

Increased clinical events in HIV-infected patients who achieve full virologic suppression but fail to attain a CD4 count ≥ 200 cells/mm³ after two years of combination antiretroviral therapy (cART)

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Background

The prognostic impact associated with a lack of immune reconstitution (CD4 ≥ 200 cells/mm³) despite virologic suppression (VL < 50 copies/mL) following cART remains unclear. Our study's purposes were to determine if this discordant state results in more clinical events and to determine the predictors of this state.

Table 1: Characteristics of CANOC patients in the 2-years after HAART Analysis

Variable	Category	n (%)	Total
Gender			1082
	Male	882 (81.5)	
History of Injection Drug Use			1050
	Yes	163 (15.5)	
Province			1082
	BC	781 (72.2)	
	ON	117 (10.8)	
	PQ	184 (17)	
Two-year CD4			1082
	< 50 - 199	123 (11.4)	
	200 - 349	322 (29.7)	
	350 - 500+	637 (58.9)	
Death or AIDS after 2 years of HAART			1082
	Yes	36 (3.3)	
Initial cART combo			1082
	NNRTI + NRTI x 2	498 (46)	
	PI + NRTI x 2	541 (50)	
	NRTI x 3	43 (4)	
	n	Interquartile Range	
Age	965	42.0 (36.0-49.0)	
Follow-up time (months)	1082	41.9 (30.9-56.4)	
Baseline CD4	1082	163.5 (70.0-240.0)	
Baseline Viral load (log10)	1082	5.0 (4.6-5.0)	
Two-year CD4	1082	384.5 (280.0-520.0)	
Two-year CD4 change	1082	220.0 (120.0-350.0)	

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Methods

ART-naïve HIV-positive individuals in the CANOC Collaboration who started cART after 31/12/1999 and achieved a VL < 50 copies/mL on three sequential occasions within two years of cART were included in the analysis. Multivariable Cox-proportional hazards regression was used to model time to death or development of an AIDS-defining illness after two years of starting cART. Covariates of interest included the CD4 count at two years and whether the two-year CD4 count was < 200 cells/mm³. Events were the first of AIDS or death before any rise of VL ≥ 50 copies/mL, while non-events were censored at VL ≥ 50 copies/mL or last contact date $\leq 09/2008$. Predictors of not achieving a two-year CD4 count ≥ 200 cells/mm³ were determined using multiple logistic regression.

Results

1082 individuals with a median follow-up of 42 months (IQR 31,56) were analyzed.

36 clinical events occurred after two years of cART. There were 11 AIDS defining illnesses reported (candida, cryptococcus, Herpes simplex virus, Kaposi's Sarcoma, Mycobacterium avium immune complex, mycobacterium tuberculosis, 3 cases of non-Hodgkins lymphoma, toxoplasmosis and wasting syndrome) and 25 deaths.

IDU (aHR=2.88; p=0.003) and two-year CD4 < 200 cells/mm³ (aHR=2.72; p=0.011) were associated with clinical events after two years of cART. Baseline VL and CD4 count were not significant: (HR=1.22; p=0.629) and (HR=0.95; p=0.734), respectively.

Significant predictors for two-year CD4 count < 200 cells/mm³ were: baseline CD4 count (OR=0.24 per 100 cells/mm³; p<0.001), hepatitis C status (OR=2.78; p<0.001) and 3rd agent (p=0.03).

Table 2: Cox model for time to AIDS or death

Variable	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Age	1.06 (1.03-1.09)	<0.001		
Male	1.45 (0.56-3.73)	0.439		
IDU	3.35 (1.70-6.62)	<0.001	2.88 (1.44-5.75)	0.003
Location				
BC	1			
Ontario	0.63 (0.19-2.06)	0.442		
Quebec	0.44 (0.13-1.43)	0.172		
Baseline CD4 (per 100 cells)	0.80 (0.60-1.06)	0.117	0.95 (0.70-1.29)	0.734
Baseline VL (log10)	1.33 (0.62-2.84)	0.465	1.22 (0.55-2.72)	0.629
Two year CD4				
<200	3.84 (1.77-8.32)	0.001		
200-349	1.30 (0.58-2.93)	0.526		
350+	1			
CD4 increase ≤ 25	1.74 (0.68-4.48)	0.251		
CD4 increase ≤ 50	2.36 (1.11-5.03)	0.026		
CD4 increase ≤ 100	2.41 (1.24-4.68)	0.009		
Two year CD4 <200	3.47 (1.73-6.95)	<0.001	2.72 (1.26-5.87)	0.011
Two year CD4 (per 50 cells)	0.85 (0.76-0.95)	0.003		

Table 3: Factors Associated with Outcome: Discordant State

Variable	Unadjusted Odds Ratio (95% CI)	p-value	Adjusted Odds Ratio (95% CI)	p-value
Male	1.59 (0.92-2.75)	0.099		
Age	1.02 (1.00-1.04)	0.092		
IDU	2.51 (1.63-3.88)	<0.001		
AIDS diagnosis prior to viral suppression	2.58 (1.73-3.86)	<0.001		
Baseline CD4 (per 100 cells)	0.31 (0.24-0.41)	<0.001	0.24 (0.18-0.33)	<0.001
Baseline Viral Load (per log10)	0.95 (0.65-1.37)	0.773		
Hepatitis C status		<0.001		<0.001
	Negative	1	1	
	Positive	2.46 (1.56-3.87)	2.78 (1.63-4.74)	
	Unknown	1.65 (1.04-2.62)	1.88 (1.12-3.14)	
Initial NRTI pair		0.013		0.098
	AZT/3TC	1	1	
	D4T/3TC	0.94 (0.60-1.49)	0.65 (0.38-1.10)	
	TDF/3TC	0.37 (0.16-0.83)	0.28 (0.09-0.82)	
	ABC/3TC	0.43 (0.17-1.12)	0.63 (0.22-1.85)	
	Other	1.25 (0.74-2.10)	0.96 (0.50-1.84)	
3rd Drug in initial cART regimen		0.15		0.033
	NEV	1	1	
	DMP	1.05 (0.60-1.84)	0.89 (0.47-1.68)	
	LDP	0.85 (0.48-1.51)	0.39 (0.20-0.75)	
	ATA	0.60 (0.29-1.25)	0.74 (0.27-2.01)	
	NEL	1.80 (0.92-3.50)	1.25 (0.55-2.82)	
	Other	1.30 (0.71-2.37)	0.82 (0.41-1.65)	
Province		0.469		
	BC	1		
	ON	0.63 (0.31-1.29)		
	PQ	1.08 (0.66-1.77)		

Conclusions

In our study population, HIV-infected patients taking cART who achieve complete viral suppression but fail to have a CD4 cell increase above the desired target of ≥ 200 cells/mm³ have an increased rate of clinical events after two years, confirming the clinical significance of the immunologic discordant state. Our study event rate was low and verification with a larger sample would be beneficial.

For more information about CANOC, please visit www.canoc.ca