Modeling trends in CD4 cell decline before the start of antiretroviral therapy

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Background

- MSM in the Netherlands infected with HIV-1 in more recent years have been shown to have a higher HIV-1 RNA concentration and a lower CD4 cell count at viral set-point (9-27 months after seroconversion) compared to 10 years ago.
- Higher viral load at set-point is associated with higher transmission probability and faster disease progression. A measure for disease progression is CD4 cell count decline in patients not on therapy.
- In the cART era analysis of CD4 cell count decline is not straight-forward because patients with a steeper decline are more likely to start cART and drop out of the study (informative drop-out).

Objective

- To investigate trends in CD4 count decline following HIV seroconversion using regression models making different assumptions about the drop-out pattern.

Methods

Patients

- Patients who seroconverted <1996 were participants of the Amsterdam Cohort Studies, patients with seroconversion ≥1996 were selected from the Dutch national HIV observational ATHENA cohort.
- MSM from W-Europe/N-America, ≥16 years of age and documented evidence of recent seroconversion (maximum seroconversion interval of 1 year). Infections with non-B subtype excluded
- Availability of ≥ 1 CD4 cell count between 9-48 months after seroconversion whilst being antiretroviral therapy-naive.

Outcome

- CD4 cell counts between 9-48 months after seroconversion were used to model the slope of CD4 cell decline before start of ART, on a cubic root scale.
- CD4 cell counts were censored and patients were considered to be a drop-out from the earliest of: date of starting ART, first date CD4 cell count <100 cells/mm^3, date 1 year prior to diagnosis of AIDS and date of death.

Statistical analysis

- Notation: i:ith subject, j=jth measurement; X_i: age at seroconversion subject i, T_{ij}: timing of measurement j, subject i; R_i: categorical drop-out variable (drop-out <2.5years , between 2.5-4, and ≥4 years after seroconversion, lost to follow-up <4 years and not enough follow-up (for patients seroconverting between 2003-2007)).
- Estimates for $E(CD4_{ij} \mid X_i, T_{ij})$ were obtained using:
  - Linear regression models assuming drop-out to be missing completely at random (MCAR). Standard errors were obtained using the sandwich estimator.
  - Mixed effect models with random intercept and slope for each patient. Assuming dropout to be missing at random (MAR).
  - Pattern-mixture models. The drop-out pattern is included in the model using the factorization $E(CD4_{ij}, R_j \mid X_i, T_{ij}) = E(CD4_{ij} \mid X_i, R_i, T_{ij})\, E(R_i \mid X_i, T_{ij})$.

Results

	Calendar year of seroconversion		
	1984-1995	1996-2002	2003-2007
Age at sc (yrs)	35.2 (29.7-42.1)	34.6 (30.2-41.1)	37.9 (31.5-43.8)
First CD4 cell count, 9-27 months after sc	580 (450-850)	550 (450-720)	510 (390-650)
Months between sc and first CD4measurement	10.3 (9.9-10.7)	10.7 (9.7-12.3)	10.5 (9.6-11.9)

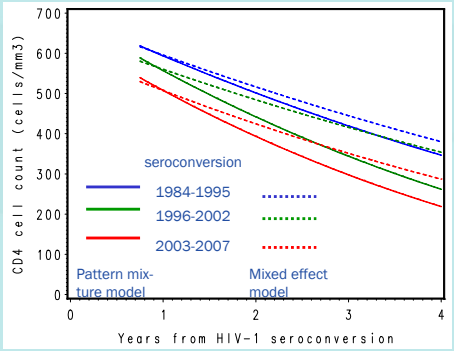
Table 1. Characteristics (median, interquartile range) of 610 included MSM with recently acquired HIV-1 infection. The first CD4 cell count obtained 9-27 after seroconversion has become lower over calendar time.

Drop-out pattern	Year of seroconversion ≤1995 N=111	1996-2002 N=139	≥2003 N=360
0.75-2.5 year	15 (14%)	49 (35%)	130 (36%)
2.5-4 year	21 (19%)	26 (19%)	72 (20%)
≥4 year	67 (60%)	57 (41%)	66 (18%)
Lost to follow-up 0.75-4 year	8 (7%)	7 (5%)	36 (10%)
Not enough follow-up	0 (0%)	0 (0%)	56 (16%)
# ART naïve CD4 cell counts taken between 9-48 months, median (IQR)	17 (12-18)	6 (4-10)	6 (4-9)
Years from sc to dropout, median (IQR)	5.4 (3.3-8.0)	3.4 (1.8-7.0)	3.2 (1.8-4.7)
Reason of drop-out <4year			
Start ART	14 (39%)	68 (91%)	189 (94%)
AIDS diagnosis	15 (42%)	5 (7%)	7 (3%)
<100 CD4 cells/mm^3	7 (19%)	2 (2%)	5 (2%)
Death			1 (1%)

Table 2. Drop-out pattern according to year of seroconversion. Because of limited cART availability, few patients seroconverting ≤1995 dropped out within 2.5 years.

Year of seroconversion	CD4 cell count at viral set-point	Difference in CD4 cells with 03-07	p-value	Slope/yr	Difference in slope/yr with 03-07	p-value
Linear regression model						
1984-1995	8.33 (0.11)	0.51 (0.12)	<0.0001	-0.22 (0.05)	-0.13 (0.06)	0.04
1996-2002	8.26 (0.10)	0.44 (0.12)	0.0002	-0.21 (0.05)	-0.12 (0.07)	0.07
2003-2007	7.82 (0.07)	ref		-0.09 (0.04)	ref	
Mixed effect model						
1984-1995	8.51 (0.11)	0.42 (0.12)	0.0007	-0.39 (0.04)	0.07 (0.05)	0.21
1996-2002	8.34 (0.09)	0.26 (0.11)	0.01	-0.39 (0.04)	0.07 (0.05)	0.19
2003-2007	8.09 (0.06)	ref		-0.46 (0.03)	ref	
Mixed effect model, restricted to patients with ≥ 5 CD4 cell measurements, done in previously published studies						
1984-1995	8.55 (0.11)	0.23 (0.13)	0.07	-0.39 (0.04)	0.07 (0.05)	0.20
1996-2002	8.60 (0.10)	0.28 (0.12)	0.01	-0.39 (0.04)	0.07 (0.05)	0.16
2003-2007	8.31 (0.06)	ref		-0.45 (0.03)	ref	
Pattern-mixture model						
1984-1995	8.52 (0.11)	0.38 (0.12)	0.001	-0.46 (0.05)	0.18 (0.06)	0.003
1996-2002	8.38 (0.08)	0.24 (0.10)	0.01	-0.61 (0.07)	0.04 (0.08)	0.61
2003-2007	8.14 (0.05)	ref		-0.65 (0.04)	ref	

Table 3. Mean (SE) CD4 cell count (cubic root cells/mm^3) at viral set-point (defined to be 9 months after seroconversion) and mean (SE) slope of CD4 cell count between 9-48 months per period of seroconversion. Only the pattern-mixture estimation of differences in the slope of CD4 cell decline between periods of seroconversion reached significance.



Difference in CD4 cell count (cells/mm^3) at 9 and 48 mths	Mixed model	Pattern mixture model
84-95	236	272
95-02	226	327
03-07	243	320

Figure 1. CD4 cell counts back transformed to original scale.

Conclusion

- In comparison to pattern mixture models, mixed effect models underestimate the slope of CD4 cell decline prior to starting cART.
- Restricting mixed effect models to patients with ≥5 CD4 cell counts results in biased intercepts estimates but not slope estimates.
- Results from the pattern mixture model suggest CD4 cell count declines more rapidly in patients infected in more recent calendar years compared to patients infected in the pre-cART era.
- Simulation studies to determine which model gives the least unbiased estimates are necessary.