CD4:CD8 NORMALIZATION BY INTEGRASE INHIBITORS AMONG TREATMENT-NAÏVE PATIENTS

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CANOC

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Background

- HIV infection leads to selective depletion of CD4+ T cells and an increase in CD8+ T cells resulting in an inverted CD4:CD8 ratio.
- Low CD4:CD8 ratio often persists despite antiretroviral therapy (ART) and virological suppression[1].
- A low CD4:CD8 ratio is associated with non-AIDS related morbidities[2].
- A positive association between CD4:CD8 ratio normalization and initiation of raltegravir containing regimens has been observed[3].

Hypothesis: Integrase Strand Transfer Inhibitor (INSTI)-containing regimens are associated with greater likelihood of CD4:CD8 ratio normalization relative to other regimens among treatment naïve patients.

Methods

- Retrospective analysis of the Canadian Observational Cohort (CANOC), an interprovincial cohort of HIV-infected adults.
- Treatment naïve participants starting combination ART regimens comprised of two Nucleoside Reverse Transcriptase Inhibitors (NRTIs) along with either an INSTI or a non-INSTI antiretroviral agent between 2011-2014 were included.
- Participants had a pre-treatment CD4:CD8 ratio of <1.2 and ≥2 follow-up ratios within 6 months of treatment.
- Kaplan Meier estimates were used to describe time to CD4:CD8 ratio normalization (defined as CD4:CD8 ratio ≥1.2 on 2 consecutive measures ≥ 30 days apart).
- Multivariable proportional hazards models were used to estimate the association between ART class and CD4:CD8 ratio normalization.

Table 1. Baseline demographic and clinical characteristics

Variable	Missing (%)	Overall (n=781)	INSTI Regimen (n=235)	Non-INSTI Regimen (n=546)	p-value
Age – yr [IQR]		38 [31,47]	38 [32, 48]	37 [31, 46]	0.252
Gender					0.21
Male		699 (89.5)	217 (92.3)	482 (88.3)	
Female		81 (10.4)	18 (7.7)	63 (11.5)	
Transgender		1 (0.1)	0 (0.0)	1 (0.2)	
Race	30.9				0.734
Caucasian		267 (49.4)	72 (51.1)	195 (48.9)	
Black		124 (23.0)	29 (20.6)	95 (23.8)	
Other		149 (27.6)	40 (28.4)	109 (27.3)	
Risk Factor	10.5				0.154
MSM only		531 (76.0)	169 (79.3)	362 (74.5)	
IDU only		11 (1.6)	4 (1.9)	7 (1.4)	
MSM+IDU		17 (2.4)	7 (3.3)	10 (2.1)	
Heterosexual		131 (18.7)	29 (13.6)	102 (21.0)	
Other		9 (1.3)	4 (1.9)	5 (1.0)	
Hepatitis C	2.7	50 (6.6)	19 (8.3)	31 (5.8)	0.273
Hepatitis B	5.0	55 (7.4)	16 (7.1)	39 (7.5)	0.957
Baseline CD4:CD8 ratio [IQR]		0.36 [0.21, 0.50]	0.39 [0.24, 0.57]	0.35 [0.20, 0.50]	0.016
Baseline CD4 [IQR]		340 [210, 450]	370 [225, 480]	330 [210, 440]	0.044
Baseline VL log10 [IQR]		4.71 [4.24, 5.19]	4.75 [4.29, 5.22]	4.68 [4.22, 5.18]	0.203

Treatment naïve patients starting regimens containing Integrase Strand Transfer Inhibitors are more likely to achieve CD4:CD8 ratio normalization.

Results

- 781 participants were included and followed for a median [IQR] 1.9 [1.0, 2.7] years. Baseline characteristics are described in Table 1.
- Participants starting on INSTI-containing regimens were more likely to have a higher pre-treatment CD4 count (370 vs. 330 cells/mm^3) and CD4:CD8 ratio (0.39 vs. 0.35) compared to those starting non-INSTI regimens.
- After adjusting for baseline characteristics, those starting INSTI-containing regimens were more likely to achieve normalization (HR=1.75, 95%CI 1.10, 2.77) (Table 2).
- Higher baseline CD4 count was associated with increased likelihood of achieving CD4:CD8 ratio normalization (Table 2).
- 15% of participants on INSTI-containing regimens normalized their ratio (vs. 12% on other regimens) with a 0.21 (95%CI 0.13, 0.28) probability of achieving normalization within 2 years (vs. 0.11 (95%CI 0.08, 0.14) among those on non-INSTI regimens, p<0.01) (Figure 1, Table 3).

Table 2. Significant factors associated with CD4:CD8 ratio normalization

Variable	Adjusted HR (95 CI)	p-value
INSTI regimen	1.75 (1.1, 2.77)	0.02
Baseline CD4		
< 100	Ref.	
100-200	1.3 (0.08, 20.91)	0.85
200-300	8.65 (1.13, 66.55)	0.04
300-500	17.43 (2.34, 129.54)	<0.01
>500	24.89 (3.27, 189.43)	<0.01
Baseline VL log10	1.15 (0.83, 1.61)	0.4
Risk Factor		0.27
MSM	0.73 (0.41, 1.28)	
IDU	0.69 (0.19, 2.5)	0.57
Hepatitis C	1.31 (0.56, 3.07)	0.54
Hepatitis B	1.34 (0.57, 3.17)	0.5

Figure 1. Cumulative distribution of time to CD4:CD8 ratio normalization by ART class

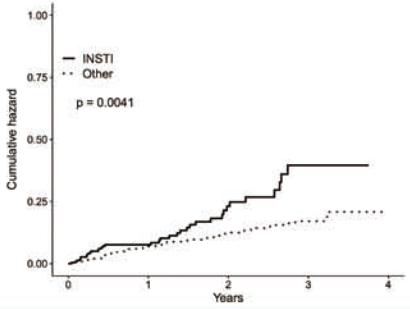


Table 3. Probability of CD4:CD8 ratio normalization by treatment duration and ART class

Year	INSTI Regimen	Non-INSTI Regimen	p-value
1	0.07 (0.04, 0.11)	0.07 (0.04, 0.09)	
2	0.21 (0.13, 0.28)	0.11 (0.08, 0.14)	
3	0.33 (0.22, 0.44)	0.16 (0.12, 0.2)	<0.01

Conclusions

- Our results provide further evidence that initiation of INSTI-containing regimens results in greater probability of CD4:CD8 ratio normalization in treatment naïve subjects.
- Whether improved ratio normalization with INSTIs is associated with lower rates of comorbidity or improved survival requires further study.
- Similar to prior reports, we found that higher baseline CD4 count is highly predictive of ratio normalization and supports current guidelines recommending early ART initiation.

References

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CANOC ^ I have no conflicts of interest