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Risk of long-term Clinical Progression in PWH Initiating a First-Line ART with Advanced HIV Disease and Failing to Have a Robust CD4 Count Response Despite Viral Suppression

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Background

A proportion of persons with HIV (PWH) do not achieve robust CD4 count response upon initiation of ART, despite sustained viral suppression, also with modern regimens. Whether impaired early CD4 count recovery may influence the long-term risk of clinical progression has been seldom evaluated.

Materials and Methods

We included PWH of the Icona Foundation Study who started a first ART over 1997-2021, with a CD4 nadir <200/mm3, achieved HIV-RNA ≤50 copies/mL over the time window 6-12 months of ART and maintained viral suppression for ≥24 months. CD4 count non-response (**CD4-NR**) was defined as having never achieved an absolute CD4 T-cell count>350/mm3 and displaying an average slope of CD4+ increase <8.3 cells/month over the 24 months with HIV-RNA ≤50 copies/mL. At month 24 after first viral suppression (baseline of these analyses) PWH were classified as CD4-NR vs. responders (**CD4-R**). Kaplan–Meier curves and standard Cox proportional-hazard regression models with baseline time-fixed covariates were used to compare the time to developing a new AIDS or SNAEs diagnosis (CVD, non-AIDS cancer, ESLD and ESRD) or death after baseline according to CD4 count response groups.

Results

A total of 2051 PWH were included; 77% were male, 51% acquired HIV through heterosexual contacts, 35% had a previous AIDS diagnosis and 11% HCVAb+ (Table 1). At baseline, 521 (25%) were classified as CD4-NR (Table 1). The proportion CD4-NR in INSTI era (after 2014) was 26 (95% CI: 23.7-28.4) (Figure 1).

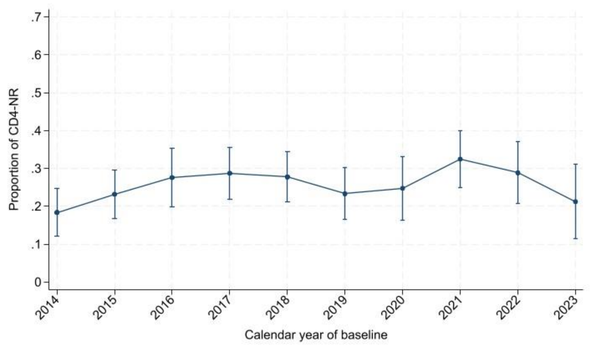


Figure 1. Proportion of CD4-NR according to calendar year of baseline

CD4-NR and CD4-R differed significantly in terms of median age (46 vs. 41 years, p<0.001), nadir CD4 (59 vs 97 cells/mm3, p<0.001), HIV load at cART start (4.98 vs 5.07 log10 cp/mL; p=0.037) and baseline CD4 count (230 vs. 460 cells/mm3, p<0.001) (Table 1).

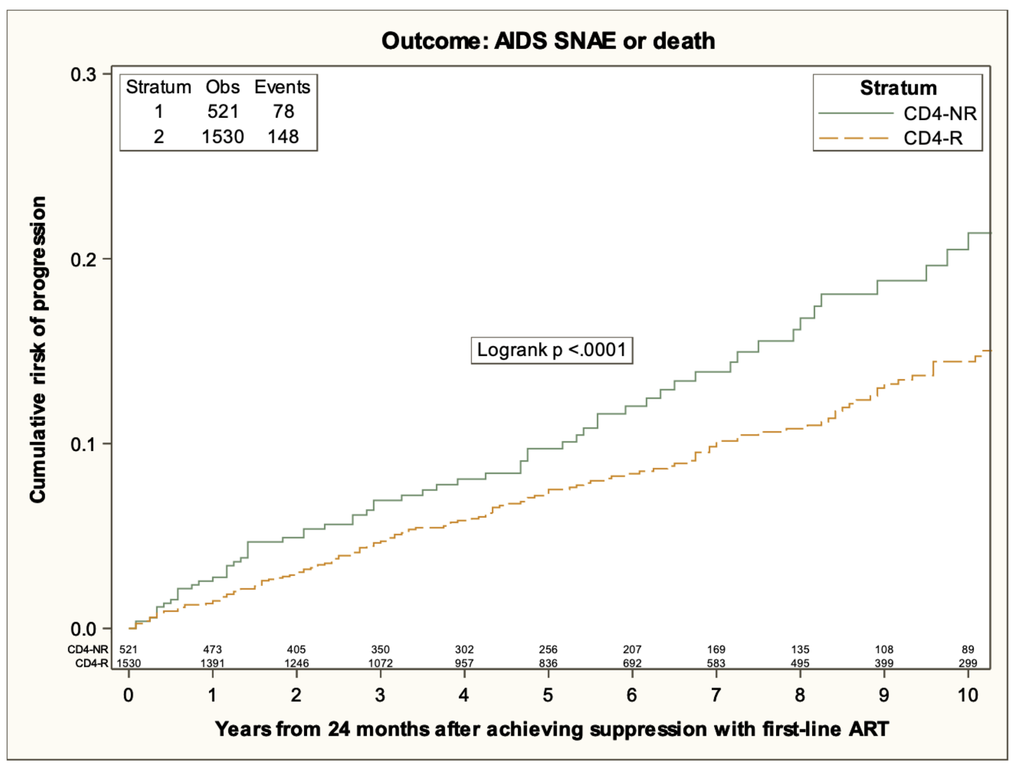
Table 1. Clinical characteristics in CD4-NR and CD4-R

Characteristic	Total N=2051	CD4-NR N=521	CD4-R N=1530	p-value*
Gender, female, n(%)	463 (22.6%)	104 (20.0%)	359 (23.5%)	0.099
Mode of HIV Transmission, n (%)				**0.023**
PWID	202 (9.8%)	56 (10.7%)	146 (9.5%)	
Homosexual contacts	653 (31.8%)	140 (26.9%)	513 (33.5%)	
Heterosexual contacts	1046 (51.0%)	278 (53.4%)	768 (50.2%)	
Other/Unknown	150 (7.3%)	47 (9.0%)	103 (6.7%)	
Nationality, foreign, n(%)	390 (19.0%)	96 (18.4%)	294 (19.2%)	0.692
Calendar year of ART initiation, median (IQR)	2013 (2009, 2016)	2014 (2010, 2017)	2013 (2009, 2016)	0.054
Age, median (IQR), years	42 (35, 51)	46 (39, 55)	41 (34, 49)	**<.001**
CD4 count nadir, median (IQR) cells/mmc	85 (33, 148)	59 (28, 114)	97 (36, 156)	**<.001**
Baseline CD4 count, median (IQR) cells/mmc	394 (282, 535)	230 (179, 270)	460 (363, 580)	**<.001**
AIDS, yes, n(%)	727 (35.4%)	201 (38.6%)	526 (34.4%)	0.083
Viral load at ART, median (IQR) log10 copies/mL	5.04 (4.35, 5.53)	4.98 (4.24, 5.45)	5.07 (4.38, 5.56)	**0.037**
Co-infections, n (%)				
HCV+	217 (10.6%)	64 (12.3%)	153 (10.0%)	0.306
Not tested for HCV	292 (14.2%)	76 (14.6%)	216 (14.1%)	
HBV+	15 (0.7%)	5 (1.0%)	10 (0.7%)	0.769
Not tested for HBV	280 (13.7%)	72 (13.8%)	208 (13.6%)	
First-line ART				0.771
3 drugs	1984 (96.7%)	505 (96.9%)	1479 (96.7%)	
4+ drugs	67 (3.3%)	16 (3.1%)	51 (3.3%)	
Anchor drug in first ART regimen				0.154
PI/r	819 (39.9%)	188 (36.1%)	631 (41.2%)	
NNRTI	396 (19.3%)	105 (20.2%)	291 (19.0%)	
INSTI	630 (30.7%)	180 (34.5%)	450 (29.4%)	
other	67 (3.5%)	16 (3.3%)	51 (3.6%)	
Time from HIV diagnosis to cART, median (IQR), months	34 (33, 37)	34 (33, 36)	35 (33, 38)	**<.001**

*Chi-square or Kruskal-Wallis test as appropriate

By 10 years from baseline, 21.4% (95% CI:15.9-26.9%) CD4-NR and 14.5% (95% CI:11.9-17.0%) CD4-R, developed AIDS, SNAE or death (log-rank test p<.0001, Figure 2).

Figure 2. Kaplan Meier estimates of the time to AIDS, SNAE/death according to CD4 response



The relative hazard of AIDS, SNAE/death associated with CD4-NR was 1.33 (0.96-1.86; p=0.090) after controlling for key confounders. Age appeared to explain most of the excess risk of SNAE/death associated with CD4-NR (Table 2).

Table 2. Relative hazards from fitting a Cox regression model

	Unadjusted RH (95% CI)	p-value	Adjusted[1] RH (95% CI)	p-value	Adjusted[2] RH (95% CI)	p-value
Outcome: new SNAE/death						
CD4-R	1		1		1	
CD4-NR	1.73(1.29, 2.33)	<.001	1.30 (0.96, 1.76)	0.085	1.28 (0.90, 1.84)	0.175
Outcome: new AIDS, SNAE/death						
CD4-R	1		1		1	
CD4-NR	1.75 (1.33, 2.30)	<.001	1.36 (1.02, 1.80)	0.033	1.33 (0.96, 1.86)	0.090

[1]for age

[2]for age, gender, nationality, mode of HIV transmission, year of baseline, CD4 nadir, baseline CD8 and at ART initiation, AIDS, INSTI use in first-line, hepatitis co-infection and VL blip before baseline

Conclusions

CD4-NR over 36 months from initiation of therapy remains frequent in the era of INSTI. CD4-NR was associated with a higher risk of clinical progression which was, however, largely explained by age and other confounding factors.

References

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