       | 4    | 0.25  | 1   | 0.08          | 0.246   |
|               |      |       |     |               | 0.938–3.167 | 0.65   |
| Hepatitis B status |      |       |     |               |         |
| negative      | 107  | 67.3  | 75  | 58.1          | 1       |
| positive      | 51   | 32.1  | 54  | 41.9          | 1.511   |
| unknown       | 1    | 0.06  | 0   | 0.00          | 0       |
|               |      |       |     |               | 0.932–2.449 | 0.109   |
| CD4+ count at the malignancies’ diagnosis (cells/mm$^3$) |      |       |     |               |         |
| (3; 51)       | 38   | 23.9  | 15  | 11.6          | 1       |
| (51; 501)     | 102  | 64.2  | 81  | 62.8          | 2.012   |
| [501; 1001)   | 19   | 11.9  | 33  | 25.6          | 4.4     |
|               |      |       |     |               | 0.039–10.011 | 0     |
| cART before malignancies’ diagnosis |      |       |     |               |         |
| no            | 89   | 56.0  | 49  | 38.0          | 1       |
| yes           | 70   | 44.0  | 80  | 62.0          | 2.076   |
|               |      |       |     |               | 1.293–3.334 | 0.003   |
| VL suppression at the malignancies’ diagnosis |      |       |     |               |         |
| no            | 121  | 76.1  | 69  | 53.5          | 1       |
| yes           | 38   | 23.9  | 60  | 46.5          | 2.769   |
|               |      |       |     |               | 1.675–4.577 | 0     |
| Death during study period |      |       |     |               |         |
| no            | 93   | 58.5  | 65  | 50.4          | 1       |
| yes           | 66   | 41.5  | 64  | 49.6          | 1.387   |
|               |      |       |     |               | 0.869–2.214 | 0.191   |
| Overall survival after malignancies’ diagnosis (years) |      |       |     |               |         |
| [0; 1)        | 55   | 34.6  | 44  | 34.1          | 1       |
| [1; 2)        | 13   | 0.82  | 20  | 15.5          | 1.923   |
| [2; 5)        | 42   | 26.4  | 38  | 29.5          | 1.131   |
| [5; 10)       | 27   | 17.0  | 23  | 17.8          | 1.065   |
| [10; 17)      | 22   | 13.8  | 4   | 03.1          | 0.227   |
|               |      |       |     |               | 0.073–0.708 | 0.007   |

**Discussion**

Between 1995 and 2012, more than 16,300 cases of HIV infections were registered in Poland (data from the National Institute of Public Health National Institute of Hygiene) [30]. In this retrospective, observational study, both the number of registered cases of HIV infections and
the number of malignancies diagnosed in these patients have been rising over the given periods of time. Not much more than a half ($n = 159/288; 55.2\%$) of the identified cases of malignancy were ADMs, among of which NHL was the most commonly reported and remains the commonest malignancy-related cause of death even in the cART era, as well as among men, while ICC was the commonest among women. Despite the introduction of cART in the mid-1990s, there has been a noticeable downward tendency in Poland over a period of time only applicable to two malignancies sets. The first, PCNSL, dominates in patients with marked immunosuppression and EBV co-infection, which may indirectly testify to partial improvement of earlier HIV diagnosis and of cART access \[4, 5, 31, 32\].

### Table 4. Characteristics of the patients at the time of malignancies’ diagnosis for non-AIDS-defining malignancies virus related (NADM-VR) versus non-AIDS-defining malignancies virus unrelated (NADM-VUR). Factors statistically associated with NADM-VUR in bold

| Characteristic                              | NADM-VR | NADM-VUR | OR 95% CI | p     |
|---------------------------------------------|---------|----------|-----------|-------|
|                                             | n %     | n %      |           |       |
| Sex                                         |         |          |           |       |
| female                                      | 8 13.8  | 19 26.8  | 1         | 0.438 | 0.176–2.015 | 0.084 |
| male                                        | 50 86.2 | 52 73.2  |           |       |
| Age at the malignancies’ diagnosis          | 20; 30  | 11 19.0  | 1 0.636   | 0.18–2.251 | 0.537 |
| (years)                                     | 30; 40  | 11 19.0  | 1 0.636   | 0.18–2.251 | 0.537 |
|                                             | 40; 50  | 21 36.2  | 0.764     | 0.127–4.596 | 1     |
|                                             | 50; 60  | 15 25.9  | 0.721     | 0.223–2.335 | 0.768 |
|                                             | 60; 81  | 4  6.9   | 1.909     | 0.436–8.533 | 0.477 |
| Mode of HIV exposure                        |         |          |           |       |
| bisexual                                    | 2  0.4  | 5  0.7   |           |       |
| heterosexual                                | 11 19.0 | 21 29.6  | 0.764     | 0.127–4.596 | 1     |
| IDU                                         | 28 48.3 | 27 38.0  | 0.386     | 0.069–2.16  | 0.427 |
| MSM                                         | 17 29.3 | 18 25.4  | 0.424     | 0.072–2.483 | 0.428 |
| Duration of HIV-infection at the malignancies’ diagnosis | 0; 1)  | 10 17.2  |           |       |
| (years)                                     | 1; 5    | 15 25.9  | 1.108     | 0.45–2.725  | 1     |
|                                             | 5; 10   | 14 24.1  | 1.875     | 0.327–10.741 | 0.68 |
|                                             | 10; 34  | 19 32.8  | 0.908     | 0.329–2.478 | 0.03 |
| Opportunistic infections before malignancies’ diagnosis | no     | 23 39.7  | 1 0.509   | 0.252–1031  | 0.077 |
|                                             | yes     | 35 60.3  | 5  1.211  | 0.415–2.286 | 1     |
| Nadir CD4 count (cells/mm³)                 | 0; 200  | 45 77.6  |           |       |
|                                             | 200; 350| 11 19.0  | 1.108     | 0.45–2.725  | 1     |
|                                             | 350; 500| 2  0.34  | 0.927     | 0.07–2.521  | 0.99 |
|                                             | > 500   | 0  0.00  | 0.805     | 0.01–2.627  | 0.96 |
| Smoking status                              | no      | 12 20.7  | 1 0.578   | 0.285–117  | 0.153 |
|                                             | yes     | 46 79.3  | 5  0.974  | 0.415–2.286 | 1     |
| Alcohol status                              | no      | 27 46.6  | 1 0.445   | 0.218–0.907 | 0.032 |
|                                             | yes     | 31 53.4  |           |       |
| Drugs status                                | no      | 29 50.0  | 1 0.578   | 0.285–117  | 0.153 |
|                                             | yes     | 29 50.0  |           |       |
| Hepatitis C status                          | negative| 27 46.6  |           |       |
|                                             | positive| 31 53.4  | 1 0.547   | 0.27–1.107  | 0.11 |
|                                             | unknown | 0  0.00  | 0.104     | 0.01–1.04  |       |
| Hepatitis B status                          | negative| 36 62.1  | 1 1.343   | 0.662–2.723 | 0.475 |
|                                             | positive| 22 37.9  | 1 1.343   | 0.662–2.723 | 0.475 |
|                                             | unknown | 0  0.00  | 0.000     | NaN-NaN-NaN | NaN |
| CD4+ count at the malignancies’ diagnosis   | 0; 51   | 8 13.8   |           |       |
| (cells/mm³)                                 | 51; 501 | 40 69.0  | 1 1.171   | 0.388–3.533 | 1     |
|                                             | > 501   | 10 17.2  | 1 1.171   | 0.388–3.533 | 1     |
| cART before malignancies’ diagnosis         | no      | 25 43.1  |           |       |
|                                             | yes     | 33 56.9  | 1 1.171   | 0.388–3.533 | 1     |
| VL suppression at the malignancies’ diagnosis | no     | 32 55.2  |           |       |
|                                              | yes     | 26 44.8  | 1 1.171   | 0.388–3.533 | 1     |
| Death during study period                   | no      | 25 43.1  | 1 1.171   | 0.388–3.533 | 1     |
|                                             | yes     | 33 56.9  | 1 1.171   | 0.388–3.533 | 1     |
| Overall survival after malignacies’ diagnosis (years) | 0; 1)  | 27 43.1  |           |       |
|                                              | 1; 2    | 4  06.9  | 1 23.1    | 6.353    | 0.186–22.229 | 0.003 |
|                                              | 2; 5    | 11 19.0  | 1 23.1    | 6.353    | 0.186–22.229 | 0.003 |
|                                              | 5; 10   | 13 22.4  | 1 23.1    | 6.353    | 0.186–22.229 | 0.003 |
|                                              | 10; 17  | 3  05.2  | 1 23.1    | 6.353    | 0.186–22.229 | 0.003 |

OR – odds ratio; 95% CI – 95% confidence limits; cART – combination antiretroviral therapy; VL – viral load

n – odds ratio; 95% CI – 95% confidence limits; cART – combination antiretroviral therapy; VL – viral load
The second malignancy set, namely ICC, the result of several genital HPV types, has been identified as the carcinogenic precursor and necessary co-factor for ICC (not only in women with advanced immunosuppression), and it has been decreasing over the periods of time presented in this study, the reason for which may be easier access and more successful prophylactic programmes, HPV vaccines, early diagnosis, and ICC treatment in Poland (mostly yearly cervical Pap smear) similarly to other studies [4, 5, 19, 25, 33]. Like in other studies, KS occurs predominantly among men (n = 49/49; 100% of the cases in our study) in whom 81.6% (n = 40/49) reported male-to-male sex contact as the mode of HIV transmission, which was probably connected to the same way and prevalence of HHV-8 known to cause of KS [4, 5, 34, 35]. We believe that our findings may reflect a considerably changing epidemiological situation in Poland and may prove this means of HIV transmission to be currently predominant. It might be too early to observe a significant decrease in the prevalence of NHL and KS, and perhaps the HIV infections are still diagnosed too late and in a too advanced phase of infection. In patients unaware of their HIV status, the ADM is often the first opportunistic infection.

Apart from ADMs, the remaining malignancies were either NADMs, with a noticeable upward tendency exceeding the number of ADMs at the time. More recent data has shown several NADMs, most of all viruses being related to HIV-positive patients, to be increasing, similarly to the risk seen in transplantation recipients compared to the general population, suggesting a link between immune suppression proven in the present study [21]. According to the classification of malignancies established hereinafter, 55% (n = 71/129) of them are NADMs-VR and 45% (n = 58/129) are NADMs-VUR, among which HD was the predominant one to be diagnosed in both sexes. It is known that EBV indicates its relation with HD, which can testify to a large number of co-infections with this virus in Poland [36]. Taken as a whole, the recent literature would suggest that HIV infection is currently an independent risk factor of lung cancer [17, 37]. In the present study, lung cancer has been a predominant malignancy among NADMs-VUR, most of which were diagnosed in men (n = 17/18; 94.4%), which suggests that HIV itself is a genuine risk factor of lung cancer, and its highest upward tendency among all NADMs proves a current epidemic of the malignancy in question [38, 39]. In addition, HIV-positive individuals who smoke tobacco are more predisposed to die of solid tumour than the general population [38, 40]. The association with smoking, on the other hand, may reflect the risk behaviour of the people who may engage in unprotected sex or drug use, which can also lead to viral co-infections [23, 40, 41]. In the study, the fact that as many as 75.8% (n = 216/285) of HIV-positive patients had at some time smoked tobacco and as many as 100% (n = 18/18) of those with a lung cancer were heavy smokers accounts for the increasing risk. However, we did not find a statistically significant association of smoking status and NADMs-VUR. Among NADMs-VR, HCC is commonly reported (n = 14/58; 4.9% of all malignancies, second place after HD) and is likely to remain important in HIV-infected populations, particularly in the context of the high level of co-infections with HBV and HCV presented in the study and associated with higher serum hepatitis DNA/RNA viral levels, progression to cirrhosis, and more frequent HCC with more aggressive course and poorer survival time than HIV-negative patients [42–44]. In our study, all the cases of HCC were HBV and/or HCV co-infected (64.3%; n = 9/14 HBV and 92.9%; n = 13/14 HCV; one individual only HBV mono-co-infection), and 78.6% (n = 11/14) also suffered from cirrhosis. We did not find a statistically significant association of HBV or HCV co-infection and NADMs-VR either, which may be explained, as in lung cancer, by low numbers, but may also be due to the inclusion of other malignancies in this analysis, depending on co-infections with other viruses. HCC was diagnosed mostly in elderly men (median age 47.5 years), men (n = 13/14; 92.9%), IDUs mode of acquisition (n = 12/14; 85.7%), after many years of the lack of treatment, or inadequate treatment of HBV and/or HCV co-infection. Furthermore, HCC was usually diagnosed too late, which resulted in poor prognosis. It may indirectly testify to the fact that HCC natural history progression takes from years to decades to occur owing to the former major way of HIV transmission in Poland, being intravenous drug injection. Attention should be drawn to a relatively increasing number of skin cancers over periods of time mostly in women (it should be mentioned that Caucasians are more predisposed to have skin cancer [7]), and few cases of breast cancer in women (n = 2/288; only 2.5% of all malignancies in women, n = 2/80) and no such cases in men. There was also no case of leiomyosarcoma in both sexes. Comparing the malignancies’ prevalence between the countries located in the same region in Europe, strikingly few anal cancers have been diagnosed [45, 46]. Anal cancer was found mostly in men (88.9%; n = 8/9) and homosexuals (77.8%; n = 7/9). It was also diagnosed in further stages, showing the general tendency to increase in recent years. Similarly, a few cases of colorectal carcinoma (only n = 5/288; 1.7%) were diagnosed in surprisingly young people (median age 37.4 years), no matter the sex, the way of HIV transmission, the immune status, and ART or prostate cancer (only n = 5/288; 1.7%, median age 70 years) [4, 45, 47, 48]. There is a necessity of oncological supervision, mostly in the group of patients in question, as well as the necessity to introduce successful methods of prevention and early treatment.

In our study, we have also found several predictors of NADMs and less of VR vs. VUR subgroup. The results presented in the final part of the study confirm the findings from previous studies [7–9, 11–13, 15, 24].

There are some limitations to this study. First, this is a retrospective, observational research on any type of malignancy in HIV-positive adult patients in Poland, without a control group. As with all cohort studies, we can only refer to the data that we have collected. Our study population might not reflect the exact distributions of malignancies occurring all over the country with a noticeable predominance of CRFs from the capital of Poland, being the largest HIV care and cure centre. Furthermore, there may be variations between the level of malignancy, screening mostly in earlier periods when there were no functional popula-
tion-based malignancy registries. The registration of all the cases of malignancies in HIV-infected population was not accurate enough as the centres are located exclusively in urban areas. Also, our distribution between NADMs-VR and NADMs-VUR may be debatable. Not all of NADMs-VR types are dependent on co-infections with certain viruses in the same way. Finally, we did not analyse the types of malignancies individually, but in selected groups, which might have masked specific data.

In conclusion, the prevalence of malignancies in an ageing and growing HIV-infected adult Polish cohort continued to grow over the period between 1995 and 2012, concerning, in particular, non-AIDS-defining virus unrelated (NADMs-VUR) malignancies. Non-Hodgkin lymphoma (NHL) was the most frequent malignancy among ADMs, and Hodgkin’s disease (HD) was the most frequent malignancy among NADMs-VR, whereas lung cancer was the most frequent malignancy among NADMs-VUR. It is possible that, withassertive prevention strategies, earlier diagnosis of HIV-infection in Poland, and starting cART adequately early among patients with a confirmed HIV diagnosis, the incidence of ADMs and NADMs-VR will decrease. An increased incidence of NADMs was confirmed in elderly men with longer duration of HIV-infection, with better virological and immunological control and prior AIDS diagnosis (defined as prior opportunistic infections, excluding ADMs). Effective primary prevention and screening strategies especially for NADMs-VUR as well as early detection and treatment of co-infections ought to be included in the routine long-term follow-up of the HIV-infected population. Further effort to resolve the direct and indirect effects of HIV itself on NADMs-VUR as well as early detection and treatment outcomes are urgently needed. Nowadays, the spectrum of cancer diagnoses in the adult HIV Poland cohort does not appear dissimilar to those noted in other Western European populations.

The authors declare no conflict of interest.

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Address for correspondence
Jacek Kowalski
Hospital for Infectious Diseases in Warsaw
Wolska 37
01-201 Warsaw, Poland
E-mail: jacekkowalski1982@gmail.com

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