Incidence of CD4/CD8 ratio normalization and its role in the onset of non-AIDS related events.

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1. INTRODUCTION

Life expectancy of patients with HIV infection receiving combined antiretroviral therapy (cART) is similar but not equal to that of uninfected subjects [1]. Actually, the main factor influencing the prognosis of patients with HIV infection is the onset of non-AIDS-defining events (nADE) as: liver diseases, cardiovascular events, renal impairment, cancers, etc [2]. These events have been related either to the life-style of patients, as intravenous drug use or smoking, or to the continuous state of immune activation that is not fully controlled by cART [3-7]. Indeed, immune-reconstitution after therapy (cART) is often either quantitatively or qualitatively incomplete, and after almost 30 years of HIV infection, CD4 count remains the most important predictive factor of clinical progression concerning HIV-AIDS, but not of immune-activation and of non-ADEs [8]. Since non-ADEs are becoming more common, there is an urgent need for surrogate markers that could be widely used in clinical practice. In patients without HIV infection, a CD4/CD8 ratio <1 has been related to immune-senescence and to all cause mortality [9-11].

In naïve HIV-infected patients with a CD4 count >200 cells/uL, a low CD4 percentage and a low CD4/CD8 ratio before starting cART were predictive of the risk of clinical progression [12]. Moreover, in patients treated with cART and with undetectable HIVRNA, CD4/CD8 ratio was independently associated with T-cell activation [13] and with markers of age-associated disease as carotid intima-media thickness (IMT), arterial stiffness, estimated glomerular filtration rate, muscle wasting and sarcopenia [14]. Aim of the present study was to evaluate in the patients of the Icona cohort the probability of reaching a CD4/CD8 ratio >=1 after starting cART and its possible protective role against the onset of serious non-AIDS related events (nADE) or death for any cause.

2. PATIENTS & METHODS

The Icona Foundation Study is a cohort of HIV-infected patients which superseded the original I.Co.N.A. (Italian Cohort of Antiretroviral-Naïve Patients) study, recruiting HIV positive patients when still ART-naïve regardless of the reason. Clinical, therapeutical, laboratory and immuno-virological parameters are measured, on average, every 4 months. All patients signed consent forms to participate in the Icona Foundation Study, locally in each of the participating clinical sites. Inclusion criteria for this specific study were: 1) starting a cART regimen (at least three drugs) from ART-naïve after the 1st January 1997; 2) reaching a confirmed HIV-RNA<80 copies/mL; 3) CD4/ CD8 ratio at undetectability <=0.8.

We conducted two analysis: a) to establish the probability of CD4/CD8 normalization and to determine factors associated to this event and b) to establish whether normalization of CD4/CD8 might be related with the clinical progression defined as the occurrence of serious non-AIDS related events (nADE) or death for any causes.

Factors associated with normalization

End-point was the normalization of the ratio defined by two consecutive value of CD4/CD8>=1. Follow-up was censored if the subject lost the HIV-RNA undetectability (first of two consecutive HIV-RNA>80 copies/mL) or the subject died or was lost to follow-up. Kaplan Meier method was used to estimate the probability of normalization. The incidence rate of normalization was calculated dividing the number of events over the total number of person year of follow-up (PYFU). Multivariable Poisson regression model was used to analyze factors independently associated with normalization. Fixed covariates were: gender, age, mode of HIV transmission, years from HIV diagnosis, CD4 nadir, log10 HIV-RNA before cART start, HCV-Ab positive, months from start of therapy, undetectable viral load, calendar year of cART start, CD4/CD8 ratio at baseline. Type of antiretroviral regimen administered was analyzed as time-varying covariate.

CD4/CD8 ratio as a predictor of clinical progression

Serious nADE were [15]: (i) any non AIDS-defining malignancy; (ii) severe non-AIDS defining infections (i.e. potentially life-threatening or requiring intravenous antibiotic); (iii) cardiovascular events (documented acute myocardial infarction, coronary disease requiring invasive procedures, congestive hearth failure, stroke); (iv) hepatic events (decompensated cirrhosis, i.e. variceal bleeding, porto-systemic encephalopathy, refractory ascites, hepatorenal syndrome); (v) acute kidney injury (confirmed estimated glomerular filtrate rate [eGFR]<60ml/min using MDRD formula) or kidney failure requiring dialysis or renal transplantation. Follow-up started with the first of two HIV-RNA<80 cp/ml after therapy start and continued until the occurrence of the following events: serious non-AIDS event, death for any causes, loss to follow-up. Multivariable Poisson regression model was used to analyze the association of CD4/C8 ratio with clinical progression, adjusting for main confounders. Two different multivariable models were fitted to investigate if the role of current CD4/CD8 ratio on clinical progression were independent from current CD4: a) containing current CD4; b) including CD4/CD8 ratio too. The contribution of the additional covariates CD4/CD8 ratio was assessed using Akaike's information criterion (AIC). The model who had the best fit was that with a lowest AIC.

3. RESULTS

Our analysis included 3,236 (81.4%) out of 3,973 subjects who reached viral suppression after cART start, and who had a CD4/CD8 ratio <=0.8.

Table 1. General characteristics of the study population

Male gender, n(%)	2471	76.4
Age, median (IQR)	39	34-46
Italian nationality, n(%)	2858	88.3
Mode of HIV transmission, n(%)		
Heterosexual contacts	1339	41.4
Homosexual contacts	1031	31.9
IVDU	669	20.7
Other/unknown	197	6.1
HIV history		
Years of infection, median (IQR)	2.6	0.7-7.4
Log_{10} HIV-RNA pre cART, median (IQR)	4.80	4.25-5.25
Nadir cd4 cell/mmc, median (IQR)	223	101-317
CDC C stage, n(%)	592	18.3
Baseline CD4, cell/mmc, median (IQR)	378	249-518
Months to reach viral suppression, median (IQR)	5.4	2.9-12.3
HCV Ab, n(%)		
Positive	717	22.2
Negative	1913	59.1
Unknown	606	18.7
HBs Ag, n(%)		
Positive	142	4.4
Negative	2431	75.1
Unknown	663	20.5
CD4/CD8 ratio at baseline, median (IQR)	0.39	0.26-0.55

Factors associated with normalization

Over 7,305 PYFU, 458 pts reached a CD4/CD8 ratio ≥1. The incidence rate of normalization during viral suppression was 6.3 per 100 PYFU (95%CI 5.7-6.9).

Table 2. Normalization analysis

	1-year	2-year	5-year
Probability of CD4/CD8 normalization	4.4 95%CI (3.7-5.2)	11.5 95%CI (10.2-13.0)	29.4 95%CI (26.7-32.4)

Median time to normalization: 10.1 years (95%CI 8.6- not calculable

Table 3. Factors associated with CD4/CD8 ratio>=1 Multivariable Poisson regression model

	ARR	95% CI		P
Age (per 10 yrs older)	0.87	0.78	0.98	0.017
Mode of HIV transmission				
Heterosual contacts	1.00			
Homosexual contacts	0.75	0.58	0.98	0.034
IVDU	0.72	0.47	1.10	0.129
Other/unknown	0.58	0.34	1.00	0.049
Nadir CD4 <=200 cells/mmc vs >200	0.72	0.56	0.94	0.014
CD4/CD8 ratio at baseline (per 0.10 higher)	1.74	1.63	1.85	0.000
Couple of NRTIs in the current regimen				
tdf+ftc	1.00			
tdf+3tc	1.00	0.62	1.61	0.989
abc+3tc	0.78	0.51	1.19	0.246
azt+3tc	0.70	0.48	1.00	0.051
d4t+3tc	0.72	0.41	1.28	0.261
d4t+ddi	0.31	0.11	0.87	0.027
ddi+3tc	0.42	0.17	1.05	0.064
other	0.47	0.26	0.86	0.014

Also adjusted for gender, years from first anti-HIV test, months to viral suppression, HCV Ab and HBs Ag status, CDC C stage, log10 HIV-RNA before cART start, calendar year of cART start, type of current antiretroviral regimen (2NRTIs+NNRTI, 2NRTI+PIb, etc…).

CD4/CD8 ratio as a predictor of clinical progression

Over a total of 14,926 PYFU, 93 subjects died and 278 experienced a serious non-AIDS event.

Table 4. Incidence rate of clinical progression stratified by current CD4/CD8 ratio.

CD4/CD8 ratio	Incidence rate per 100 PYFU	95%CI
<0.30	4.8	3.9-5.9
0.30-0.45	2.4	1.9-3.1
>0.45	2.0	1.7-2.3

Table 5. Multivariable Poisson regression models estimating the association between clinical progression and
i) current CD4 cell count in the Model 1
ii) current CD4 cell count and current CD4/CD8 in the Model 2

Model 1 AIC=4247	ARR*	95% CI	P
Current CD4 count (per 100 cell/mmc higher)	0.94	0.89 0.99	0.013
Model 2 AIC=4239	**ARR***	**95% CI**	**P**
Current CD4 count (per 100 cell/mmc higher)	0.94	0.89 0.99	0.013
Current CD4/CD8 T-cell ratio			
>0.45	1.00		
0.30-0.45	0.99	0.73 1.34	0.934
<0.30	1.64	1.20 2.24	0.002

*Both models were adjusted for gender, mode of HIV transmission, white race, and the following variables measured at baseline: age, HCV co-infection, CDC C stage and log_{10} HIV-RNA.

The model 2 including current CD4 e current ratio CD4/CD8 was compared with the model 1 including only current CD4. The data fit seemed improved, in fact the Akaike's information criterion (AIC) reduced by more than 4 (empiric rule from Burnham and Anderson).

4. DISCUSSION

In conclusion, a minority of patients who start cART reaches a CD4/CD8 ratio≥*1*. Younger patients, those with a higher CD4/CD8 ratio at time of viral suppression and those starting cART more recently and with higher CD4 count have higher possibilities to achieve normalization. The CD4/CD8 ratio was predictive of serious non AIDS event or death independently from CD4 cell count.

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