Temporal Trends in CD4 Cell Count Soon After Seroconversion and HIV-RNA Viral Set-Point

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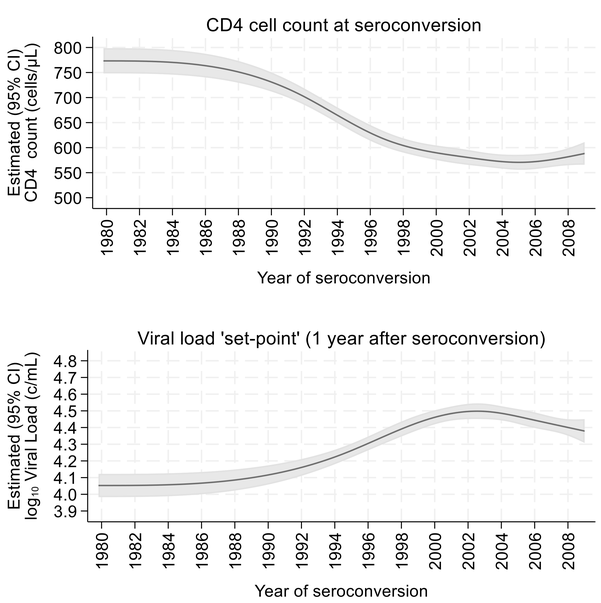
BACKGROUND

- We have previously (*Lancet HIV, 2014*) reported on a temporal decrease in CD4 cell count at seroconversion (SC) and an increase in HIV-RNA viral load (VL) levels at 1 year after SC (set-point) over the period 1980-2008 (**Figure 1**).
- **Objective**: To investigate whether these trends had continued, stabilized or reversed, focusing on changes since the introduction of combination ART in 1996, using newly collected data.

Figure 1. Results from a previous CASCADE analysis: estimated CD4 cell count at seroconversion and viral load set-point by year of SC.



METHODS

- Data are derived from the CASCADE study (https://www.cascadestudy.net); Multinational study of cohorts from France, Netherlands, Spain, Sweden, Greece, Canada, and UK.
- Clinical data and laboratory results were obtained from individuals with well estimated dates of HIV-1 seroconversion (HIV-1 test window ≤12 months or laboratory evidence of SC).
- **Inclusion criteria**: Seroconversion year ≥1996, age ≥16 years, CD4 and VL measurements available while ART naïve and AIDS-free.

Statistical analysis:

- Exploratory analysis revealed gradient changes at ~4 months (increase then decrease) and ~1 year (decrease then increase) after SC for CD4 and VL evolution during natural history, respectively.

- In a previous analysis of seroconverters data from the CASCADE collaboration, we estimated that during the first 20 years of the HIV-1 epidemic, CD4 cell count close to seroconversion decreased by ~200 cells/μl and viral load set-point increased by ~0.45 $\log_{10}$ copies/ml
- In the current analysis of more recent data we found minimal changes from 2004 onwards, suggesting that **these markers of HIV virulence may have now plateaued**

- Analyses based on piecewise linear mixed models (1 knot at 4 months and 12 months after SC for CD4 and VL analyses, respectively).
- Calendar time (i.e. SC year) effects introduced through natural cubic splines.
- Those seroconverting ≥2015 and ≥2014 excluded from CD4 and VL analyses, respectively (reliable estimation not feasible due to ART initiation close to SC).
- All models adjusted for age, sex, transmission mode, region of origin, acute infection (HIV test interval <30 days) and type of viral assay (VL analysis only).
- Main estimates of interest: CD4 at 4 months after SC, VL set-point.

RESULTS

- Of 28545 individuals in CASCADE, 15066 (52.8%) fulfilled the inclusion criteria.
- Demographic and other characteristics along with numbers of available markers' measurements pre-ART/AIDS are shown in **Table** below.
- Changes in the estimated CD4 cell count soon after SC and VL set-point, during the study period, were statistically significant (p<0.001 for both) but within a limited range: between 558 and 598 CD4 cells/μL and between 4.30 and 4.48 $\log_{10}$ HIV-RNA copies/mL, respectively (**Figure 2**).

Table. Characteristics of study population by year of HIV-1 seroconversion

	1996-03	2004-08	2009-14
Characteristic	*n=4027 (26.7%)*	*n=4534 (30.1%)*	*n=6505 (43.2%)*
Age at SC (years; median/IQR)	32.4 (26.9, 39.5)	33.9 (27.8, 41.4)	33.2 (26.8, 42.0)
Sex and transmission mode			
– Sex between men (MSM)	2224 (55.2%)	3220 (71.0%)	5099 (78.4%)
– Men - heterosexual contact	166 (4.1%)	70 (1.5%)	70 (1.1%)
– Women - heterosexual contact	591 (14.7%)	461 (10.2%)	496 (7.6%)
– Injecting drug use	881 (21.9%)	646 (14.2%)	631 (9.7%)
– Unknown/Other	165 (4.1%)	137 (3.0%)	209 (3.2%)
Acute infection	2207 (54.8%)	2105 (46.4%)	2663 (40.9%)
HIV subtype			
– B	235 (5.8%)	648 (14.3%)	850 (13.1%)
– Non-B	31 (0.8%)	83 (1.8%)	208 (3.2%)
– Unknown	3761 (93.4%)	3803 (83.9%)	5447 (83.7%)
CD4 measurements (#; median/IQR)	4 (2, 9)	6 (3, 11)	2 (1, 5)
VL measurements (#; median/IQR)	3 (1, 9)	5 (2, 9)	2 (1, 4)

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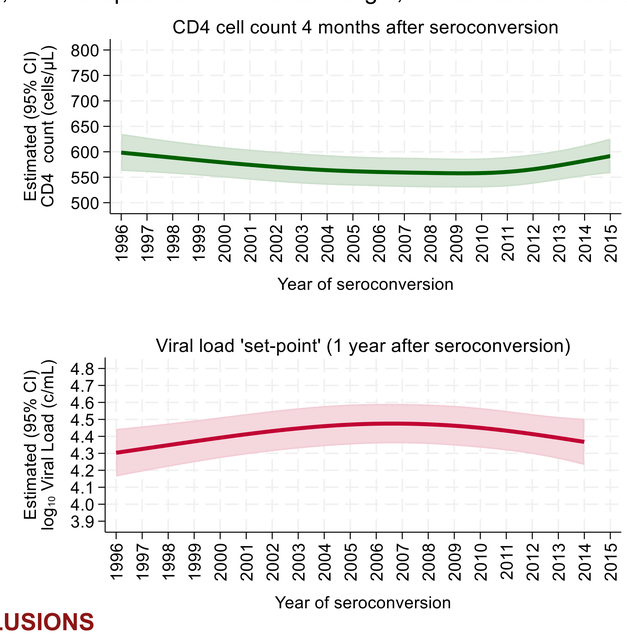
- HIV-1 subtype was known for 2055/15066 (13.6%) study participants. 84.3% of them had a B subtype.
- Individuals with CRF02_AG subtype had a CD4 cell count at 4 months after SC that was approximately 58 cells/μL lower (p=0.035) compared to those with B subtype.
- All non-B subtypes were associated with non-significantly lower viral set-points compared to the B subtype.

Figure 2. Estimated CD4 cell count 4 months after seroconversion and viral load set-point by year of seroconverion (estimates for MSM, aged 30-40, with European or N. American origin, without acute infection)



CONCLUSIONS

- Our results showed that since 2004 there have been minimal changes in levels of both the CD4 cell count soon after SC and the viral load set-point.
- These results suggest that, after the changes observed during the first 2 decades of the epidemic, these markers of HIV virulence may have now plateaued.

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