CD4 cell count and the risk of infective and non-infective serious non AIDS events in HIV-infected persons seen for care in Italy

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Background

- CD4 cell count is the most used indicator of immune function in patients with HIV-infection and is the strongest predictor of disease progression and survival.
- Even in the cART era, serious non-AIDS events (SNAE) are frequent in HIV patients receiving cART.
- Current CD4 count has been shown to be more strongly associated with infective compared to non-infective SNAE and unable to predict cardiovascular events.

Objective

- We investigated the relation between baseline and current CD4 count and the risk of both infective and non-infective SNAE in HIV infected patients according to current ART use

Methods

- We included all HIV-infected persons enrolled in the Icona Foundation Study cohort who had at least one follow-up visit.
- Patients were grouped according to their treatment in naive, currently off and currently on ART.
- SNAE were grouped in infective (pneumonia, sepsis, endocarditis and meningitis) and non-infective (malignancies, chronic kidney disease, cardiovascular events, hepatic events and pancreatitis) etiology.
- *Malignancies included: Carcinoma of the cervix, anus, rectum, colon, lung, bladder, prostate, kidney, head and neck, skin; Hodgkin lymphoma and leukemia; malignant melanoma.*
- *Cardiovascular events included: Myocardial infarction, stroke, cerebral hemorrhage, dilated cardiomyopathy, angioplastic procedures*.
- *Hepatic events included: decompensate cirrhosis, hepatic encephalopathy, esophageal varices bleeding or HCC.*
- *Renal events included: acute renal failure, chronic renal failure or a confirmed eGFR<60 mL/min.*

Methods

- Incidence of these event groups were calculated overall and according to baseline and current CD4 count (grouped as 0-200, 201-350, 351-500, 501-750, and >750 cells/mm^3) as number of events divided by person years of follow-up (PYFU).
- Participants' follow-up accrued from the date of enrolment (baseline) to a diagnosis of SNAE or their last visit.
- An event was defined the first time one of the considered SNAE occurred so that each person contributed a single event.
- A Poisson regression model for each of the two endpoints was used.
- A competing risk approach was used (e.g. morbidity for a reason different from that under analysis and mortality were considered competing risk events). Thus, for example, in the analysis with non-infective SNAE as the endpoint, follow-up of a person who developed an infective SNAE was truncated at the date of his/her last clinical visit (administrative censoring).

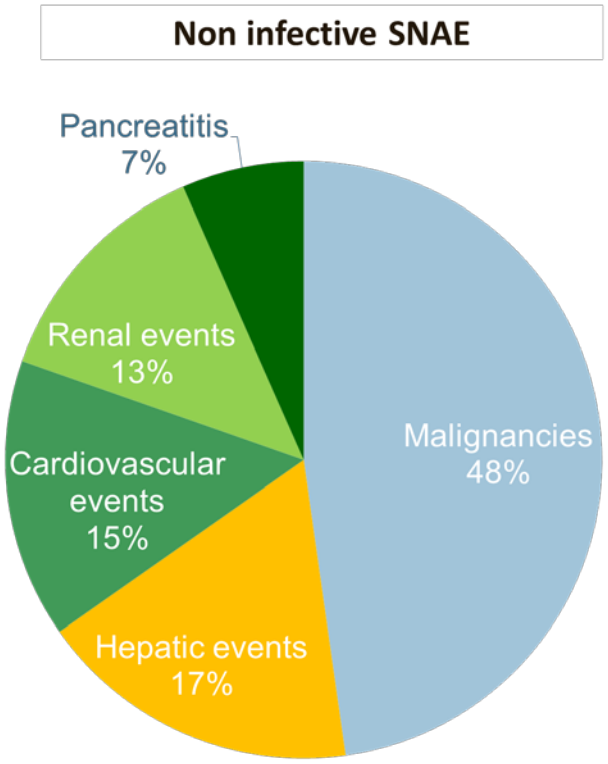
Results 1: Main patients' charachterisitics

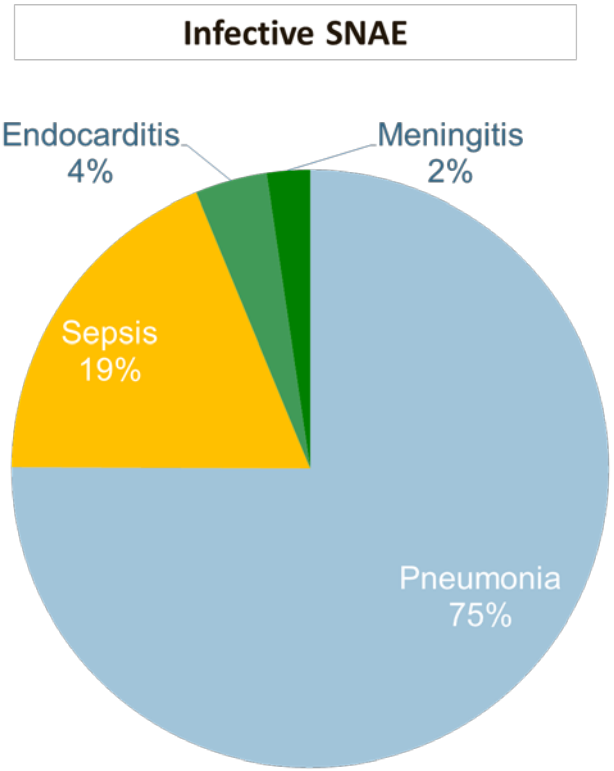
Characteristics	Total
	N= 10822
Gender, n(%)	
Female	2734 (25.3%)
Mode of HIV Transmission, n(%)	
IDU	2571 (23.8%)
Homosexual contacts	3423 (31.7%)
Heterosexual contacts	4137 (38.2%)
Other/Unknown	674 (6.2%)
Ethnicity, n(%)	
Black	514 (4.7%)
Hepatitis co-infection*, n(%)	2880 (26.6%)
Calendar year at enrolment*	2003 (1998, 2011)
Age, years*	36 (31, 42)
CD4 count at enrolment, cells/mmc*	405 (214, 590)
Viral load at enrolment, log10 copies/mL*	4.43 (3.64, 5.04)

* HCVAb+ or HBsAg+, **Data expressed as Median (IQR)

Results 2: frequency and type of events

- Overall, 423 non-infective and 385 infective SNAE were included.
- The most frequent non-infective SNAE were malignancies (n=202, 48%), followed by hepatic (n=74, 17%) and cardiovascular (n=64, 15%).
- The most frequent infective SNAE were pneumonia (n=289), sepsis (n=72) and endocarditis (n=15)





Results 3: crude rates of developing events

Patient group	Number with infective SNAE	Number with non-infective SNAE	PYFU	Crude rate of developing infective SNAE/100PYFU (95% CI)	Crude rate of developing non-infective SNAE/100PYFU (95% CI)
ART naives	136	107	13656	1.00 (0.84-1.18)	0.78 (0.64-0.95)
Currently off ART	17	36	3321	0.51 (0.30-0.82)	1.08 (0.76-1.50)
Currently on ART	232	280	35185	0.66 (0.58-0.75)	0.80 (0.71-0.89)
All groups	385	423	52162	0.73 (0.67-0.82)	0.81 (0.74-0.89)

Results 4: crude rates of events

Infective SNAE				
Patient group	**Baseline CD4<200**	**Baseline CD4 501-750**	**Current CD4<200**	**Current CD4 501-750**
ART naives	14.78 (11.29-19.33)	0.62 (0.45-0.87)	13.33 (10.26-17.32)	0.40 (0.26-0.62)
Currently on ART	1.18 (0.99-1.41)	0.56 (0.30-0.60)	3.80 (3.16-4.57)	0.31 (0.22-0.43)
Non infective SNAE				
Patient group	**Baseline CD4<200**	**Baseline CD4 501-750**	**Current CD4<200**	**Current CD4 501-750**
ART naives	5.30 (3.38-8.31)	0.57 (0.40-0.81)	5.48 (3.64-8.24)	0.50 (0.34-0.74)
Currently on ART	0.91 (0.74-1.12)	0.74 (0.57-0.97)	2.05 (1.60-2.64)	0.67 (0.53-0.84)

Results 5: Adjusted rate ratios (ARR) for Infective SNAE in relation with CD4 cell count

	Infective SNAE			
	Baseline CD4 count		Current CD4 count	
	ART-Naive	Currently on ART	ART-Naive	Currently on ART
CD4 count (cells/mmc)	ARR* (95% CI) p-value	ARR** (95% CI) p-value	ARR* (95% CI) p-value	ARR** (95% CI) p-value
≤200	1.00	1.00	1.00	1.00
201-350	0.12 (0.05, 0.27) <.001	0.59 (0.39, 0.88) <0.001	0.19 (0.10, 0.34) <.001	0.35 (0.23, 0.52) <0.001
351-500	0.10 (0.05 , 0.19) <.001	0.53 (0.35, 0.80) 0.003	0.11 (0.06 , 0.34) <.001	0.24 (0.16, 0.37) <.001
501-750	0.09 (0.05, 0.16) <.001	0.49 (0.31, 0.76) 0.002	0.08 (0.04, 0.16) <.001	0.21 (0.13, 0.32) <.001
>750	0.07 (0.03, 0.14) <.001	0.49 (0.24, 1.02) 0.055	0.11 (0.05, 0.22) <.001	0.14 (0.08, 0.26) <.001
Per 50% higher	0.57 (0.51, 0.62) <.001	0.83 (0.77, 0.89) <.001	0.65 (0.58, 0.72) <.001	0.74 (0.70, 0.77) <.001
Interaction p-value#	<0.001		0.010	

*Adjusted for gender, ethnicity (Black vs. Caucasian), age, HBV and HCV co-infection, current calendar year and current viral load; **Also adjusted for drug class currently used (NRTI, NNRTI, PI, other), #To test the consistency of the association between 50% higher CD4 count and the risk of SNAE across ART-strata.

Results 6: Adjusted rate ratio (ARR) for non-infective SNAE in relation with CD4 cell count

	Non Infective SNAE			
	Baseline CD4 count		Current CD4 count	
	ART-Naive	Currently on ART	ART-Naive	Currently on ART
CD4 count (cells/mmc)	ARR* (95% CI) p-value	ARR** (95% CI) p-value	ARR* (95% CI) p-value	ARR** (95% CI) p-value
≤200	1.00	1.00	1.00	1.00
201-350	0.34 (0.15, 0.79) 0.012	1.27 (0.91, 1.76) 0.154	0.40 (0.20, 0.81) 0.011	0.48 (0.32, 0.72) <0.001
351-500	0.15 (0.07, 0.33) <.001	0.89 (0.62, 1.27) 0.523	0.18 (0.09, 0.36) <.001	0.56 (0.37, 0.84) 0.005
501-750	0.16 (0.08, 0.32) <.001	1.09 (0.76, 1.56) 0.643	0.19 (0.10, 0.35) <.001	0.47 (0.33, 0.71) <0.001
>750	0.21 (0.10, 0.42) <.001	0.72 (0.38, 1.34) 0.298	0.16 (0.07, 0.35) <.001	0.32 (0.20, 0.52) <.001
Per 50% higher	0.65 (0.58, 0.72) <.001	0.94 (0.88, 1.00) 0.052	0.67 (0.61, 0.74) <.001	0.81 (0.76, 0.86) <0.001
Interaction p-value#	<0.001		<0.001	

*Adjusted for gender, ethnicity (Black vs. Caucasian), age, HBV and HCV co-infection, current calendar year and current viral load; **Also adjusted for drug class currently used (NRTI, NNRTI, PI, other), #To test the consistency of the association between 50% higher CD4 count and the risk of SNAE across ART-strata.

Limitations

- We were not able to include in the analysis other important non AIDS defining events such as neurocognitive impairment.
- Due to the relatively small number of events, we were not able to evaluate the role of CD4 count in infection-related and other malignancies separately.
- The observational nature of our study did not allow us to adjust for other possible confounders.

Conclusions

- In a large cohort of HIV infected patients seen for care in Italy the majority of SNAE were of non-infective origin.
- Higher baseline and current CD4 count are associated with a reduction in the risk of infective SNAE.
- Furthermore, there is evidence that the association between CD4 count and risk of both endpoints is stronger in ART-naïve compared to treated participants.
- In particular, for the risk of non-infective SNAE and when fitting baseline CD4 count as categorical there was no evidence for a difference in the risk comparing different CD4 count strata, suggesting that baseline CD4 is a much less useful predictor for this endpoint in ART-treated patients.
- This emphasize the importance of achieving CD4 count recovery on ART to prevent non-infective SNAE.

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