The relationship between inflammatory biomarkers and CD4 count decline during antiretroviral-untreated HIV: A substudy of the VALIDATE (CTN-240) trial

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Background

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- HIV is associated with multi-component inflammatory response
  - Microbial translocation,
  - Inflammatory cytokines
  - Acute phase reactants
  - Coagulation cascade
- Chronic immune activation and systemic inflammation are associated with adverse health outcomes among those with advanced HIV
- Few studies have examined their significance during early infection
- **Objective:** To quantify the relationship between inflammatory biomarkers and rate of HIV progression in ART-untreated adults

Methods

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- VALIDATE (CTN-240) was a multicentre RCT of valacyclovir vs placebo for slowing HIV disease progression in antiretroviral-untreated adults
  - N=198 in Canada, Brazil, Argentina and the UK
  - No difference in CD4 count decline but modestly lower HIV VL on valacyclovir
- Participants underwent quarterly plasma sampling until 1° endpoint of either 2 consecutive CD4≤350 or ART initiation for any reason
- Stored plasma tested for D-dimer, soluble CD14, C-reactive protein, interleukin-6
- Linear mixed models adjusted for study arm, baseline CD4 to estimate relationship between time-update biomarker levels and rate of CD4 count decline

Results

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Table 1. Participant characteristics (n=183)

Characteristics	Value[a]
Male sex	147 (80.3)
Age	35 (30,42)
On study drug	89 (48.6)
Country	
Canada	81 (44.3)
Brazil	72 (39.3)
UK	30 (16.4)
Baseline CD4	
Absolute (cells/mm^3)	593 [492, 692]
Percentage	28 [23, 33]
Viral load	4.0 [3.6, 4.5]
# plasma samples	5 [3,8]

Table 2. Relationship between time-updated biomarker levels and rate of change in CD4 count decline

	Baseline value[a]	Difference in CD4 count decline/year per unit increase in biomarker (95% CI)
D-dimer (log10)	2.27 [2.07, 2.46]	-60.4 (-108, -12.7)
sCD14 (per 0.1 of a $\log_{10}$)	33 [32, 34]	-6.19 (-13.6, 1.24)
CRP ($\log_{10}$)	33 [32, 34]	-22.5 (-46.5, 1.43)
Detectable IL-6	108 (69.7)	5.85 (-16.9, 28.5)

[a] Median [IQR] or n (%) detectable

Conclusions

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- Higher D-dimer levels were associated with more rapid CD4 cell count decline during ART-untreated HIV infection, independent of baseline CD4 count and baseline viral load
- Further work will examine relationship between baseline biomarker levels and time to reaching primary endpoint
- In current era of universal ART, long-term clinical significance of inflammatory biomarker levels during untreated infection uncertain

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