The CD4 Depletion Model Does Not Differentiate Incident from Chronic Infection

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Background

- The Ending the HIV Epidemic (EHE) initiative targets a 75% decline in HIV incidence in 5 years, and a 90% decline in 10 years.
- Current population incidence estimates are derived from a CD4 depletion model developed by the Centers for Disease Control and Prevention. An evaluation of this model in cohorts with well documented dates of infection is lacking in the literature.
- Biomarker based approaches and viral diversity have been evaluated as a potential markers of recent infection.

Objective

- To determine the accuracy of the CD4 depletion model for differentiating incident and chronic infections.
- To evaluate viral diversity as a predictor of recency.

Methods

- 830 individuals from the San Diego Primary Infection Resource Consortium (PIRC), enrolled between 1996 to 2019 were included in this analysis.
- The PIRC algorithm estimates date of infection (EDI) at study enrollment based on combination of ART-naïve serologic, virologic, recency assay (Limiting Antigen) and prior testing criteria. A precise EDI can be calculated for participants with acute and early HIV infection (AEH, defined as ≤6 months).
- The CD4 depletion model estimates EDI from an ART-naïve CD4 count via a linear relationship between the square-root of CD4 and time after infection.
  - Model parameters depend on age, gender and transmission risk factors.
- A chronic cohort was created from the subset of participants who presented with AEH who had ART-naïve follow up ≥1 year after EDI.
- Sequence ambiguity was determined using available ART-naïve genotypic resistance sequencing, using a cutoff of ≤0.5% for incident infections.
- Bivariate linear regression, two-tailed matched T-tests, and sensitivity/specificity were used to test whether the CD4 depletion model or sequence ambiguity correlated with PIRC EDI for estimating proportion of incident infections.

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Figure 1: PIRC vs CD4 Depletion Model Duration of infection

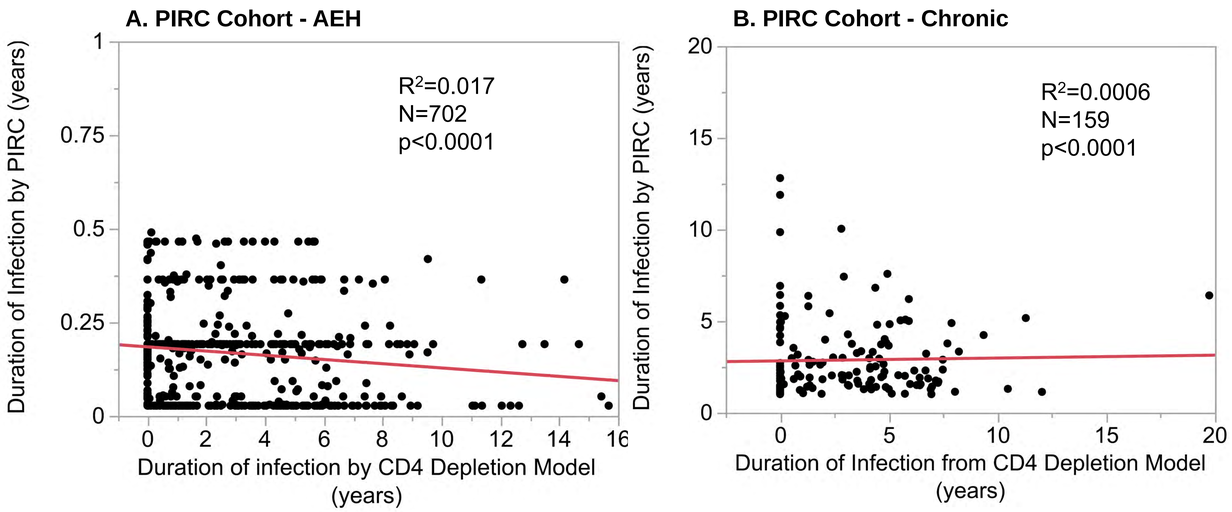


Table 1: Baseline Characteristics

Baseline Characteristics	Total Cohort N=830
Age (median, IQR)	32 (26 – 40)
Male sex (N, %)	799 (96)
Race/ethnicity (N, %)	
White non-Hispanic	432 (53)
Black non-Hispanic	49 (6)
Hispanic	262 (32)
Other (including multi-racial)	65 (8)
HIV transmission risk (N, %)*	
Men who have sex with men	799 (92%)
Injectable drug use	39 (5%)
Heterosexual male	27 (3%)
Other/unknown	30 (4%)
Log_{10}VL at study entry (median, IQR)	4.8 (4.1-5.6)
CD4 count at entry cells/mm^3 (median, IQR)	492 (354-643)
Classification at Diagnosis (N, %)	
Acute (NAT+/Ab-)	181 (22)
Early (<6 months)	522 (63)
Chronic (≥1 year)	125 (15)

*Some individuals had more than 1 transmission risk factor

Table 2: Contingency Tables

A. PIRC vs CD4 Depletion Model

	PIRC - Incident	PIRC - Prevalent	Total
CD4 Model - Incident	279	105	384
CD4 Model - Prevalent	267	179	446
Total	546	284	830

B. PIRC vs Sequence ambiguity

	PIRC - Incident	PIRC - Prevalent	Total
Viral Diversity - Incident	531	53	584
Viral Diversity - Prevalent	160	77	237
Total	691	130	821

Results

- Baseline characteristics are shown in **Table 1**.
- 702 participants had precise EDIs from both PIRC and CD4 depletion models that could be evaluated.
  - o Median age 32, 96% male, 93% MSM, with median initial CD4 of 505 cells/mm^3.
  - o 159/702 participants were included in the chronic cohort.
- There was poor correlation between PIRC and CD4 model EDIs - in both the PIRC AEH (R^2 0.017, p<0.0001, **Figure 1A**) and chronic cohorts (R^2 0.0006, p<0.0001, **Figure 1B**).
- Compared to the PIRC algorithm, the CD4 depletion model had 51% sensitivity (95% CI 47-55%), and 63% specificity (95% CI 57-68%) for predicting which infections were incident; overall concordance was 55% (**Table 2A**).
- Compared to the PIRC algorithm, sequence ambiguity had 77% sensitivity (95% CI 74-80%), and 59% specificity (95% CI 51-67%) for predicting which infections were incident; overall concordance was 74% (**Table 2B**). False recency rate (FRR) was 41%.

Conclusions

- On an individual level, the CD4 depletion model inaccurately classifies both incident and chronic HIV infections. Using the CD4 depletion model as the foundation of population scale estimates will lead to inaccurate estimates of population incidence (See Poster 0904).
- Estimating changes in incidence following roll-out of EHE prevention and treatment interventions within high burden jurisdictions using the CD4 depletion model is not expected to provide accurate estimates of changes in incidence given annual new diagnoses (200-2000) in these regions.

References

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