CD4 Cell Dynamics in untreated HIV-1: Overview and Determinants

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1. Background and objective

- CD4 cell count is a key measure of HIV disease progression, and the basis of successive international guidelines for treatment initiation.
- CD4 cell dynamics are used in mathematical and econometric models for evaluating public health need and interventions.
- Here, we estimate rates of CD4 decline, stratified by relevant covariates, in a form that is clinically transparent and can be directly used in such models.

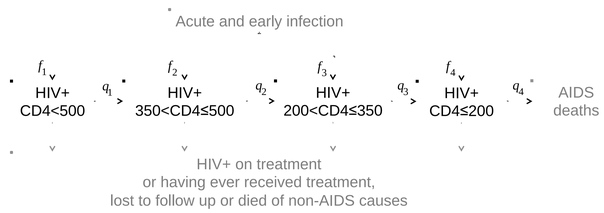
2. Data

- We used data from the AIDS Therapy Evaluation in the Netherlands (ATHENA) observational Cohort[1] including the >20,000 HIV-infected patients followed in one of the 27 HIV treatment centres in the Netherlands since 1996.
- We selected the 753 patients with
  - a seroconversion window known within a year,
  - $n_{VL} \geq 2$ viral load (VL) measurements taken between 6 and 24 months following the first positive HIV test and before the initiation of HAART,
  - $n_{CD4} \geq 6$ CD4 counts prior to HAART initiation.
- We compute the Set Point Viral Load (SPVL) of each patient as the geometric mean of the n_{VL} VL measurements.

3. Individual CD4 progression model

- We used the CD4 progression model shown in Figure 1 to describe the dynamics of "smoothed" CD4 counts. We assumed that actual CD4 counts are subject to additional random variability.

***Figure 1**: CD4 progression model*



- We used a monotonic cubic spline to describe the decline in CD4 counts after seroconversion and prior to HAART initiation in each patient, as shown in Figure 2. The splines were fitted independently to each patient's observed CD4 counts.
- Smoothed CD4 counts in the >500 and the <200 categories have a very high predictive value, whereas there are more misclassifications in the intermediate categories (Table 1).

***Figure 2**: Fit of monotonic splines for a random sample of 8 patients. Initial CD4 counts as well as rates of decrease are very heterogeneous.*

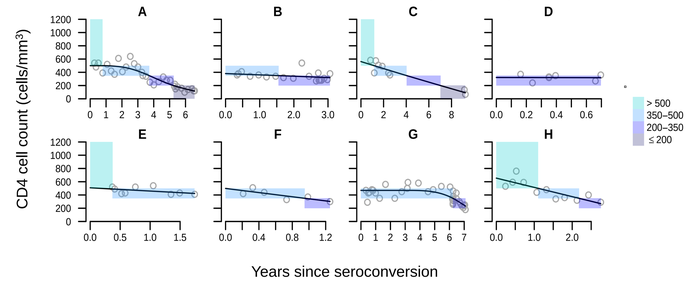


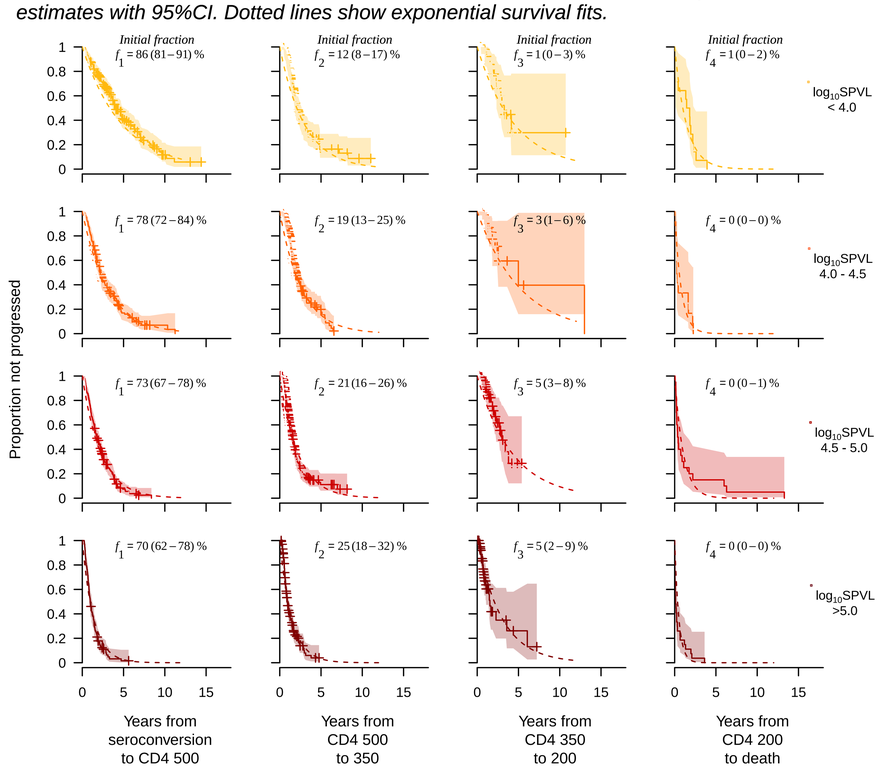
***Table 1**: Predictive value of smoothed CD4 count category*

Observed CD4	Smoothed CD4 >500	Smoothed CD4 350-500	Smoothed CD4 200-350	Smoothed CD4 ≤200
>500	3784 (84.8%)	637 (17.8%)	13 (0.7%)	1 (0.3%)
350-500	626 (14.0%)	2348 (65.5%)	395 (20.4%)	1 (0.3%)
200-350	43 (1.0%)	586 (16.3%)	1377 (71.2%)	35 (10.1%)
≤200	7 (0.2%)	14 (0.4%)	150 (7.8 %)	310 (89.3%)

4. Estimated CD4 dynamics and main determinants

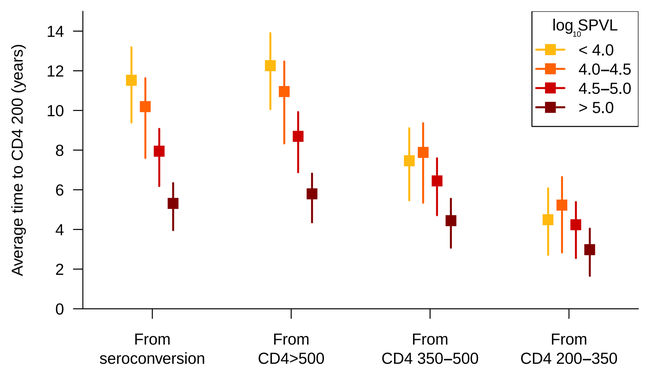
- From the smoothed CD4 count, we estimated
  - the proportion of patients starting in each CD4 category after seroconversion (f_k, directly given by the smoothed CD4 counts),
  - the rates at which patients move through decreasing CD4 categories (q_k, derived using exponential survival models of the smoothed CD4 counts).

***Figure 3**: Survival figures stratified by SPVL, showing decline to CD4 500, 350, 200 and to AIDS death from left to right. SPVL categories are log_{10}SPVL <4, 4-4.5, 4.5-5, >5 log_{10}copies/ml of peripheral blood plasma. Crosses and shaded areas show Kaplan-Meier survival estimates with 95%CI. Dotted lines show exponential survival fits.*



- The analysis was performed overall and stratified by:
  - SPVL → main determinant of CD4 dynamics, see Figure 3
  - Age at seroconversion → no significant effect
  - Gender and transmission route → no significant effect, but small power
  - Time (<1995, 1995-2000, >2000) → no significant effect if adjusted for SPVL
- From the estimates of f_k and q_k, we derived the average time to reaching CD4 200, stratified by SPVL, from various clinical stages (Figure 4).
- These results highlight the influence of SPVL on clinical progression and suggest that, in contexts where it is not already the case, VL monitoring should be considered for patients prior to treatment initiation.

***Figure 4**: Estimated average time to reaching CD4 200, stratified by SPVL, from various clinical stages.*



5. Sensitivity analyses

- We performed extensive sensitivity analyses varying:
  - the smoothing method (linear model and unconstrained spline)
  - the condition on n_{CD4} (down to $n_{CD4} \geq 5$ and even ≥ 3 for the linear model)
  - the selection of patients (selecting patients diagnosed >1997 to assess impact of survival biases in the cohort)
  - the definition of HAART initiation in patient selection (mono vs dual therapy)
- All sensitivity analyses provided results consistent with main analysis.

6. Conclusions and Implications

- Our results validate the progression model chosen, with:
  - a substantial fraction of patients having CD4<500 immediately after seroconversion,
  - an ~exponentially distributed time in each CD4 category,
  - broad agreement between fitted and observed CD4 counts.
- We find a single strong determinant of CD4 progression: SPVL. This suggests that
  - Mathematical models of HIV transmission should stratify disease progression by SPVL,
  - Both CD4 counts and VL are markers of clinical need.
- We provide estimates of CD4 progression stratified by SPVL which can be used directly in mathematical models.
- The ATHENA cohort, with frequent patient monitoring, provides a great opportunity for quantitative studies of HIV clinical progression.
- Further studies should assess whether results are similar in other populations, in particular with regards to:
  - HIV subtype,
  - gender and transmission route,
  - ethnicity.

7. References

[1] van Sighem A., al. Monitoring of Human Immunodeciency Virus (HIV) Infection in the Netherlands, 2011

8. Acknowledgements

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