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Secular trends in the survival of HIV-infected homosexual men in Amsterdam and Vancouver estimated from a death-included CD4-staged Markov model

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Background The purpose of this study was to investigate secular trends in waiting times in CD4-based stages of human immunodeficiency virus (HIV) disease progression in two cohorts of homosexual men, one in Vancouver and one in Amsterdam. All HIV-positive men with two or more CD4 counts in their AIDS-free period between 1 January 1985 and 1 January 1997 were included in this study. Data regarding clinical AIDS diagnoses (using the 1987 Centers for Disease Control and Prevention [CDC] AIDS case definition) and death were collected through active follow-up, review of hospital records, and municipal/national registries. The Vancouver Lymphadenopathy-AIDS Study (VLAS), was started in November 1982 and had enrolment until December 1984. Both HIV-negative and HIV-positive men were followed at intervals of 3–6 months until 1986 and annually thereafter. The Amsterdam cohort study on HIV and AIDS (ACS) started in December 1984, has ongoing enrolment and follow-up of both HIV-negative and HIV-positive homosexual men. The HIV-positive men were followed at intervals of 3 months.

Methods The CD4-based stage of an individual at each visit was determined using smoothed data. For each cohort and in each calendar time period, a CD4-based Markov model with death as the absorbing stage was fitted to the data. The parameters in this model were estimated using the method of maximum likelihood and confidence intervals were calculated using bootstrap methods.

Results A total of 509 homosexual men participating in the VLAS were included in this study, providing 5356 visits. Some 292 men developed AIDS before 1 January 1997 and 239 died before this date. In all, 232 of the 239 deaths were AIDS related. Thirty-seven per cent of all visits were related to treatment. A total of 543 homosexual men participating in the ACS were included in this study, providing 10 043 visits; 277 men developed AIDS before 1 January 1997 and 250 died before this date. The date of AIDS diagnosis was known for 225 of the 250 deaths. Twenty per cent of all visits were related to treatment. We found that in both cohort studies the stage-specific waiting times were longer in the low CD4-based stages (stages 4, 5 and 6: i.e. CD4 count <500 cells per mm^3) after March 1990 compared to waiting times before March 1990. The increase in mean waiting time in these stages with low CD4 count was 21%, 33% and 53%, respectively in the ACS and 20%, 2% and 29% in the VLAS. Because waiting times alone

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are not exclusive for progression in a reversible model we also calculated the stage-specific median incubation periods till death. Men spent considerably longer in these CD4-based stages after March 1990 compared to before March 1990.

Conclusions Data from these population-based cohort studies showed that HIV disease progression in the calendar period where treatment was administered was slower for individuals in stages with low CD4 counts. We found no evidence for shortening of the incubation period that may have appeared from increasing virulence of the HIV in the population.

Keywords HIV disease progression, incubation period distribution, CD4 count, trends in waiting time, homosexual men, Markov model

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Changes in the rate of progression from HIV infection to either AIDS or death can be expected for several reasons. In the literature, both an increase,[1,2] and a decrease in the risk of AIDS in more recent years,[3,4] is reported. Increasing virulence and the addition of new conditions or AIDS defining events[5] will result in a shorter incubation period to AIDS, while treatment may slow HIV disease progression both to AIDS and death.[6,7] Also, changes in the incidence of certain AIDS diagnoses may have affected the incubation period. For instance, if less cases of Kaposi's sarcoma were observed, one may expect that the mean incubation time to AIDS will be longer, since Kaposi's sarcoma is known to occur early in HIV disease.[8] Furthermore, there may be differences in methodology concerning censoring or in the effect of diagnostic suspicion bias. Several co-factors for HIV disease progression affect the incubation period after certain stages of progression, while progression up to that specific stage may be similar.[9] To evaluate changes in the incubation period it is therefore necessary to take into account different stages of disease progression.

Survival techniques have been used to estimate the incubation period from seroincident cohort studies, possibly after imputing seroprevalent data. However, using a Markov model full use of the data of a seroprevalent cohort is made, and in addition progression through stages of HIV infection are estimated. The Markov assumption is in agreement with the property of biological systems that the present state of the system is most predictive for progression. An advantage of studying staged disease progression is that only short study periods are needed, i.e. short relative to the long incubation period (median 8–10 years[10]). Short study periods are especially of interest when (temporal) time trends or the effect of treatment are studied.

Markers of immune function are the main indicators for HIV disease progression and from these, CD4 T-cell count is widely accepted as the best marker for disease progression. Even in the presence of viral load measurements, CD4 cell count is a significant predictor of disease progression.[11] Subsequently, stages of the incubation period to AIDS (i.e. the time from infection, approximated by the date of HIV seroconversion, to a diagnosis of AIDS) can be defined by ranges of CD4 cell count. The waiting time of a stage is the time spent in that stage before going to another stage.

The purpose of this study was to investigate secular trends in waiting times in CD4-based stages of HIV disease progression by calendar time. Stages of CD4 cell count in a reversible continuous-time Markov model in two calendar time intervals in a cohort of homosexual men in Vancouver and in a cohort of homosexual men in Amsterdam were used. March 1990 was chosen *a priori* as the cutoff point because antiretroviral treatment was generally available at that time and its use became widespread. Consequently, these calendar time intervals were characterized by low and high percentages of participants for whom treatment was administered. In addition, data from two cohort studies were used because, next to secular trends, there may be geographical differences in progression times due to underlying geographical variation in viral strains and in virulence. If this was not the case, our study gained significant power because of the repeated confirmation of results.

Materials and Methods

Study Population

We used data from homosexual men participating in cohort studies in Vancouver and Amsterdam. From all participants in both cohorts, behavioural, clinical, virological and immunological data were collected at enrolment and at regular visits thereafter. All HIV-positive men with two or more CD4 counts in their AIDS-free period between 1 January 1985 and 1 January 1997 were included in this study. Data regarding clinical AIDS diagnoses (using the 1987 Centers for Disease Control and Prevention [CDC] AIDS case definition[12]) and death were collected through active follow-up, review of hospital records and linkages with municipal/national registries.

The Vancouver Lymphadenopathy-AIDS Study (VLAS), was started in November 1982 and had enrolment until December 1984. Both HIV-negative and HIV-positive men were followed at intervals of 3–6 months until 1986 and annual visits occurred thereafter. In all 5356 visits from 509 homosexual men were included in this study. Some 292 men developed AIDS before 1 January 1997 and 239 died before this date, whereas 232 had a known date of AIDS diagnosis. Thirty-seven per cent of all visits of the asymptomatic HIV-positive men were related to treatment with the potential to delay the onset of AIDS: 10% to AZT alone, 21% to AZT and additional treatment (i.e. PCP prophylaxis, DDC, DDI) and 6% to treatment other than AZT.

The Amsterdam cohort study on HIV and AIDS (ACS) started in December 1984, and has ongoing enrolment and follow-up of both HIV-negative and HIV-positive homosexual men. The HIV-positive men were followed at intervals of 3 months. In all,

10 043 visits from 543 homosexual men were included in this study and 277 men developed AIDS before 1 January 1997; 250 died before this date, whereas 225 had a known date of an AIDS diagnosis. Twenty per cent of all visits of the asymptomatic HIV-positive men were related to treatment with the potential to delay onset of AIDS: 13% to AZT alone, 5% to AZT and additional treatment (i.e. PCP prophylaxis, DDC, DDI) and 2% to treatment other than AZT.

Staged Markov model

We modelled HIV disease progression using a continuous-time Markov model with eight stages (Figure 1). Stages 1–6 are transient states defined by ranges of the number of CD4+ cells, as used previously.[13–16] This scheme has been successful in dividing the incubation period into relatively even periods in cohort studies of homosexual men[14] and injecting drug users.[16] Stage 7 was a transient state defined by being diagnosed with AIDS (using the 1987 Centers for Disease Control and Prevention [CDC] AIDS case definition[12]), and stage 8 (the only absorbing state in our model) corresponded to death. Our model allowed transitions between adjacent CD4 stages, an AIDS diagnosis directly from the last three CD4-based stages, and transition from an AIDS diagnosis to death. Consequently, the model was specified by 14 transition parameters (λ_{ij}'s), indicating the instantaneous hazard of moving between stages. For example, λ_{47} was the instantaneous hazard of an AIDS diagnosis (stage 7) from stage 4 (CD4: 351–500 cells/mm^3).

Because CD4 measurements are subject to both measurement error and short time-scale variability we fitted the Markov model to smoothed data. As with our previous studies among homosexual men[14] and among injecting drug users,[16] the stage of an individual at each visit was determined using a kernel smoother applied to the log-transformed data. The bandwidth of the smoother was chosen so that the variance of the residuals (i.e. the difference between the observed and the smoothed values) was equal to an estimate of the variance of the measurement error and short time-scale variability of CD4 measurements. We obtained this estimate by considering additional data (ACS: n = 1237, VLAS: n = 1750) obtained from visits that occurred between the (3-monthly or 6-monthly) planned study visits as replicate measurements. The additional data were related to participation in clinical experiments, confirmation of seroconversion or confirmation of laboratory measurements and they covered the range of the 'regular' CD4 measurements. We estimated the standard error to be $e = 0.23$ (ACS) and $e = 0.19$ (VLAS) of the log transformed data, corresponding to a bandwidth of the smoother of 1.2 years and 1.5 years, respectively. Our estimate for the short time-scale variability is almost identical to that we obtained in our study of injecting drug users[16] and homosexual men.[14]

The model parameters (λ's) were estimated using maximum likelihood methods.[17] The distributions of the times that each stage was first entered (first passage times) were generated from 10 000 simulations using the estimated λ's and exponential waiting times. To account for both the variability introduced by the smoothing step and the variability in the data, we calculated confidence intervals for the λ's and median first passage times using the bootstrap procedure. Specifically, first we sampled with replacement from the members of the study population and, second, we constructed bootstrap replicates for each 'individual' of this new dataset by sampling from the set of observed residuals. The sampled residual was added to the observed value, and then the data were re-smoothed. This procedure was repeated 200 times, resulting in 200 replicate datasets. The model was fit to each replicate dataset, and bootstrap confidence intervals were obtained using the percentiles' method.[18] We also calculated the expected number of stages visited before an AIDS diagnosis as a measure of how well the staged CD4 model predicted disease progression.

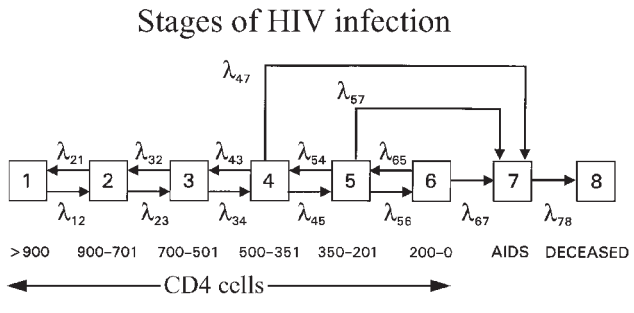

Figure 1 The reversible human immunodeficiency staged process used in the Markov model. The stages 1–6 are based on smoothed CD4 counts. People in stages 1–6 were infected but have not developed AIDS, those in stage 7 had an AIDS diagnosis and those in stage 8 were dead. The model permits backflow and direct progression from stages 4 and 5 to AIDS, as from AIDS to death. The λ_{ij}'s were the monthly transmission rates. The definitions of stages used in the model are indicated beneath each stage

Results

This study included 1052 homosexual men (ACS: n = 543; age at entry: 19–58 years; median age: 34 years, VLAS: n = 509; age at entry: 17–54 years; median age: 32 years), who provided a total of 15 399 visits (ACS: 10 043 visits, VLAS: 5356 visits). The mean number of visits per participant in the ACS was 18.5 (range 2–48) and in the VLAS 10.5 (range 2–22). In the ACS mean time between two visits was 4.0 months and 3.3 months between two visits with a measurement of CD4 count. In the VLAS the mean time was 9.5 months and 8.5 months, respectively. Therefore, on average the follow-up period in the ACS (6.2 years) is shorter than in the VLAS (8.3 years). In all 788 homosexual men (75%, ACS: 372 [69%], VLAS: 416 [82%]) were seropositive at study entry and 264 (25%) seroconverted during follow-up. Some 569 participants (ACS: 277 men; VLAS: 292 men) developed AIDS; 489 (ACS: 250 men; VLAS: 239 men) had died by 1 January 1997, of whom 32 died without an AIDS diagnosis (ACS: 25; VLAS: 7).

Plots of the measured and the smoothed CD4 count of an individual, as presented in Hendriks *et al.*,[14] clearly reveal that the smoother effectively removes the noise. The CD4-based stage of an individual at each visit was determined using smoothed CD4 count. Table 1 shows the number of observed transitions from each stage to any other stage between two subsequent visits in both cohort studies in each time period. Although exact comparison of these numbers between both cohorts was not possible, because the intervals between two successive visits are different, one may conclude from Table 1 that the pattern in

Table 1 The number of observed transitions between all two successive follow-up visits in a cohort of homosexual men in Amsterdam and in Vancouver by calendar time period

		To State															
		1		2		3		4		5		6		7		8	
From State	Period[a]	ACS[b]	VLAS[c]	ACS	VLAS	ACS	VLAS	ACS	VLAS	ACS	VLAS	ACS	VLAS	ACS	VLAS	ACS	VLAS
1	before	167	273	36	64	0	12	0	1	0	0	0	0	1	4	0	0
	after	127	43	16	19	0	6	0	0	0	0	0	0	0	2	0	0
2	before	14	28	500	224	103	106	0	3	0	2	0	0	2	1	0	0
	after	8	5	197	96	39	60	1	2	0	1	0	1	0	2	0	1
3	before	0	2	29	26	1000	354	123	129	0	15	0	1	7	14	2	0
	after	0	3	11	4	805	368	104	118	1	6	0	2	7	7	2	0
4	before	0	0	0	0	27	13	878	243	114	86	1	6	17	21	0	0
	after	0	0	0	0	29	19	1214	452	133	107	0	8	16	16	5	0
5	before	0	0	0	0	0	0	18	8	580	127	54	32	23	22	0	1
	after	0	0	0	0	0	0	28	10	1317	428	92	99	38	37	2	3
6	before	0	0	0	0	0	0	0	0	1	1	192	50	41	35	0	0
	after	0	0	0	0	0	0	0	0	7	5	741	284	104	109	0	2
7	before	0	0	0	0	0	0	0	0	0	0	0	0	35	30	49	52
	after	0	0	0	0	0	0	0	0	0	0	0	0	44	47	119	132

[a] Before and after 1 March 1990.

[b] Amsterdam cohort study on HIV and AIDS.

[c] Vancouver Lymphadenopathy-AIDS Study.

Note that the CD4-based stage of an individual at each visit was determined using smoothed CD4-count.

both cohort studies was similar. The differences that appeared in the relative frequencies per stage or in the mean number of months between two visits were likely due to the differences in study design. The time-continuous staged model as presented in Figure 1 was fitted to these data (using smoothed CD4 count). This model does not allow direct transitions from stages other than 7 ('AIDS') to death. So, this limited number of transitions (Table 1) is forced through stage 7.

The maximum likelihood estimates of the monthly transition rates (λ_{ij}'s) were used to compute the cumulative probability distributions of the first passage time from any stage to any other stage. The incubation period distribution from seroconversion to AIDS (stage 7) and to death (stage 8) was the weighted sum of the cumulative probability distributions of the first passage time from any CD4-based stage to AIDS (to death, respectively), weighted by the stage-occupation frequencies of the first HIV-positive sample among the seroconverters with narrow seroconversion intervals (<1 year, ACS: n = 117, VLAS: n = 71). Note that the stage-occupation frequencies also are based on the smoothed CD4 counts. For the ACS these frequencies were 0.16, 0.26, 0.29, 0.22, 0.06 and 0.01 for stages 1–6, respectively, and for the VLAS these frequencies were 0.27, 0.34, 0.25, 0.13, 0.01 and 0.00 for stages 1–6, respectively. The median time from seroconversion to both AIDS and to death was longer in the VLAS compared to the ACS, 0.7 years and 1.3 years, respectively. In the ACS the median time to AIDS was 7.9 years (95% CI : 7.6–8.7 years) and in the VLAS 8.6 years (95% CI : 8.3–9.4 years). In addition, the median time to death was 9.3 years (95% CI : 8.9–10 years) in the ACS compared to 10.6 years (95% CI : 10.1–11.5 years) in the VLAS. When we used Kaplan-Meier estimators these differences were confirmed. In general, a plot of the Kaplan-Meier estimates and the estimates based on the Markov model showed rough agreement. In Hendriks *et al.*[14] this check of model validity was presented using data from the ACS though March 1993.

Table 2 shows the percentage of visits in each stage that were related to treatment by calendar time interval for each cohort separately. Although treatment in both cohorts was similar before March 1990, as expected, treatment increased considerably after this time and even more so in the VLAS. Note that these percentages in the VLAS overestimate the actual number of visits related to treatment. In contrast to the ACS, visits are counted when they occurred after start of treatment. This may lead to subtle differences where treatment was (temporarily) stopped.

Table 3 shows the maximum likelihood estimates of the monthly transition rates (λ_{ij}'s) with 95% CI by cohort and by calendar time period fitting the model of Figure 1. These transition rates were used to calculate for example, the median incubation times, stage-specific incubation times, stage-specific waiting times and stage-specific forward progression. As a result of the systematic differences in the transition parameters between the calendar time intervals in Amsterdam, we found that both the median incubation time from seroconversion to AIDS and to death were about 1.5 years longer in the interval after March 1990 compared to before March 1990. Surprisingly this trend was not observed in VLAS data, in which both the median time from seroconversion to AIDS and to death before March 1990 and after March 1990 were similar (Table 4).

Despite this apparent inconsistency, we found that in both cohort studies the stage-specific waiting times were longer in the low CD4-based stages (stages 4, 5 and 6: i.e. CD4 count <500 cells per mm^3) after March 1990 compared to before March 1990 (Table 5). The increase in mean waiting time in stages with low CD4 count (i.e. stage 4, 5 and 6) was 21%, 33% and 53%, respectively in the ACS and 20%, 2% and 29% in the VLAS. Because waiting times alone are not exclusive for progression in a reversible model we also calculated the stage-specific median incubation periods, which also were considerably longer in these CD4-based stages after March 1990 compared to before March 1990 (Table 4).

Discussion

The incubation period from low CD4-count based stages to death was found to be longer after 1990 when treatment has generally been available for HIV-infected homosexual men in a cohort in Amsterdam (ACS) and in a cohort in Vancouver (VLAS). This finding was in agreement with other studies[13,19,20] which have reported increasing incubation periods. Therefore, the data from these population-based cohort studies support the idea that the effect of treatment on HIV disease progression most likely dominated reverse effects like those that may have appeared from increasing virulence of HIV in the population.

The breakpoint March 1990 was arbitrarily chosen in that it was (1) near halfway data collection, (2) the treatment given in the first interval was limited and (3) the calendar time intervals were long enough to have consistent results from

Table 2 The number of visits in each CD4-based stage and the percentage related to treatment by calendar time period and by cohort study

	1 January 1985–1 March 1990				1 March 1990–1 January 1997			
	ACS[a]		VLAS[b]		ACS		VLAS	
CD4-based stage	n	%	n	%	n	%	n	%
1	212	1	418	7	153	0	74	24
2	644	2	422	7	251	0	175	27
3	1235	4	629	6	973	3	539	35
4	1114	12	646	11	1452	16	646	63
5	746	13	256	22	1548	39	623	82
6	257	22	102	17	889	64	439	89

[a] Amsterdam cohort study on HIV and AIDS.

[b] Vancouver Lymphadenopathy-AIDS Study.

Note that the CD4-based stage of an individual at each visit was determined using smoothed CD4-count.

Table 3 Estimated monthly transition rates (95% CI) of the CD4 staging system of human immunodeficiency virus infection by cohort and by calendar time period, using a reversible Markov model

	1 January 1985–1 March 1990				1 March 1990–1 January 1997			
Rate	ACS[a]		VLAS[b]		ACS		VLAS	
λ_{12}	0.064	(0.041–0.069)	0.029	(0.020–0.032)	0.033	(0.014–0.045)	0.052	(0.044–0.072)
λ_{21}	0.009	(0.005–0.015)	0.013	(0.007–0.016)	0.011	(0.000[c]–0.013)	0.006	(0.000–0.013)
λ_{23}	0.059	(0.045–0.066)	0.046	(0.036–0.050)	0.053	(0.036–0.068)	0.066	(0.048–0.081)
λ_{32}	0.009	(0.005–0.012)	0.009	(0.005–0.011)	0.004	(0.000–0.006)	0.000	(0.000–0.004)
λ_{34}	0.038	(0.032–0.042)	0.038	(0.028–0.040)	0.039	(0.030–0.044)	0.043	(0.035–0.049)
λ_{43}	0.009	(0.006–0.013)	0.006	(0.004–0.011)	0.007	(0.004–0.009)	0.006	(0.002–0.007)
λ_{45}	0.036	(0.027–0.038)	0.037	(0.026–0.039)	0.031	(0.025–0.035)	0.032	(0.024–0.038)
λ_{47}	0.007	(0.006–0.012)	0.009	(0.007–0.015)	0.005	(0.004–0.009)	0.006	(0.004–0.010)
λ_{54}	0.010	(0.004–0.011)	0.007	(0.002–0.011)	0.007	(0.004–0.009)	0.003	(0.000–0.005)
λ_{56}	0.028	(0.020–0.035)	0.027	(0.018–0.035)	0.022	(0.016–0.025)	0.034	(0.024–0.036)
λ_{57}	0.008	(0.004–0.014)	0.011	(0.004–0.018)	0.006	(0.004–0.011)	0.006	(0.004–0.013)
λ_{65}	0.000	(0.000–0.008)	0.002	(0.000–0.010)	0.000	(0.000–0.005)	0.002	(0.000–0.005)
λ_{67}	0.064	(0.039–0.070)	0.057	(0.036–0.066)	0.039	(0.035–0.044)	0.044	(0.033–0.046)
λ_{78}	0.057	(0.044–0.081)	0.043	(0.032–0.058)	0.048	(0.038–0.063)	0.043	(0.033–0.055)

[a] Amsterdam cohort study on HIV and AIDS.

[b] Vancouver Lymphadenopathy-AIDS Study.

[c] λ_{ij}, monthly transition rate from stage i to stage j.

[d] 0.000, value < 0.001.

Note that the CD4-based stage of an individual at each visit was determined using smoothed CD4-count.

Table 4 Estimated mean number of stages passed before, and the median time to death (95% CI) by cohort and by calendar time period, using a reversible Markov model

	1 January 1985–1 March 1990				1 March 1990–1 January 1997			
	ACS[a]		VLAS[b]		ACS		VLAS	
Starting stage	No.	median	No.	median	No.	median	No.	median
1	8.4	11.5	8.2	13.9	8.1	14.5	7.3	12.4
		(11.0–13.4)		(13.8–16.1)		(13.8–18.6)		(11.7–14.0)
2	7.4	10.1	7.2	11.0	7.1	11.9	6.3	10.8
		(9.4–11.6)		(10.5–13.1)		(11.2–13.5)		(10.2–12.0)
3	6.1	8.5	5.7	8.7	5.7	10.3	5.1	9.5
		(7.9–9.7)		(8.3–10.4)		(9.6–11.5)		(8.9–10.6)
4	4.5	6.2	4.1	6.5	4.4	8.1	4.1	7.6
		(5.7–7.3)		(5.9–7.9)		(7.3–9.0)		(7.0–8.5)
5	2.4	4.6	3.1	5.0	3.3	6.3	3.1	5.7
		(4.2–5.7)		(4.5–6.4)		(5.6–7.2)		(5.3–6.7)
6	2.0	2.8	2.1	3.4	2.0	4.0	2.1	3.8
		(2.4–3.7)		(2.9–4.4)		(3.2–4.6)		(3.3–4.8)
7	1.0	1.5	1.0	2.0	1.0	1.8	1.0	2.0
		(1.1–1.9)		(1.5–2.6)		(1.2–2.2)		(1.6–2.5)
S-7[c]		7.5		8.7		9.0		8.6
		(6.8–8.5)		(8.5–10.6)		(8.3–10.3)		(8.0–9.5)
S-8[d]		9.0		10.7		10.8		10.6
		(8.2–10.1)		(10.3–12.6)		(10.1–12.2)		(9.8–11.6)

[a] Amsterdam cohort study on HIV and AIDS.

[b] Vancouver Lymphadenopathy-AIDS Study.

[c] Seroconversion to AIDS.

[d] Seroconversion to death.

Note that the CD4-based stage of an individual at each visit was determined using smoothed CD4-count.

this method of analysis. Using these conditions any other cutoff point, say within one year of the cutoff point used, gave similar results.

In our model we did not allow progression directly from a CD4-based stage to death, assuming that these cases were unobserved AIDS cases. This may be so, because the time since the

Table 5 Estimated mean waiting time and the percentage moving to a higher stage (95% CI) in each stage by cohort and by calendar time period, using a reversible Markov model

	1 January 1985–1 March 1990				1 March 1990–1 January 1997			
	ACS[a]		VLAS[b]		ACS		VLAS	
Stage	mean in month	% forward	mean in month	% forward	mean in month	% forward	mean in month	% forward
1	15.7	100%	34.0	100%	30.0	100%	19.1	100%
	(14.6–24.1)		(30.8–50.8)		(22.1–72.8)		(13.8–29.7)	
2	14.8	87%	16.8	77%	15.5	82%	13.7	91%
	13.4–18.6)		(16.2–22.2)		(13.5–23.5)		(11.7–18.5)	
3	21.3	81%	21.4	81%	23.1	91%	23.3	100%
	19.4–25.2)		(20.2–28.3)		(20.7–29.0)		(19.4–28.2)	
4	18.9	83%	19.3	88%	22.9	84%	23.2	86%
	17.4–23.0)		(17.3–23.4)		(20.5–27.2)		(19.4–28.8)	
5	21.8	79%	21.9	84%	29.0	81%	23.3	92%
	19.1–27.7)		(17.7–29.2)		(24.6–35.8)		(20.2–29.2)	
6	15.7	100%	16.7	98%	25.4	100%	21.6	95%
	13.1–24.2)		(14.2–27.1)		(20.4–30.6)		(20.2–29.1)	
7	17.4	100%	23.5	100%	21.0	100%	23.3	100%
	(12.4–22.9)		(17.2–30.9)		(15.7–26.6)		(18.3–30.0)	

[a] Amsterdam cohort study on HIV and AIDS.

[b] Vancouver Lymphadenopathy-AIDS Study.

Note that the CD4-based stage of an individual at each visit was determined using smoothed CD4-count.

last visit was on average more than 3 years and only limited information about AIDS-related causes of death were available for these cases. It should also be noted that municipal and national registries were used to complete these data. Finally, omitting these data gave similar results.

The VLAS participants were recruited about 2 years earlier than the participants in the ACS and the VLAS was designed, unlike the cohort in Amsterdam, to be a closed cohort study. Thus, there could be subtle differences between the cohorts with respect to factors that may affect the progression rates, but these factors may be difficult to identify. One of these differences was the relatively short waiting times in stage 1 in the VLAS after March 1990 and in the ACS before March 1990. One may argue that this resulted from the changing patterns of the number of seroconverters in secular time. Since HIV-negative men were followed in both cohorts, ageing may explain this difference in the VLAS. Although, this may be less in the ACS since it is not a (completely) closed cohort study. Also, from this point of view one may expect a relative short number of seroconverters in the ACS in the early years of this study. However, the pattern of number of visits per stage in each calendar time interval was similar to the overall pattern in the ACS. To overcome these differences, we studied the changes in the incubation period by studying the changes in the incubation time from either stage to death. We used death as the endpoint rather then an AIDS diagnosis, as this is not subject to change in definition like AIDS diagnosis is.

These data from the cohort in Amsterdam provided information on the changes in progression rates in a population-based cohort, possibly indicating changes in progression rates in the population from which this cohort was drawn. However, these changes may be overestimated as, for instance, the men participating in the cohort study may have better access to therapy than other homosexual and bisexual men.

Several studies have suggested that there have been no major changes in the incubation period up to 1991–1992.[21–23] Our findings were in agreement with other studies that report an extension in the time from seroconversion to death in more recent years.[1–3] There is little doubt that improved treatment and prophylaxis for HIV-related diseases are the underlying cause. Given that this observed extension occurred in the early years of implementation of triple combination therapies, even greater delay in progression is to be expected in the future.

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References

[1] Hessol NA, Koblin BA, Van Griensven GJP *et al*. Progression of human immunodeficiency virus type 1 (HIV-1) infection among homosexual men in Hepatitis B vaccine trial cohorts in Amsterdam, New York City, and San Francisco, 1978–1991. *Am J Epidemiol* 1994; **139:**1077–87.

[2] Veugelers PJ, Page KA, Tindall B *et al*. Determinants of HIV disease progression among homosexual men registered in the Tricontinental Seroconverter study. *Am J Epidemiol* 1994;**140:**747–57.

[3] Muñoz A, Xu J. Models for the incubation period of AIDS and variations according to age and period. *Stat Med* 1996;**15:**2459–73.

[4] Keet IPM, Veugelers PJ, Koot M *et al*. Temporal trends of the natural history of HIV-1 infection following seroconversion between 1984 and 1989. *AIDS* 1996;**10:**1601–02.

[5] Van Griensven GJP, Boucher EC, Roos M, Coutinho RA. Expansion of the AIDS case definition. *Lancet* 1991;**338:**1011–12.

[6] Schechter MT, Craib KJP, Le TN *et al*. Influence of zidovudine on progression to AIDS in cohort studies. *Lancet* 1989;**i:**1026–27.

[7] Hoover DR. The effects of long term Zidovudine therapy and *Pneumocystis carinii* prophylaxis on HIV disease. *Drug* 1995;**49:**20–36.

[8] Veugelers PJ, Strathdee SA, Moss AR *et al*. Is the Human immunodeficiency virus-related Kaposi's sarcoma epidemic coming to an end? Insights from the tricontinental seroconverter study. *Epidemiology* 1995;**6:**382–86.

[9] Keet IPM, Krol A, Koot M *et al*. Predictors of disease progression in HIV-infected homosexual men with CD4+ cells $<200 \times 10^6$/l but free of AIDS-defining clinical disease. *AIDS* 1994;**8:**1577–83.

[10] Muñoz A, Sabin CA, Phillips AN. The incubation period of AIDS. *AIDS* 1997;**11(Suppl.A):**S69–S76.

[11] Simons P, Muylderman G, Lacor P, Zissis G, Lauwers S. False-negative HIV viral load in AIDS patients. *AIDS* 1997;**11:**1783–84.

[12] Centers for Disease Control: Revision of the CDC surveillance case definition of acquired immnunodeficiency syndrome. *MMWR* 1987; **36:**3S–15S.

[13] Longini IM, Clark WS, Karon JM. Effect of routine use of therapy in slowing the clinical course of human immunodeficiency virus (HIV) infection in a population-based-cohort. *Am J Epidemiol* 1993;**137:** 1229–40.

[14] Hendriks JCM, Satten GA, Longini IM *et al*. Use of immunological markers and continuous-time Markov models to estimate progression of HIV infection in homosexual men. *AIDS* 1996;**10:**649–56.

[15] Satten GA, Longini IM Jr. Markov chains with measurement error: estimating the 'true' course of a marker of HIV disease progression. *Appl Stat* 1996;**45:**275–311.

[16] Hendriks JCM, Satten GA, van Ameijden EJC, van Druten JAM, Coutinho RA, van Griensven GJP. The incubation period to AIDS among injecting drug users estimated from prevalent cohort data, accounting for death prior to an AIDS diagnosis. *AIDS* 1998;**12:** 1537–44.

[17] Longini IM, Clark WS, Byers RH *et al*. Statistical analysis of the stages of HIV infection using a Markov model. *Stat Med* 1989;**8:** 831–43.

[18] Efron B, Tibshirani RJ. *An Introduction to the Bootstrap*. New York: Chapman & Hall, 1993.

[19] Graham NHM, Zeger SL, Park LP *et al*. The effects on survival of early treatment of human immunodeficiency virus infection. *New Engl J Med* 1992;**326:**1037–42.

[20] Veugelers PJ, Cornelisse PGA, Craib KJP *et al*. Models of survival in HIV infection and their use in the quantification of treatment benefits. *Am J Epidemiol* 1998;**148:**487–96.

[21] Taylor JMG, Kuo JM, Detels R. Is the incubation period of AIDS lengthening? *J Acquir Immune Defic Syndr* 1991;**4:**69–75.

[22] O'Brien TR, Hoover DR, Rosenberg PS *et al*. Evaluation of secular trends in CD4+ lymphocyte loss among human immunodeficiency virus type 1 (HIV-1)-infected man with known dates of seroconversion. *Am J Epidemiol* 1995;**142:**636–42.

[23] Galai N, Cozzi Lepri A, Vlahov D, Pezotti P, Sinicco A, Rezza G for the Human Immunodeficiency Virus Italian Seroconversion Study. Temporal trends of initial CD4 cell counts following human immunodeficiency virus seroconversion in Italy, 1985–1992. *Am J Epidemiol* 1995;**143:**278–82.