Faster CD4 Cell Count Decline before the Start of Antiretroviral Therapy in Patients with HIV-1 Seroconversion in More Recent Calendar Years

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for the ATHENA observational cohort

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Background

- Recently we reported an increase in viral load and decline in CD4 cell count at viral set-point in patients with subtype B HIV-1 infection in more recent years compared to 10 years ago [1]. This suggests that HIV-1 may have become more virulent leading to a faster disease progression.
- A surrogate marker of disease progression is the rate of CD4 cell count decline in patients not on therapy.
- Studying CD4 cell count change in untreated HIV infection is problematic because patients with a steeper decline are more likely to start ART.
- Standard analysis of longitudinal CD4 cell counts not accounting for dropout (mainly because of ART initiation, but before 1996 also because of disease progression) may give biased estimates.

Objective

- To investigate trends in CD4 cell count decline prior to starting ART using models that make different assumptions about the dropout pattern.

1. Gras L, Jurriaans S, Bakker M, van SA, Bezemer D, Fraser C, *et al.* Viral load levels measured at set-point have risen over the last decade of the HIV epidemic in the Netherlands. *PLoS ONE* 2009; **4(10)**:e7365.

Methods

Patients

- MSM from W-Europe/N-America with recent HIV-1 infection (last negative and first positive antibody test <1 year apart or laboratory evidence of recent infection) and 1 HIV-1 RNA concentration and CD4 cell count available 9-27 months after seroconversion without having received antiretroviral therapy were selected from the ATHENA observational cohort.
- HIV-1 subtypes other than B were excluded.

Outcome

- Slope of cube root transformed CD4 cell counts 9-48 months after estimated seroconversion.

Statistical analyses

- CD4 cell counts censored from the earliest date of: starting ART, first CD4 cell count <100 cells/mm^3, 1 year prior to diagnosis of AIDS (because CD4 cell count decline might be accelerated during the final disease phase) or death.
- Estimates were obtained using 3 methods:

1. Random effect models with random intercept and slope for each patient. Naïve analysis assuming dropout only depends on observed CD4 cell counts (given covariates).
2. and 3. Pattern-mixture and selection models. Dropout and longitudinal CD4 cell counts are simultaneously modeled. In the pattern-mixture analysis an interaction effect between seroconversion period and dropout is modeled (drop-out <27 months , between 27-48, and ≥48 months after seroconversion, lost to follow-up <48 months and end of follow-up).

- All models assumed a linear decline and included a random slope and intercept for each patient, and age and year of seroconversion (1984-1995, 1996-2002 and 2003-2007) as covariates. Intervals were chosen such that each period had a sufficient length and a sufficient number of patients included.

Results

Table 1. Characteristics of 607 included MSM with recently acquired HIV infection. Between 1984 and 2007, the median first CD4 cell count taken ≥9 months after seroconversion and before ART initiation has decreased.

Because of limited ART availability, few patients seroconverting prior to 1995 dropped out within 48 months. The number of CD4 cell counts per patient available for analysis was therefore highest between 1984-1995. Starting antiretroviral therapy was the most common reason for drop-out in or after 1996.

	Year of seroconversion		
	1984-1995 N=111	1996-2002 N=139	2003-2007 N=357
First CD4 cell count ≥9months after seroconversion	580 (450-850)	550 (450-720)	510 (390-650)
Median number (IQR) CD4 cell counts 9-48 months	17 (12-18)	6 (4-10)	6 (4-9)
Age at seroconversion (years)	35.2 (29.7-42.1)	34.6 (30.2-41.1)	37.9 (31.5-43.8)
Timing of drop-out			
9-27 months	6 (5%)	34 (24%)	77 (32%)
27-48 months	36 (32%)	41 (29%)	135 (38%)
⩾48 months	67 (60%)	57 (41%)	75 (21%)
Lost to follow-up 9-48 months	8 (7%)	7 (5%)	24 (7%)
Not enough follow-up	0 (0%)	0 (0%)	46 (13%)
Reason of drop-out within 48 months			
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%)
Years from seroconverion to dropout, median (IQR)	5.4 (3.3-8.0)	3.4 (1.8-7.0)	3.2 (1.8-4.7)

Figure 1. Mean CD4 cell count (cube root transformed) decline and standard error per period of seroconversion using 3 methods . For seroconversion during 1984-1995 the 3 methods give similar estimates because dropout is infrequent. For 1996-2002 and 2003-2007 (when drop-out is more frequent), pattern-mixture and selection models taking dropout into account estimate a steeper decline in CD4 cell counts compared to the random effects model.

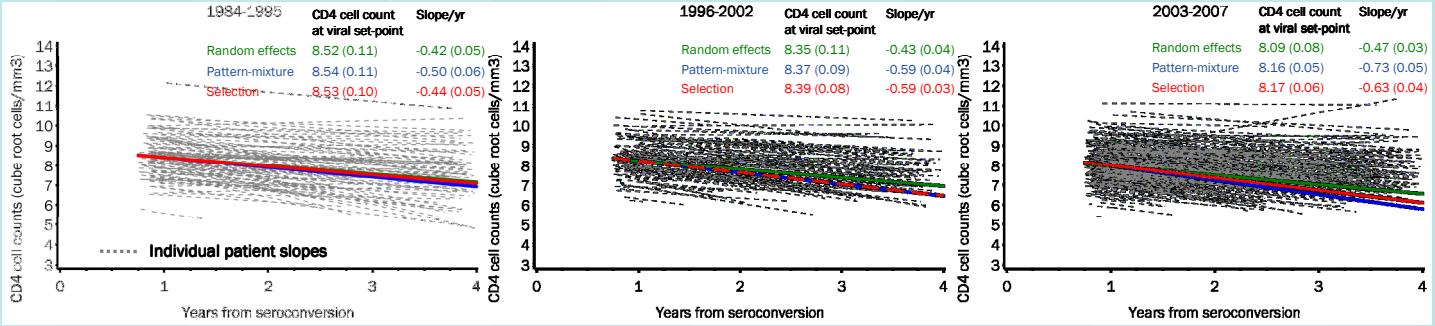
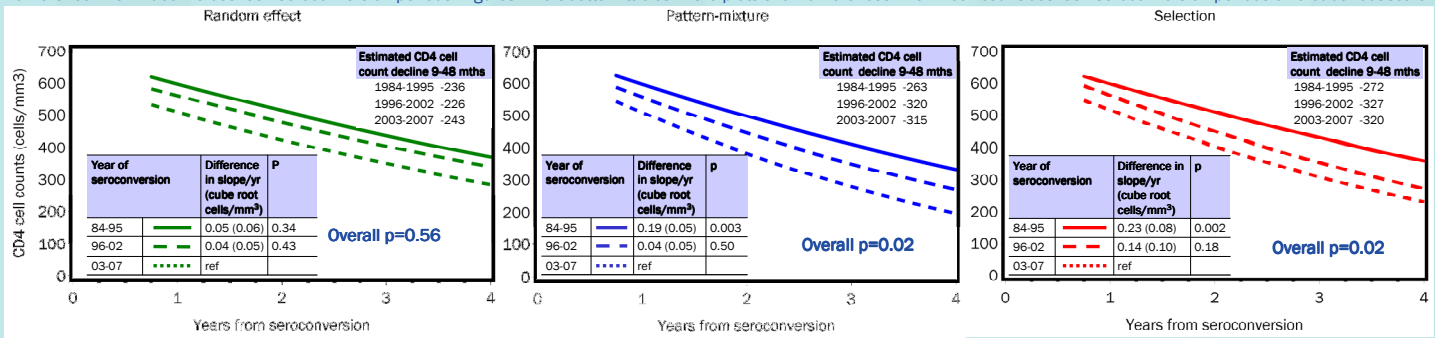


Figure 2. CD4 cell count decline (back-transformed to original scale) per period of seroconversion for each method. Only the pattern-mixture and selection models show a significant difference in CD4 decline between seroconversion periods. Figures in left bottom tables in the plots show differences in CD4 cell count between seroconversion periods on a cube root scale.



Conclusion

- In comparison to models taking dropout into account, naïve standard random effect models underestimate the slope of CD4 cell decline prior to starting ART.
- Results from models taking account of non-random dropout suggest CD4 cell count declines more rapidly in patients infected in more recent calendar years compared to patients infected in the pre-cART era
- Results are in agreement with the earlier reported higher viral load levels and lower CD4 cell count at viral set-point in more recent calendar years [1].