6 giugno 2019 - 16.30 - 18.00 **Aula 201**

Oral Communications

Cancers and bacterial infections

N. prog: OC 45

Title: **CD4/CD8 ratio predicts the onset of virus-related cancers in HIV-positive patients on effective cART**

Authors: E. Suardi[1], A. Cozzi Lepri[2], G. Madeddu[3], V. Spagnuolo[4], S. Vita[5], V. Manfrin[6], A. Bandera[7], A. Cingolani[8], A. Antinori[9], C. Mussini[10], G. Marchetti[1], A. d'Arminio Monforte[1], for the Icona Foundation Study Group

Affiliation: [1]Clinic of Infectious Diseases, San Paolo Hospital-ASST Santi Paolo e Carlo, University of Milano, Milano, Italy, [2]Institute for Global Health, University College of London, London, UK, [3]Department of Medical, Surgical and Experimental Sciences, Division of Infectious Diseases, University of Sassari, Sassari, Italy, [4]Division of Infectious Diseases, IRCCS San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy, [5]Department of Public Health and Infectious Diseases, University Sapienza of Rome, [6]Department of Infectious and Tropical Diseases, St. Bortolo Hospital, Vicenza, Italy, [7]Infectious Diseases Unit, Departement of Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy, [8]Institute of Clinical Infectious Diseases, Catholic University of Sacred Heart, Policlonico Gemelli, Rome, Italy, [9]Clinical Division of HIV/AIDS, INMI "L. Spallanzani" IRCCS, Rome, Italy, [10]Infectious Diseases Clinic, University of Modena and Reggio Emilia, Modena, Italy

Abstract body
Background: We assessed the role of CD4/CD8 in predicting virus-related and non-virus related cancers in a large cohort of patients on effective cART.
Methods: We included patients of the Icona cohort free from cancer at baseline, i.e. at time of first achievement of viral suppression (HIV-RNA<50 cp/ml) on cART.CD4/CD8 ratio was grouped as low (0-0.4), intermediate (0.4-1) and high (>1). The 0.4 cut-off was chosen as largely used in other cohorts as a prognostic marker for non-AIDS and AIDS-related events123.Virus-related cancers included non-Hodgkin and Hodgkin lymphoma (NHL, HL), Kaposi's sarcoma, hepatocellular carcinoma, HPV-related cancers. Non-virus related cancers included invasive cancers not listed above.Cox regression models were used to estimate the relationship between CD4/CD8 ratio and risk of cancer; time at risk accrued from baseline until the date of cancer diagnosis or last clinical visit. Multivariable models were adjusted for common causes of CD4/CD8 ratio and outcomes including CD4 nadir and current CD4 count and HIV-RNA (see Tables footnotes). Time-varying confounding was controlled using inverse probability of weighting. Because of the frequency of measurements in the cohort, the risk for the most recent value reflects that associated with the CD4/CD8 ratio measured on average 4 months prior to the event.
Results: 10,231 patients who achieved viral suppression were included. Over a median follow up of 50 (IQR:26,87) months, 117/10227 (1.1%) incident cases of virus-related cancer and 134/10494 (1.3%) of non virus-related cancer were observed. The most frequent virus-related and not virus-related cancers were NHL (30 cases, 25%) and HL (28 cases,24%) and lung cancer (35 cases, 26%) and breast cancer (15 cases, 11%) respectively. Patients' characteristics at baseline stratified by whether they develop cancer or not are described in Table 1. The CD4/CD8 ratio was not associated with the risk of non-virus related cancers, either at baseline or at most recent value(Table 2). In contrast, baseline CD4/CD8 ratio showed some association with the risk of virus-related cancers (HR0.59, 95%CI 0.37-0.94 for intermediate vs. low) and overall per one unit higher of CD4/CD8 ratio there was a risk reduction of 63%. The association between the most recent CD4/CD8 ratio and the risk of virus-related cancers was more consistent and stronger with low values (HR0.32, 95%CI 0.16-0.64 for high vs. low, HR0.48, 95%CI 0.28-0.81 for intermediate vs. low, Table3)from fitting the weighted Cox regression model.
Conclusions: There was some evidence that CD4/CD8 at the time of viral suppression was associated

with a lower risk of virus-related cancers.The association was more consistent and stronger and independent of key confounders such as current CD4 count and HIV-RNA when considering the most recent value. This finding should be used to tailor virus related cancer screening and prevention strategies in high risk patients.

Table 1. Characteristics of patients with virus related and non-virus related cancer at baseline

Table 1a. Characteristics of patients with virus-related cancer	Endpoint disposition			
Characteristics at baseline	**Viral related cancer**	**Viral related cancer-free**	**p-value***	**Total**
	N= 117	N= 10110		N= 10227
Gender, n(%)			0.897	
Female	27 (23.1%)	2282 (22.6%)		2309 (22.6%)
Mode of HIV Transmission, n(%)			<.001	
PWIDU	38 (32.5%)	1340 (13.3%)		1378 (13.5%)
MSM	35 (29.9%)	4081 (40.6%)		4116 (40.5%)
Heterosexual contacts	38 (32.5%)	3997 (39.5%)		4035 (39.5%)
Other/Unknown	6 (5.1%)	640 (6.4%)		646 (6.3%)
AIDS diagnosis, n(%)			0.413	
Yes	15 (12.8%)	1060 (10.5%)		1075 (10.5%)
Calendar year of baseline			<.001	
Median (IQR)	2008 (2002, 2012)	2012 (2007, 2015)		2012 (2007, 2015)
Age, years			0.007	
Median (IQR)	43 (37, 49)	40 (33, 47)		40 (33, 47)
CD4 count, cells/mmc			<.001	
Median (IQR)	407 (207, 580)	488 (328, 667)		486 (326, 666)
CD4 count nadir, cells/mmc			<.001	
Median (IQR)	224 (102, 314)	295 (163, 424)		294 (162, 423)
CD8 count, cells/mmc			0.496	
Median (IQR)	883 (680, 1378)	902 (653, 1244)		902 (653, 1245)
VL at starting cART, log10 copies/mL			0.751	
Median (IQR)	4.70 (3.73, 5.16)	4.62 (3.91, 5.15)		4.62 (3.91, 5.15)
Time from HIV diagnosis to baseline, months			<.001	
Median (IQR)	586 (512, 633)	634 (566, 666)		634 (565, 666)
Number of viral failures before baseline			0.232	
Median (IQR)	3 (2, 10)	0 (0, 1)		3 (1, 12)
Smoking, n(%)			<.001	
No	53 (45.3%)	1271 (14.7%)		4495 (44.0%)
Yes	56 (47.9%)	4424 (51.2%)		3910 (38.2%)
Unknown	8 (6.8%)	1513 (17.5%)		1822 (17.8%)

*Chi-square or Kruskal-Wallis test as appropriate

Table 1b. Characteristics of patients with non virus-related cancer	Endpoint disposition			
Characteristics	**Non-viral related cancer**	**Non-viral related cancer-free**	**p-value***	**Total**
	N= 134	N= 10360		N= 10494
Gender, n(%)			0.082	
Female	38 (28.4%)	2288 (22.1%)		2326 (22.2%)
AIDS diagnosis, n(%)			0.375	
Yes	21 (15.7%)	1354 (13.1%)		1375 (13.1%)
Calendar year of baseline			<.001	
Median (IQR)	2007 (2001, 2010)	2012 (2007, 2015)		2012 (2007, 2015)
Age, years			<.001	
Median (IQR)	48 (40, 56)	40 (33, 47)		40 (33, 47)
CD4 count, cells/mmc			0.266	
Median (IQR)	481 (242, 637)	483 (321, 663)		483 (321, 663)
CD4 count nadir, cells/mmc			0.129	
Median (IQR)	274 (133, 391)	290 (156, 420)		290 (156, 420)
CD8 count, cells/mmc			0.826	
Median (IQR)	890 (678, 1220)	904 (653, 1247)		904 (653, 1247)
VL at starting cART, log10 copies/mL			0.464	
Median (IQR)	4.56 (3.93, 5.04)	4.63 (3.92, 5.17)		4.63 (3.92, 5.17)
Time from HIV diagnosis to baseline, months			<.001	
Median (IQR)	564 (503, 609)	634 (565, 666)		633 (564, 665)

Number of viral failures before baseline			0.190	
Median (IQR)	2 (1, 7)	0 (0, 1)		3 (1, 12)
Smoking, n(%)			<.001	
No	54 (40.3%)	1314 (14.8%)		4644 (44.3%)
Yes	74 (55.2%)	4547 (51.3%)		3994 (38.1%)
Unknown	6 (4.5%)	1541 (17.4%)		1856 (17.7%)

*Chi-square or Kruskal-Wallis test as appropriate

Table 2. Hazard ratios of developing a new non-virus related cancer according to CD4/CD8 ratio from fitting a Cox regression analysis (unweighted and weighted)

Hazard Ratios of non-viral malignancies from fitting a Cox regression analysis			
		Hazard Ratio (95% CI) p-value	
	Unadjusted	Adjusted[1]	Adjusted[2]
CD4/CD8 ratio			
Baseline value			
0-0.4	1.00	1.00	
0.4-1	0.79 (0.54, 1.15)	0.89 (0.59, 1.34)	
	0.212	0.574	
1+	1.15 (0.69, 1.93)	1.21 (0.66, 2.22)	
	0.592	0.531	
Most recent value			
0-0.4	1.00	1.00	1.00
0.4-1	0.57 (0.37, 0.89)	0.62 (0.40, 0.96)	0.72 (0.45, 1.15)
	0.013	0.031	0.168
1+	0.69 (0.43, 1.09)	0.71 (0.42, 1.21)	1.02 (0.58, 1.77)
	0.113	0.213	0.955
per unit higher	0.87 (0.63, 1.21)	0.88 (0.65, 1.18)	0.99 (0.93, 1.05)
	0.415	0.392	0.690

**(1)Adjusted for age, mode of HIV transmission, nationality,calendar year of baseline, nadir CD4, time spent on ART, AIDS diagnosis priorto baseline and -for the most recent value only- also current HIV-RNA and CD4 count(included as time varying variables)

**(2)Adjusted for age, mode of HIV transmission, nationality,calendar year of baseline, nadir CD4, time spent on ART, AIDS diagnosis priorto baseline as well as current HIV-RNA and CD4 count (using inverse probability weighting)

Table 3. Hazard ratios of developing a new virus related cancer according to CD4/CD8 ratio from fitting a Cox regression analysis (unweighted and weighted)

Hazard Ratios of viral malignancies from fitting a Cox regression analysis			
		Hazard Ratio (95% CI) p-value	
	Unadjusted	Adjusted[1]	Adjusted[2]
CD4/CD8 ratio			
Baseline value			
0-0.4	1.00	1.00	
0.4-1	0.49 (0.34, 0.73)	0.59 (0.37, 0.94)	
	<.001	0.027	
1+	0.32 (0.15, 0.70)	0.42 (0.18, 1.02)	
	0.005	0.055	
Most recent value			
0-0.4	1.00	1.00	1.00
0.4-1	0.47 (0.31, 0.71)	0.89 (0.54, 1.46)	0.48 (0.28, 0.81)
	<.001	0.633	0.006
1+	0.34 (0.19, 0.59)	1.02 (0.55, 1.88)	0.32 (0.16, 0.64)
	<.001	0.954	0.001
per unit higher	0.36 (0.20, 0.64)	0.94 (0.68, 1.29)	0.37 (0.19, 0.69)
	<.001	0.683	0.002

**(1)Adjusted for age, mode of HIV transmission, nationality,calendar year of baseline, nadir CD4, time spent on ART, AIDS diagnosis priorto baseline and -for the most recent value only- also for current HIV-RNA and CD4 count(included as time varying variables)

**(2)Adjusted for age, mode of HIV transmission, nationality,calendar year of baseline, nadir CD4, time spent on ART, AIDS diagnosis prior to baseline as well as current HIV-RNA and CD4 count (using inverse probability weighting)