12° CONGRESSO NAZIONALE
Italian Conference on AIDS and Antiviral Research

Reach out for including all

12-16 ottobre 2020
DIGITAL EDITION

Promosso da SIMIT Società Italiana di Malattie Infettive e Tropicali

OP39

POSTER 4 YOU ICAR 2020

# RISK OF MULTIPLE PRIMARY NEOPLASMS AND IMPACT ON SURVIVAL OF PERSON LIVING WITH HIV (PLWH)

V Mazzotta[1], P Lorenzini[1], A Bandera[2], A Gori[2], L Sighinolfi[3], S Rusconi[4], P Bonfanti[5], A Cingolani[6], G Marchetti[7], C Mussini[8], A d'Arminio Monforte[7], A Antinori[1] ICONA FOUNDATION STUDY GROUP

[1]HIV/AIDS Unit, INMI L. Spallanzani IRCCS, Roma; [2]IRCCS Policlinico Ospedale Maggiore, University of Milano; [3] Division of Infectious Disease, Hospital of Ferrara, Ferrara; [4]ASST L. Sacco Hospital, University of Milano; [5] Division of Infectious Disease, ASST Lecco, Lecco; [6]Fondazione Policlinico A. Gemelli, Catholic University, Roma; [7]ASST Santi Paolo e Carlo, University of Milano; [8] Clinic of Infectious Disease, University hospital of Modena, Modena.

## Introduction/Summary

- PLWH are diagnosed with cancer, both AIDS-defining (ADC) and Non-AIDS-defining (NADC), at an increased rate over the general population. Expanding ART use and standardized cancer treatment protocols dramatically increased life expectancy, increasing the number of cancer survivors, who are at high risk of other primary neoplasms. Proportion of multiple primary cancers in PLWH has been recently reported about 14-18%, close to that observed in the general population. Aims of this study were to investigate frequency, incidence rates and possible risk factors for multiple primary cancers in PLWH and to examine survival probability according to the number of cancer diagnoses (1, >=2).

## Study design and Methods

- Patients (pts) in ICONA Foundation cohort enrolled between 1997 and 2019 were analyzed for relative frequencies of first or subsequent primary cancer diagnosed till 9 years before first HIV test. Comparisons of patients' characteristics between the group with single diagnosis and the group with multiple diagnosis were made using Mann-Whitney for continuous parameters and Chi square test for categorical variables. Poisson regression was used to investigate factors recorded at first cancer associated with the onset of a second diagnosis. Weighted Cox regression was used to estimate causal HR of death for patients with a second diagnosis of cancers (time-varying exposure), adjusting for the main confounders (age, gender, HCV/HBV/CMV coinfection at baseline and time-varying CD4, CD4/CD8 ratio, HIVRNA and virus-related first cancer). Baseline of this analysis was the date of first cancer.

### TABLE 1. MAIN CHARACTERISTICS

| | Overall | Single cancer | >=2 cancers | |
|---|---|---|---|---|
| | n = 1177 | n = 1116 | n = 61 | p - value |
| **Variables measured at first diagnosis** | | | | |
| | | 94.8% | 5.2% | |
| **Female gender, n(%)** | 294 (25.0%) | 276 (24.7%) | 18 (29.5%) | 0.401 |
| **Age, yrs, median (IQR)** | 45 (37-54) | 45 (37 - 53) | 44 (36 - 56) | 0.892 |
| **Nationality, n(%)** | | | | |
| **Italian** | 1041 (88.5%) | 988 (88.5%) | 53 (86.9%) | 0.696 |
| **Not italian** | 136 (11.6%) | 128 (11.5%) | 8 (13.1%) | |
| **Years from first HIV test to diagnosis, median (IQR)** | 1.3 (0.04-8.5) | 1.3 (0.04-8.5) | 0.9 (0.04 - 10.4) | 0.635 |
| **Smoke** | | | | |
| **No** | 570 (48.4%) | 542 (48.6%) | 28 (45.9%) | 0.864 |
| **Yes** | 463 (39.3%) | 437 (39.2%) | 26 (42.6%) | |
| **not known** | 144 (12.2%) | 137 (12.3%) | 7 (11.5%) | |
| **Alchol** | | | | |
| **No** | 405 (34.4%) | 388 (34.8%) | 17 (27.9%) | 0.083 |
| **Yes occasionally** | 190 (16.1%) | 186 (16.7%) | 4 (6.6%) | |
| **Yes regularly** | 69 (5.9%) | 65 (5.8%) | 4 (6.6%) | |
| **Abuse** | 21 (1.8%) | 20 (1.8%) | 1 (1.6%) | |
| **not known** | 492 (41.8%) | 457 (41.0%) | 35 (57.4%) | |
| **BMI** | | | | |
| **<18.5** | 65 (8.1%) | 59 (7.7%) | 6 (15.8%) | 0.138 |
| **18.5-25** | 502 (62.4%) | 480 (62.6%) | 22 (57.9%) | |
| **25-30** | 191 (23.7%) | 181 (23.6%) | 10 (26.3%) | |
| **30+** | 47 (5.8%) | 47 (6.1%) | 0 | |
| **Drug abuse** | | | | |
| **No** | 1164 (98.9%) | 1105 (99.0%) | 59 (96.7%) | 0.095 |
| **Yes** | 13 (1.1%) | 11 (1.0%) | 2 (3.3%) | |
| **Mode of HIV transmission** | | | | |
| **heterosexual** | 481 (40.9%) | 460 (41.2%) | 21 (34.4%) | 0.081 |
| **IDU** | 214 (18.2%) | 196 (17.6%) | 18 (29.5%) | |
| **MSM** | 395 (33.6%) | 379 (34.0%) | 16 (26.2%) | |
| **Other/unknown** | 87 (7.4%) | 81 (7.3%) | 6 (9.8%) | |
| **HCV co-infection** | | | | |
| **Negative** | 746 (63.4%) | 722 (64.7%) | 24 (39.3%) | <0.001 |
| **Positive** | 236 (20.0%) | 220 (19.7%) | 16 (26.2%) | |
| **not known** | 195 (16.6%) | 174 (15.6%) | 21 (34.4%) | |
| **HBV co-infection** | | | | |
| **Negative** | 910 (77.3%) | 874 (78.3%) | 36 (59.0%) | 0.001 |
| **Positive** | 63 (5.3%) | 59 (5.3%) | 4 (6.6%) | |
| **not known** | 204 (17.3%) | 183 (16.4%) | 21 (34.4%) | |
| **CD4 cell/mm, median (IQR)** | 300 (103-553) | 304 (105-554) | 178 (58 - 521) | 0.081 |
| **<200** | 366 (31.1%) | 344 (30.8%) | 22 (6.1%) | 0.097 |
| **200-351** | 156 (13.2%) | 149 (13.4%) | 7 (11.5%) | |
| **350+** | 418 (35.6%) | 404 (36.2%) | 14 (23.0%) | |
| **Missing** | 237 (20.1%) | 219 (19.6%) | 18 (29.5%) | |
| **HIV-RNA, copies/mL** | | | | |
| **<=200 copie/mL** | 394 (33.5%) | 383 (34.3%) | 11 (18.0%) | 0.013 |
| **>200 copies/mL** | 531 (45.1%) | 501 (44.9%) | 30 (49.2%) | |
| **Missing** | 252 (21.4%) | 233 (20.8%) | 20 (32.8%) | |
| **Nadir CD4, median (IQR)** | 178 (51-319) | 181 (51-320) | 135 (48 - 261) | 0.148 |
| **<200** | 528 (44.9%) | 501 (44.9%) | 27 (44.3%) | 0.146 |
| **200+** | 442 (37.6%) | 424 (38.0%) | 18 (29.5%) | |
| **Missing** | 207 (17.6%) | 191 (17.1%) | 16 (26.2%) | |
| **CD4/CD8 ratio** | | | | |
| **<0.30** | 287 (24.4%) | 273 (24.5%) | 14 (23.0%) | 0.460 |
| **0.30-0.45** | 104 (8.8%) | 98 (8.8%) | 6 (9.8%) | |
| **0.45-1.00** | 196 (16.7%) | 187 (16.8%) | 9 (14.8%) | |
| **1.00+** | 80 (6.8%) | 79 (7.1%) | 1 (1.6%) | |
| **Missing** | 510 (43.3%) | 479 (42.9%) | 31 (50.8%) | |
| **cART exposure** | | | | |
| **Naive** | 772 (65.6%) | 429 (65.3%) | 43 (70.5%) | 0.408 |
| **Experienced** | 405 (34.4%) | 387 (34.7%) | 18 (29.5%) | |
| **Calendar year of diagnosis, median (IQR)** | 2011 (2004-2015) | 2011 (2004-2015) | 2004 (2000-20123) | <0.001 |
| **Type of cancer** | | | | |
| **AIDS-related** | 635 (54.0%) | 604 (54.1%) | 31 (50.8%) | 0.614 |
| **Non AIDS-related** | 542 (46.0%) | 512 (45.9%) | 30 (49.2%) | |
| **Type of cancer** | | | | |
| **Virus-related** | 789 (67.0%) | 747 (66.9%) | 42 (68.9%) | 0.756 |
| **Not virus-related** | 388 (33.0%) | 369 (33.1%) | 19 (31.2%) | |

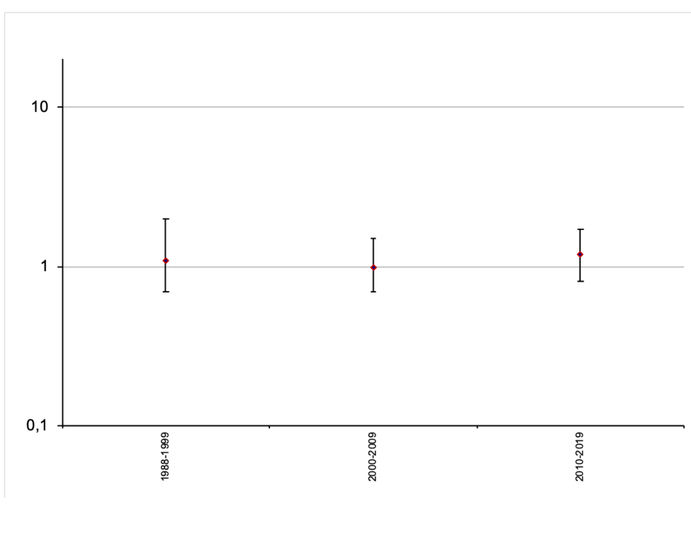
## Results

- Among 1177 patients with cancer we identified 1116 (94,8%) with single and 61 (5,2%) with a second cancers; only one of 61 had a third primary cancer. Out of the population study, 294 (25%) were female and median age was 45 years. (see table 1). Follow up median duration from first cancer diagnosis was 3.2 (0.9-7.3) years, 3.0 (0.9-7.1) for single and 6.9 (1.4-13.6) for multiples cancers.

## Results of 2

- Incidence of multiple cancers was 1.1 per 100 PYFU (95%CI 0.8-1.4) (1988-1999 IR 1.1, 2000-2009 IR 1.0, 2010-2019 IR 1.2) (See figure 1).

### FIGURE 1. INCIDENCE OF MULTIPLE CANCERS




- Kaposi sarcoma, Non-Hodgkin Lymphoma and Hodgkin Lymphoma were the 3 more common first neoplasm in the two groups (59.8%, 34.6% and 13.3% in single and 54.8%, 41.9% and 16.7% in multiple, respectively).

### TABLE 2. TYPES OF CANCER

| TYPES OF CANCER | SINGLE | MULTIPLES | | |
|---|---|---|---|---|
| | N=1116 | 1° diagnosis N=61 | 2° diagnosis N=61 | 3° diagnosis N=1 |
| **AIDS-related** | N=604 | N=31 | N=26 | N=1 |
| **LNH** | 209 (34.6%) | 13 (41.9%) | 18 (69.2%) | |
| **Kaposi sarcoma** | 361 (59.8%) | 17 (54.8%) | 5 (19.2%) | 1 (100%) |
| **invasive cervical cancer** | 34 (5.6%) | 1 (3.2%) | 3 (11.5%) | |
| **non-AIDS related** | N=512 | N=30 | N=35 | |
| **LH** | 68 (13.3%) | 5 (16.7%) | 2 (5.7%) | |
| **lung** | 61 (11.7%) | | 5 (14.3%) | |
| **cervical dysplasa/in situ cancer** | 50 (9.8%) | 5 (16.7%) | | |
| **kidney and urinary tract** | 38 (7.4%) | 3 (10.0%) | 2 (5.7%) | |
| **breast** | 37 (7.2%) | | 2 (5.7%) | |
| **head and neck** | 36 (7.0%) | 1 (3.3%) | 5 (14.3%) | |
| **uterus** | 24 (4.7%) | 3 (10.0%) | | |
| **liver** | 25 (4.9%) | 1 (3.3%) | 5 (14.3%) (2HCC) | |
| **prostate** | 23 (4.5%) | | | |
| **anus** | 21 (4.1%) | 1 (3.3%) | 3 (8.6%) | |
| **colon** | 18 (3.5%) | 1 (3.3%) | | |
| **melanoma** | 16 (3.1%) | 1 (3.3%) | 1 (2.9%) | |
| **rectum** | 14 (2.7%) | 1 (3.3%) | 1 (2.9%) | |
| **testicles** | 13 (2.5%) | 3 (10.0%) | | |
| **pancreas** | 11 (2.1%) | | 2 (5.7%) | |
| **other gynecological** | 9 (1.8%) | 1 (3.3%) | 1 (2.9%) (vulva) | |
| **leukemia (limphoid or myeloid)** | 6 (1.2%) | 1 (3.3%) | | |
| **thyroid** | 7 (1.4%) | | 2 (5.7%) | |
| **esophagus/stomach** | 12 (2.3%) | | 1 (2.9%) | |
| **lip and mouth** | 4 (0.8%) | 1 (3.3%) | | |
| **SNC** | 4 (0.8%) | | | |
| **myeloma** | 2 (0.4%) | 1 (3.3%) | | |
| **biliary tract** | 3 (0.6%) | | | |
| **bone** | 2 (0.4%) | | | |
| **connective tissue** | 1 (0.2%) | | 1 (2.9%) | |
| **other** | 7 (1.4%) | 1 (3.3%) | 2 (5.7%) | |

## Results of 3

### RISK FACTORS

- Comparing pts with single cancer vs those with multiple diagnoses (Table 1) HCV coinfection (20% vs 26%) and HIV RNA>200 cp/mL (45% vs 49%) were more frequent in multiple cancers group. At multivariable Poisson regression, HCV coinfection, older age and CD4<200 mmc were associated with higher probability of a subsequent diagnosis of cancer. (See table 3).

### TABLE 3. FACTORS ASSOCIATED WITH MULTIPLE CANCERS AT MULTIVARIABLES ANALYSIS

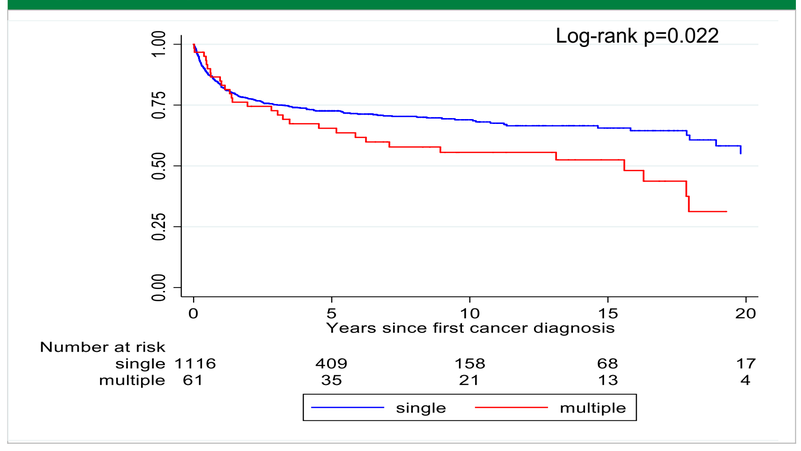
| Variables measured at first diagnosis | IRR | 95%CI | | p | Adj IRR | 95%CI | | p |
|---|---|---|---|---|---|---|---|---|
| Female gender vs male | 0.96 | 0.55 | 1.66 | 0.878 | 1.05 | 0.58 | 1.89 | 0.882 |
| **Age**, per 10 yrs older | 1.26 | 1.02 | 1.56 | **0.036** | 1.36 | 1.08 | 1.71 | **0.008** |
| Nationality, n(%) | | | | | | | | |
| Italian | 1.00 | | | | 1.00 | | | |
| Migrants | 1.37 | 0.65 | 2.87 | 0.411 | 1.68 | 0.76 | 3.71 | 0.197 |
| Years from first HIV test to diagnosis, per 1 year more | 1.01 | 0.97 | 1.05 | 0.683 | | | | |
| Smoke | | | | | | | | |
| No | 1.00 | | | | | | | |
| Yes | 1.04 | 0.61 | 1.78 | 0.882 | | | | |
| unknown | 1.21 | 0.53 | 2.77 | 0.654 | | | | |
| Alchol | | | | | | | | |
| No | 1.00 | | | | | | | |
| Yes occasionally | 0.50 | 0.17 | 1.49 | 0.214 | | | | |
| Yes regularly | 1.57 | 0.53 | 4.67 | 0.417 | | | | |
| Abuse | 1.07 | 0.14 | 8.06 | 0.946 | | | | |
| unknown | 1.36 | 0.76 | 2.42 | 0.302 | | | | |
| BMI | | | | | | | | |
| <18.5 | 1.92 | 0.73 | 5.08 | 0.187 | 2.16 | 0.80 | 5.85 | 0.129 |
| 18.5-25 | 1.00 | | | | 1.00 | | | |
| 25+ | 1.01 | 0.48 | 2.14 | 0.970 | 1.18 | 0.54 | 2.56 | 0.681 |
| unknown | 1.46 | 0.82 | 2.61 | 0.198 | 1.31 | 0.60 | 2.84 | 0.501 |
| Drug abuse | | | | | | | | |
| No | 1.00 | | | | | | | |
| Yes | 2.54 | 0.62 | 10.40 | 0.195 | | | | |
| Mode of HIV transmission | | | | | | | | |
| heterosexual | 1.00 | | | | | | | |
| IDU | 1.84 | 0.98 | 3.45 | 0.058 | | | | |
| MSM | 1.02 | 0.53 | 1.95 | 0.953 | | | | |
| Other/unknown | 2.07 | 0.84 | 5.13 | 0.116 | | | | |
| **HCV co-infection** | | | | | | | | |
| Negative | 1.00 | | | | 1.00 | | | |
| **Positive** | 1.97 | 1.05 | 3.71 | **0.035** | 2.42 | 1.25 | 4.70 | **0.009** |
| unknown | 2.69 | 1.50 | 4.83 | 0.001 | 1.96 | 0.61 | 6.27 | 0.257 |
| HBV co-infection | | | | | | | | |
| Negative | 1.00 | | | | 1.00 | | | |
| Positive | 1.95 | 0.70 | 5.49 | 0.203 | 1.88 | 0.66 | 5.33 | 0.236 |
| unknown | 2.27 | 1.33 | 3.89 | 0.003 | 1.84 | 0.58 | 5.84 | 0.304 |
| **CD4 cell/mmc** | | | | | | | | |
| **<200** | 2.21 | 1.13 | 4.33 | **0.020** | 2.01 | 0.92 | 4.40 | **0.079** |
| 200-351 | 1.54 | 0.62 | 3.81 | 0.354 | 1.24 | 0.46 | 3.33 | 0.669 |
| 350+ | 1.00 | | | | 1.00 | | | |
| unknown | 1.76 | 0.88 | 3.55 | 0.111 | 0.97 | 0.17 | 5.61 | 0.970 |
| HIV-RNA, copies/mL | | | | | | | | |
| <=200 copie/mL | 1.00 | | | | 1.00 | | | |
| >200 copies/mL | 1.60 | 0.80 | 3.20 | 0.180 | 1.36 | 0.61 | 3.04 | 0.450 |
| unknown | 1.66 | 0.79 | 3.46 | 0.178 | 1.17 | 0.24 | 5.70 | 0.844 |
| Nadir CD4 | | | | | | | | |
| 200+ | 1.00 | | | | | | | |
| <200 | 1.57 | 0.86 | 2.85 | 0.138 | | | | |
| unknown | 1.51 | 0.77 | 2.97 | 0.229 | | | | |
| CD4/CD8 ratio | | | | | | | | |
| <0.30 | 1.00 | | | | | | | |
| 0.30-0.45 | 0.97 | 0.37 | 2.52 | 0.946 | | | | |
| 0.45-1.00 | 0.72 | 0.31 | 1.65 | 0.433 | | | | |
| 1.00+ | 0.30 | 0.04 | 2.28 | 0.245 | | | | |
| unknown | 1.01 | 0.53 | 1.89 | 0.987 | | | | |
| cART exposure | | | | | | | | |
| naive | 0.97 | 0.56 | 1.67 | 0.901 | | | | |
| experienced | 1.00 | | | | | | | |
| Days from HIV test and ART start | 1.00 | 1.00 | 1.00 | 0.331 | | | | |
| Calendar year of diagnosis, per 1 yr more | 0.99 | 0.95 | 1.03 | 0.593 | | | | |
| Type of cancer | | | | | | | | |
| AIDS-related | 0.86 | 0.52 | 1.43 | 0.564 | | | | |
| Non AIDS-related | 1.00 | | | | | | | |
| Type of cancer | | | | | | | | |
| Virus-related | 0,93 | 0,54 | 1,60 | 0,800 | | | | |
| Not virus-related | 1,00 | | | | | | | |

## Results of 4

### SURVIVAL

- The 5-years survival probability was 72.6% (95% CI 69.6%-75.4%) and 65.5% (95%CI 51.7%-76.2%) in single and multiple cancers, respectively. The causal HR of death for pts with a second cancers was 4-fold higher than those who had single cancer (HR 4.09 [95%CI 2.06 -8.13]) after adjusting for main confounders.

### FIGURE 2. SURVIVAL PROBABILITY




## Conclusion

- Multiple primary cancers occurred in our cohort at a relatively low frequency than previously reported and stable over time.
- Older age, HCV coinfection and immunological impairment seem to increase risk of subsequent neoplasms. Role of oncogenic viruses as persistent predisposing factor could be responsible for the relative frequencies of multiple cancers.
- The finding of worse survival in pts with multiple neoplasms, suggests the importance of early identification of risk group and of appropriate prevention strategies.

## *References*

1. Hessol N, Whittemore H, Vittinghoff E et al. Incidence of first and second primary cancers diagnosed among people with HIV, 1985–2013: a population-based, registry linkage study. Lancet HIV 2018; 5: e647–55.
2. Travis LB, Demark Wahnefried W, Allan JM, Wood ME, Ng AK. Aetiology, genetics and prevention of secondary neoplasms in adult cancer survivors. Nat Rev Clin Oncol 2013; 10: 289–301.
3. Patel P, Hanson DL, Sullivan PS, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992–2003. Ann Intern Med 2008; 148: 728–36.
4. Engels EA, Pfeiffer RM, Goedert JJ, et al. Trends in cancer risk among people with AIDS in the United States 1980–2002. AIDS 2006; 20: 1645–54.
5. Mahale, Paraga; Ugoji, Chinenyeb; Engels, Eric A.a; Shiels, Meredith S.a; Peprah, Sallya; Morton, Lindsay M.c Cancer risk following lymphoid malignancies among HIV-infected people, AIDS: July 1, 2020 - Volume 34 - Issue 8 - p 1237-1245.
6. Engels EA, Biggar RJ, Hall HI, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. Int J Cancer 2008; 123: 187–94.