STILL HIGH RISK OF VIRUS-RELATED CANCER DESPITE 20 YEARS OF cART IN ICONA COHORT

Pierluca Piselli[1], Diego Serraino[2], Alessandra Bandera[3], Andrea Antinori[1], Enrico Girardi[1], Claudia Cimaglia[1], Alessandro Tavelli[4], Francesca Bai[5], Gianmaria Baldin[6], Andrea Calcagno[7], Antonella D'Arminio Monforte[5], Antonella Cingolani[6], for the ICONA Foundation Study Group

[1]Lazzaro Spallanzani National Institute for Infectious Diseases, Rome, [2]CRO Aviano National Cancer Institute, Aviano, [3]San Gerardo Hospital, Monza, [4]Icona Foundation, Milan, [5]University of Milan, Milan, [6]Catholic University of the Sacred Heart, Rome, [7]University of Turin

ID: 651

CROI 2018
Boston, March 4–7, 2018

INTRODUCTION

- The advent of combination antiretroviral therapy (cART) in 1996, led to a decreased incidence of several cancers, in particular AIDS-defining malignancies (ADMs, i.e. Kaposi sarcoma-KS, Non-Hodgkin lymphoma-NHL and Invasive Cervical Cancer-ICC), and among non-AIDS defining malignancies (NADMs) of virus-related e.g. Hodgkin's lymphoma (HL) or anal cancer.
- OBJECTYIVE: To quantified the incidence of cancer in a Large Italian cohort of ART-naïve persons with HIV or AIDS (PWHAs) HIV-diagnosed in the last 20 years (ICONA cohort) and compare it with the incidence in the general population.

MATERIALS AND METHODS

Inclusion and exclusion criteria:

- All PWHAs individuals included in the ICONA Foundation Study between 1996 and 2016 aged <70 years at enrolment (first HIV-diagnosis) were included.
- Individuals with a history of cancer prior enrolment or with a cancer diagnosis in the first 30 days after enrolment, follow-up less than 30 days were excluded.

Cancer diagnoses

- All malignant cancer diagnoses were histologically confirmed and coded according to the *International Classification for Disease and Related Health Problems 10th revision* (ICD-10). Cancers were classified in AIDS-defining malignancies (ADMs, namely Kaposi Sarcoma, KS; Non-Hodgkin Lymphoma, NHL; Invasive Cervical Cancer, ICC) and Non AIDS-defining (NADMs, all remaining types). NADMs were furtherly classified in virus-related cancers (cancers of the anus, liver, vulva, Merkel Cell Carcinoma-MCC and Hodgkin's lymphoma-HL) and not virus-related cancers (all remaining types).

Person-years (PYs) at risk of cancer:

- Follow up was accrued from 30 days after first HIV-diagnosis to the cancer diagnosis, death, reaching 70 years of age, drop out or last follow-up.

Incidence estimates

- Age-and sex-standardized incidence rates (ASR) were computed using the entire cohort as reference population and stratified for calendar periods (1996-2000; 2001-2005; 2006-2009; 2010-2013; 2014-2016)).
- Standardized incidence ratios (SIRs, and 95% confidence intervals - CIs - determined using the Poisson distribution) were computed dividing the number of observed incident cancer cases by the number of those expected computed from sex- and age-specific incidence rates from all Italian cancer registries as published by the International Agency for Cancer (IARC) in Cancer Incidence in Five Continents, vol. VII (for the period until 1992), vol. VIII (1993–1997), vol. IX (1998-2002) and by the Italian Association of Cancer Registries (AIRTUM) in ITACAN (ITAlian CANcer registries' database, from 2003 thereafter).

RESULTS

In the final cohort of 11688 PWHAs (**Table 1**) during 67449,91 PYs (median follow-up 4.6 years) 426 single new cancers were diagnosed in 415 individuals (3.6%), with an overall incidence of 6.2 cases/10^3 PYs (median time at diagnosis of 2.3 years).

Figure 1 shows the cumulative incidence for all de novo malignancies after first HIV-test and separately for AMDs and NADMs. Overall 5% of all patients developed a cancer within 5 years form enrolment.

Table 1. Baseline Characteristics of 11688 PWHAs under study

Characteristics	
Female sex, n (%)	2602 (22.3)
Age at enrollment (years), median (IQR)	37 (30-45)
Age at enrollment (years), n (%)	
<30	2613 (22.4)
30-39	4440 (38.0)
40-49	2909 (24.9)
50-59	1278 (10.9)
60-69	448 (3.8)
Year of enrolment, median (IQR)	2011 (2004-2014)
Mode of HIV transmission, n (%)	
Homosexual/ Bisexual	4946 (42.3)
Heterosexual	4826 (41.3)
IVDU	1052 (9.0)
Other or unknown	864 (7.4)

Table 2, reports the list of all cancer cases diagnosed in the cohort, where ADMs represented most of cancers cases (N=222, 52.1%), with a median time at cancer diagnosis after enrolment of 0.9 years (vs. 4.1 among NADMs, p<0.001).

Table 2. List of malignancies diagnosed in the ICONA cohort: 1996-2016.*

Type/Site[a]	ICD-10 codes	All	M/F
AIDS defining malignancies (ADMs)		**219**	**185/34**
Kaposi's sarcoma	C46	132	123/9
Cervix uteri	C53	14	-/14
NHL	C82-85, C96	76	65/11
Non AIDS defining malignancies (NADMs)		**200**	**156/44**
NADMs virus-related[a]		**60**	**50/10**
Anus	C21	12	11/1
Liver	C22	12	11/1
Hodgkin's lymphoma	C81	34	27/7
NADMs not virus-related[b]		**140**	**106/34**
Oral cavity	C00-14	7	6/1
Stomach	C16	3	3/0
Colon	C18	8	7/1
Rectum	C20	5	5/0
Pancreas	C25	4	3/1
Bronchus and lung	C34	29	22/7
Skin, melanoma	C43	7	4/3
Skin, non-melanoma	C44	13	11/2
Breast female	C50	11	-/11
Prostate	C61	7	7/-
Testis	C62	5	5/-
Kidney	C64	7	6/1
Bladder	C67	17	17/0
Central Nervous System	C71	3	2/1
Thyroid gland	C73	4	2/2
All cancer diagnoses (C00-C97)		**415**	**338/77**

* Since some patients were diagnosed with more than one malignancy, the sum can exceed the total
ICD-10: International Classification of Diseases tenth revision.
[a] It includes one case each of vulvar cancer (C51) and Merkel cell carcinoma (C4A).
[b] It includes also the following malignancies with less than 4 cases. Two cases each for: esophagus (C15), larynx (C32) and myeloma (C90). One case each for: gallbladder (C24), connective and soft tissue (C49) corpus uteri (C54) and leukemia (C91-95).

Fig. 1. Cumulative incidence of *de novo* malignancies after first HIV+ test

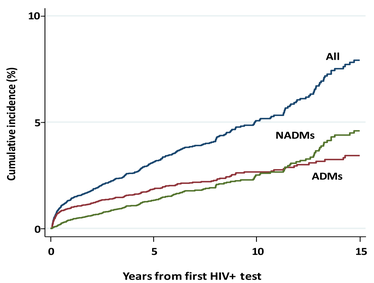


Figure 2 compares, for all cancers and for selected cancer groups, age-specific incidence rates observed in PWHAs with those expected in the corresponding general population of Italy.

Cancer incidence rates were higher in PWHAs for ADMs and virus-related NADMs than in the general population, with the difference inversely related to ageing and a tendency to equivalence for older age groups.

No difference in terms of incidence over age was observed for non virus-related NADMs.

Fig. 2. Age-specific incidence rates (IR) for all cancers and selected cancer groups in ICONA cohort and in the general population

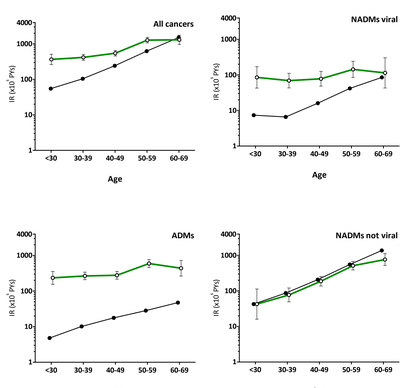


Figure 3 shows standardized incidence ratios (SIRs) as comparison of cancer incidence incidence vs general population for all cancers overall and for selected groups or types. Significantly increased SIRs were noted for all cancers (SIR=2.2, 95%CI: 2.0-2.4) and for ADMs overall (SIR=19.8, 95%CI: 17.3-22.6) and for their single types (KS 216, NHL 8.5, ICC 8.8).

Virus-related NADMs and their single entities (HL, Liver and Anal cancer) showed a significant increase (SIR=4.7, 95% CI: 3.6-6.0) while a decreased risk for virus unrelated NADMs was observed (SIR=0.8, 95% CI: 0.7-1.0).

Among virus unrelated NADMs a significant increase was observed fro lung (SIR=1.7) and bladder cancer (SIR=2.0) while a decreased incidence for female breast, prostatic and thyroid cancer was noticed.

Fig. 3. Standardized incidence ratios (SIR) and 95% Confidence Intervals (CI) for selected cancers

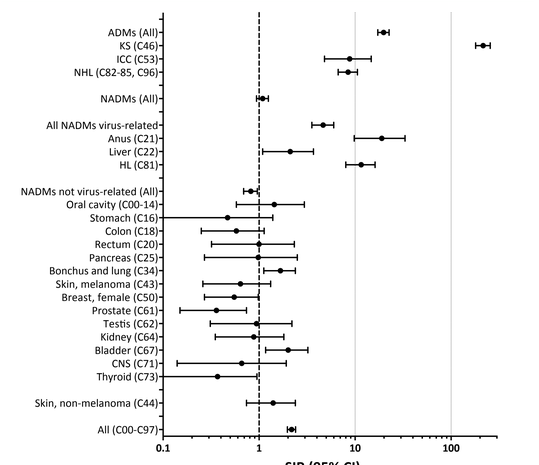


Figure 4 shows incidence trend over time for all cancers according to gender (males constantly with a higher risk) and risk group with a substantial equivalence in the last period. In the lower panels it is shown the decreased incidence after the first period for ADMs and specifically for KS and ICC while not for NHL. Among NADMs, an augmented risk over time was observed for virus-related NADMs but for the remaining types.

Fig. 4. Age and sex standardized rates (ASR) overt time according to gender (panel A) and risk group (panel B). In the lower panels trend over time for ADMs (panel C) and NADMs (panel D) are shown.

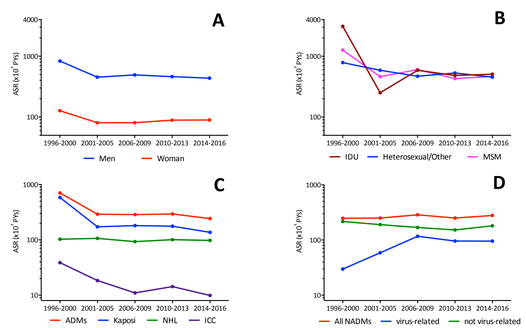
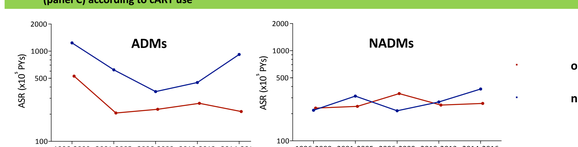


Figure 5 shows incidence trend separately for ADMs and NADMs according to cART use. While cART seems not have any effect on NADMs incidence overall, ADMs are strongly affected constantly over time, with an increase risk in the last period for those not on cART.

Fig. 5. Age and sex standardized rates (ASR) overt time for all cancers (panela A) and separately for ADMs (panel B) and NADMs (panel C) according to cART use



CONCLUSIONS

- A substantial higher incidence of cancer compared to general population was observed (2.2-fold increased risk for all cancers).
- Despite a decline over time for ADMs, risk of virus-related cancers remains elevated in the modern treatment era, possibly due either to sexual transmission of the causative virus or to persistent inflammation/immune activation.
- For not virus related cancers the incidence was comparable to that of general population and may represent an ageing effect, strongly suggesting additional efforts aimed at cancer prevention and screening among PWHAs

ICONA FOUNDATION STUDY GROUP

BOARD OF DIRECTORS: A d'Arminio Monforte (President), A Antinori, A Castagna, F Castelli, R Cauda, G Di Perri, M Galli, R Iardino, G Ippolito, A Lazzarin, GC Marchetti, CF Perno, G Rezza, F von Schloesser, P Viale.
SCIENTIFIC SECRETARY: A d'Arminio Monforte, A Antinori, A Castagna, F Ceccherini-Silberstein, A Cozzi-Lepri, E Girardi, S Lo Caputo, C Mussini, M Puoti, CF Perno
STEERING COMMITTEE: M Andreoni, A Ammassari, A Antinori, C Balotta, A Bandera, P Bonfanti, S Bonora, M Borderi, A Calcagno, L Calza, MR Capobianchi, A Castagna, F Ceccherini-Silberstein, A Cingolani, P Cinque, A Cozzi-Lepri, A d'Arminio Monforte, A De Luca, A Di Biagio, E Girardi, N Gianotti, A Gori, G Guaraldi, G Lapadula, M Lichtner, S Lo Caputo, G Madeddu, F Maggiolo, G Marchetti, S Marcotullio, L Monno, C Mussini, S Nozza, M Puoti, E Quiros Roldan, R Rossetti, S Rusconi, MM Santoro, A Saracino, M Zaccarelli.
STATISTICAL AND MONITORING TEAM: A Cozzi-Lepri, I Fanti, L Galli, P Lorenzini, A Rodano', M Shanyinde, A Tavelli.
BIOLOGICAL BANK INMI: F Carletti, S Carrara, A Di Caro, S Graziano, F Petrone, G Prota, S Quartu, S Truffa.
PARTICIPATING PHYSICIANS AND CENTERS: Italy A Giacometti, A Costantini, V Barocci (Ancona); G Angarano, L Monno, C Santoro (Bari); F Maggiolo, C Suardi (Bergamo); P Viale, V Donati, G Verucchi (Bologna); F Castelnuovo, C Minardi, E Quiros Roldan (Brescia); B Menzaghi, C Abeli (Busto Arsizio); B Cacopardo, B Celesia (Catania); J Vecchiet, K Falasca (Chieti); L Sighinolfi, D Segala (Ferrara); P Blanc, F Vichi (Firenze); G Cassola, C Viscoli, A Alessandrini, N Bobbio, G Mazzarello (Genova); C Mastroianni, I Pozzetto (Latina); P Bonfanti, C Molteni (Lecco); A Chiodera, P Milini (Macerata); G Nunnari, G Pellicanò (Messina); A d'Arminio Monforte, M Galli, A Lazzarin, G Rizzardini, M Puoti, A Castagna, G Marchetti, MC Moioli, R Piolini, AL Ridolfo, S Salpietro, C Tincati, (Milano); C Mussini, C Puzzolante (Modena); A Gori, G Lapadula (Monza); A Chirianni, G Borgia, V Esposito, F Di Martino, I Gentile, L Maddaloni (Napoli); AM Cattelani, S Marinello (Padova); A Cascio, C Colomba (Palermo); F Baldelli, E Schiaroli (Perugia); G Parruti, F Sozio (Pescara); G Magnani, MA Ursitti (Reggio Emilia); M Andreoni, A Antinori, R Cauda, A Cristaudo, V Vullo, R Acinapura, G Baldin, M Capozzi, S Cicalini, A Cingolani, M Rivano Capparucia, G Iaiani, A Latini, I Mastrorosa, MM Plazzi, S Savinelli, A Vergori (Roma); M Cecchetto, F Viviani (Rovigo); G Madeddu, P Bagella (Sassari); A De Luca, B Rossetti (Siena); A Franco, R Fontana Del Vecchio (Siracusa); D Francisci, C Di Giuli (Terni); P Caramello, G Di Perri, S Bonora, GC Orofino, M Sciandra (Torino); M Bassetti, A Londero (Udine); G Pellizzer, V Manfrin (Vicenza); G Starnini, A Ialungo (Viterbo).
FUNDING: ICONA Foundation is supported by unrestricted grants from BMS, Gilead Science, Janssen, MSD and ViiV Healthcare.

Contact information: ***PIERLUCA PISELLI MSc ScD*** e-mail: pierluca.piselli@inmi.it phone: +39-06-55170-900