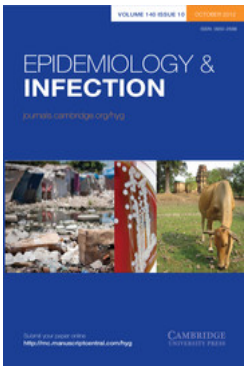

The relationships between the HIV test interval, demographic factors and HIV disease progression

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The relationships between the HIV test interval, demographic factors and HIV disease progression

CASCADE European Collaborative Project*

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SUMMARY

Individuals developing an HIV seroconversion illness may experience rapid disease progression. Information on seroconversion illness is rarely collected in most cohort studies; thus the aim of this study was to assess the value of the HIV test interval (the time between last negative and first positive HIV tests) as a proxy for seroconversion illness. Among 8229 seroconverters, test intervals ranged from 0–5282 days, and varied by gender, risk group, age and calendar year of seroconversion. Those with intervals $\leqslant 31$ days had an increased hazard of AIDS (RH 1·42, $P = 0{\cdot}07$), which was reduced slightly after adjusting for baseline factors, calendar year of follow-up, treatment and the declining CD4 count, but there was no effect on survival. Thus, it appears that if information on acute seroconversion illness is not available, then analyses of progression to AIDS in seroconverter studies could use a short test interval as a proxy measure.

INTRODUCTION

Many individuals may develop some type of clinical manifestation at the time of primary infection with HIV [1]. Typically, seroconversion 'illness' resembles a flu-like illness and can include fever, malaise, headaches, night sweats, nausea and diarrhoea [2–6]. The presence, severity and duration of a clinically recognized seroconversion illness is associated with more rapid progression to AIDS and shorter survival [5, 7–13]. The high HIV RNA levels seen at the time of primary infection [14, 15] and the subsequent rapid rate of CD4 loss [11] in these individuals may suggest a mechanism for this effect.

Cohort studies of HIV seroconverters (i.e. individuals with known dates of HIV negative and positive test results) often select individuals for inclusion retrospectively. In such cases, information on symptomatic primary infection may not always be available in patient notes: Where this information is available, it is likely to be subject to recall bias. Even prospectively followed cohorts of HIV negative individuals may not necessarily detect all seroconversion illnesses due to the wide spectrum of clinical events that may be manifest [16]. Thus, the impact of symptomatic primary infection on HIV-1 disease progression is often difficult to assess or control for in such studies.

Many cohort studies estimate the time of seroconversion as the mid-point between the dates of the last negative and first positive HIV test result (the 'mid-point method') [17]. The development of a seroconversion illness may prompt some individuals to present for medical care and, if seroconversion illnesses is suspected, the clinician may request an HIV test following this presentation. If the individual is still in the process of seroconverting to HIV, then this first test may be negative and clinicians are likely

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to follow this up with a repeat test, which will be positive, a few weeks later. Thus, these individuals are likely to have very short intervals between their last negative and first positive tests (the HIV test interval). Alternatively, the individual may have already seroconverted at the time of the first test, which will be positive. In this case, the test interval, depending on the regularity of HIV testing, is still likely to be shorter than that of patients without a seroconversion illness in whom the first positive test is likely to occur later in time. Thus, measurement of the length of the HIV test interval may provide a simple means to assess the impact of symptomatic primary infection on HIV disease progression in cohorts where this information is not collected prospectively.

The aim of this study is to describe HIV test intervals in a large, multi-cohort study of HIV seroconverters. In particular, we wished to describe the factors which are related to the HIV test interval, and to assess the relationship between a very short test interval, progression to AIDS and death and immunological decline.

METHODS

The CASCADE Study

The CASCADE Study has been described fully elsewhere [18]. Briefly, the study aims to bring together European and Australian data and expertise to address questions on natural history which cannot be adequately addressed through single studies. Currently, 19 cohorts participate in the collaboration, which includes a total of 8729 HIV seroconverters. Information on the estimated seroconversion date (estimated date, dates of first positive and last negative HIV tests, method of estimating seroconversion date, and of verifying the date of the last HIV negative test result) was collected for each individual in the study. The analysis in this paper is based on 8229 individuals from the CASCADE data set in whom dates of last negative and first positive HIV tests were both available.

Statistical methods

The HIV test interval was defined as the time interval between the dates of the last negative and first positive HIV test results for each individual. The test intervals were compared in different demographic groups using unpaired *t*-tests and ANOVA methods after taking a log transformation to normalize the values and to obtain approximately equal variances in the groups. Multiple regression analysis was performed on the transformed data to assess the independent effects of each of the factors on the length of the test interval.

The impact of a short test interval on progression to AIDS and death were assessed using the Cox proportional hazards regression model [19]. Short test intervals were defined to be 31 days or less. Time to AIDS and survival were calculated from the estimated date of seroconversion until the date of developing AIDS or death, as appropriate. In individuals who remained AIDS-free at the end of the study, or who had not died, follow-up was right-censored. The method of right-censoring was cohort-specific, according to individual cohort protocols. All models were stratified by study cohort and, as follow-up on some individuals did not begin until some time after seroconversion, allowed for late entry into the cohort ('left truncation').

Relative hazards, 95% confidence intervals and *P*-values are presented unadjusted and adjusted for baseline demographic factors (age at seroconversion, sex, exposure group, ethnicity, calendar year of seroconversion and the method by which the last negative test was determined), calendar year of follow-up (< 1991, 1991–2, 1993–4, 1995–6, 1997 onwards) and antiretroviral treatment (dates of starting monotherapy, double therapy, triple therapy excluding protease inhibitors, triple therapy including protease inhibitors). The latter two variables were included as time-updated covariates in the models. All other variables were considered fixed at baseline.

In order to assess whether any effect of a short test interval could be explained by more rapid CD4 loss in individuals with short test intervals, two additional sets of analyses were performed. Firstly, the relationship between a short test interval and the time to a CD4 count < 200 cells/mm^3 was performed in those individuals whose baseline CD4 count was above 200 cells/mm^3 using the Cox proportional hazards model. As the CD4 count is known to drop at the time of seroconversion, before increasing to near pre-seroconversion levels over the first 6 months of infection or so, the baseline CD4 count for this analysis was defined as the first CD4 count measured at least 9 months after the estimated date of seroconversion. For this analysis, follow-up was right-censored 6 months after the last available CD4 count, to ensure that individuals with infrequent CD4 monitoring could not bias the results. Secondly, the

Table 1. *Demographic details of 8229 individuals included in study, and of reduced data set used for proportional hazards regression analysis examining progression to AIDS, death and a CD4 count* < 200 *cells/mm*^{3}

		Full data set ($n = 8229$)		Reduced data set* ($n = 6451$)	
Age at seroconversion (years)	< 20	475	(5·8%)	310	(4·8%)
	20–29	4203	(51·1%)	3338	(51·7%)
	30–39	2363	(28·7%)	1899	(29·4%)
	40–49	853	(10·4%)	660	(10·2%)
	$\geqslant 50$	335	(4·1%)	244	(3·8%)
Sex	Male	6536	(79·4%)	5071	(78·6%)
	Female	1693	(20·6%)	1380	(21·4%)
Exposure group	Homo/bisexual	4196	(51·0%)	3414	(52·9%)
	Injecting drug users	2073	(25·2%)	1582	(24·5%)
	Heterosexual	1517	(18·4%)	1290	(20·0%)
	Haemophilia	248	(3·0%)	0	(—)
	Other/not stated	195	(2·4%)	165	(2·6%)
Ethnic group	White	3400	(41·3%)	2097	(32·5%)
	Black	152	(1·8%)	126	(2·0%)
	Other	112	(1·4%)	112	(1·7%)
	Not stated	4565	(55·5%)	4116	(63·8%)
Date of last negative HIV test	Verified by lab/clinic	5845	(71·0%)	4492	(69·6%)
	Reported by subject	2384	(29·0%)	1959	(30·4%)
Determination of seroconversion date	Midpoint method	7176	(87·2%)	6351	(98·4%)
	Laboratory evidence of seroconversion	100	(1·2%)	100	(1·6%)
	Evidence of symptomatic infection from notes	28	(0·3%)	0	(—)
	Other	925	(11·2%)	0	(—)
Calendar year of seroconversion	$\leqslant 1985$	894	(10·9%)	522	(8·1%)
	1986–7	1170	(14·2%)	936	(14·5%)
	1988–9	1471	(17·9%)	1104	(17·1%)
	1990–1	1423	(17·3%)	1156	(17·9%)
	1992–3	1344	(16·3%)	1138	(17·6%)
	1994–5	1125	(13·7%)	941	(14·6%)
	1996–8	802	(9·7%)	654	(10·1%)

* Described in Methods section.

models for progression to AIDS and death were repeated adjusting for the changing CD4 count as a time-updated covariate (modelled on the $\log_{10}$ scale). All analyses were performed using the SAS software package [17].

For all progression analyses, individuals were only included if their date of seroconversion had been estimated using the mid-point method or on the basis of laboratory evidence of seroconversion. Other individuals were excluded from the analysis, as anecdotal evidence suggested that in many cohorts notes would be searched for other evidence of seroconversion (i.e. symptoms, sudden drop in CD4 count) only when the test interval was particularly long, in order to provide a more accurate estimate of the date of seroconversion. In addition, haemophilic men (who were all infected prior to 1985) and those whose first positive HIV test was prior to 1985 (which must have been obtained retrospectively, as an HIV test did not become available until 1985), were also excluded from progression analyses as it was felt that the length of the test interval in these individuals was more likely to relate to clinic policy on the collection and storage of blood samples at the time, than to presentation because of symptomatic primary infection. Finally, patients from three centres who had not provided follow-up CD4 data for all patients, were excluded. Thus, the progression analysis was

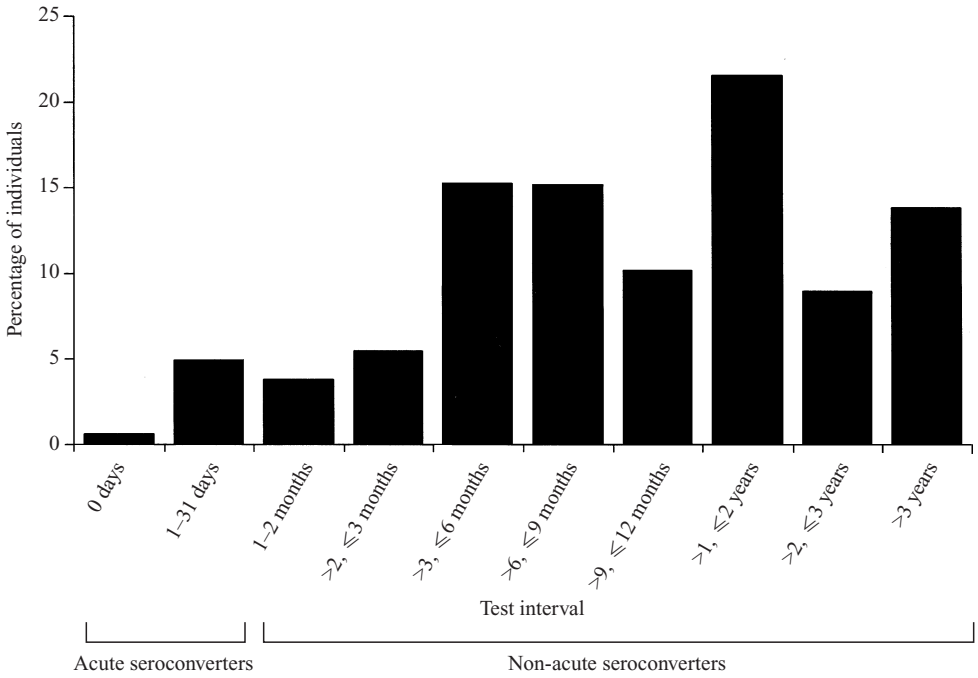

Fig. 1. Distribution of HIV test intervals among 8229 individuals from the CASCADE study.

based on 6451 individuals from the full data set (78·4%).

A number of sensitivity analyses were performed. Firstly, the analysis was repeated defining a short test interval as less than 45 days. Secondly, the analysis was repeated after excluding those patients whose last negative test result had not been verified by the laboratory and was based on subject report only.

RESULTS

Details of the 8229 individuals with both last negative and first positive HIV test results, and of the 6451 individuals included in the progression analyses are shown in Table 1. The majority of individuals in the study were male, reported a sexual risk for HIV infection and were aged between 20 and 40 years at the time of seroconversion. Of those in whom ethnicity was recorded, the majority were white, although many cohorts did not collect this information. In 71% of individuals in the whole cohort, the date of the last negative test result had been verified by the laboratory or clinic and the seroconversion date was estimated using the mid-point method in 87% of individuals. Seroconversion was estimated to have occurred between 1979 and 1998, with a similar proportion of individuals seroconverting in each calendar period. With the exception of the exclusion of haemophilic men, the demographic details of the reduced population used in the progression analyses were similar to those of the whole population.

Test intervals among the 8229 seroconverters ranged from 0–5282 days (geometric mean 283 days) and are shown in Figure 1. It should be noted that some of the individual cohort studies had placed eligibility restrictions on the length of test interval that was permissible in a seroconverter. Thus, this figure is likely to underestimate the distribution of test intervals in all individuals with a prior negative test.

Geometric mean test intervals (and 95% confidence intervals [CI]) for subgroups of the study population are shown in Table 2. The test interval tended to get progressively shorter with increasing age at seroconversion ($P = 0{\cdot}0005$). Haemophilic men had longest test intervals and those from other/not stated exposure groups the shortest ($P = 0{\cdot}0001$). Black individuals also had longer test intervals than those of other ethinicities ($P = 0{\cdot}02$). Those whose negative date was verified by the laboratory or clinic had shorter test intervals, on average, than those whose negative date had been reported by the subject only ($P = 0{\cdot}0001$). In addition, those in whom there was laboratory evidence of seroconversion had particularly short test intervals and those whose seroconversion date had been based on knowledge of a putative seroconversion illness had long test intervals ($P = 0{\cdot}0001$). Finally, there were differences in the length of test interval according to calendar year of

Table 2. *Relationships between baseline factors and HIV test interval – univariate results*

		Geometric mean (days)	95% Confidence interval	*P*-value*
Age at seroconversion (years)	< 20	296	(256–342)	
	20–29	295	(282–308)	
	30–39	284	(265–304)	
	40–49	257	(224–295)	
	⩾ 50	200	(145–275)	0·0005
Sex	Male	283	(272–294)	
	Female	282	(258–308)	0·93
Exposure group	Homo/bisexual	265	(253–278)	
	Injecting drug users	306	(289–324)	
	Heterosexual	306	(279–335)	
	Haemophilia	626	(545–720)	
	Other/not stated	97	(55–173)	0·0001
Ethnic group	White	279	(262–297)	
	Black	413	(337–507)	
	Other	347	(246–490)	
	Not stated	281	(269–274)	0·02
How was negative date determined?	Verified by lab/ clinic	210	(201–220)	
	Reported by subject	585	(558–613)	0·0001
How was sc date determined?	Midpoint method	304	(294–315)	
	Lab evidence of seroconversion	31	(15–65)	
	Seroconversion illness	1171	(849–1616)	
	Other	194	(169–223)	0·0001
Calendar year of sc	⩽ 1985	222	(189–250)	
	1986–7	235	(219–253)	
	1988–9	305	(284–338)	
	1990–1	347	(323–373)	
	1992–3	345	(319–373)	
	1994–5	306	(279–336)	
	1996–8	188	(162–217)	0·0001

* From ANOVA or unpaired *t*-tests, after log transformation, as appropriate.

seroconversion ($P = 0{\cdot}0001$), although this effect did not appear to be linear. In univariable analyses, gender did not appear to be related to the test interval. All of the factors remained significantly associated with the test interval in multivariable analyses (Table 3). In addition, after adjusting for the other factors, women were found to have a shorter test interval than men ($P = 0{\cdot}005$).

A total of 459 (5·6%) individuals in the whole cohort, and 342 (5·3%) individuals in the reduced cohort, had test intervals of ⩽ 31 days. Treatment uptake among those with short test intervals and other individuals was generally similar, although a slightly higher proportion of those with short test intervals (43·6%) started monotherapy over follow-up than those with longer test intervals (32·8%, $P < 0{\cdot}0001$). No differences were seen in the proportion of individuals starting dual therapy, triple therapy or a protease inhibitor.

The effect of a short test interval on progression to AIDS, death and a CD4 count of 200 cells/mm^3 is shown in Table 4. Of the 6451 individuals in the progression analysis population, 1417 (22·5%) developed AIDS over follow-up. Before adjusting for other factors, those with a short test interval had a 42% increased hazard of developing AIDS over

Table 3. *Relationships between baseline factors and HIV test interval – coefficients, 95% confidence intervals and p-values from multiple regression model*

		Estimate	95% Confidence interval	*P*-value
Overall estimate of mean log (test interval)*		1·869	1·781 to 1·957	0·0001
Age at seroconversion	(per 10 year increase in age)	−0·025	−0·042 to −0·008	0·004
Sex	Male	0	—	—
	Female	−0·059	−0·104 to −0·015	0·01
Exposure group	Homo/bisexual	0	—	—
	Injecting drug users	0·117	0·075 to 0·159	0·0001
	Heterosexual	0·025	−0·023 to 0·074	0·30
	Haemophilia	0·711	0·608 to 0·813	0·0001
	Other/not stated	−0·356	−0·454 to −0·258	0·0001
Ethnic group	White	0	—	—
	Black	0·162	0·051 to 0·274	0·004
	Other	0·127	−0·001 to 0·255	0·05
	Not stated	−0·082	−0·117 to −0·046	0·0001
How was negative date determined?	Verified by lab/ clinic	0	—	—
	Reported by subject	0·432	0·397 to 0·466	0·0001
How was sc date determined?	Midpoint method	0	—	—
	Lab evidence of seroconversion	−0·867	1·002 to −0·732	0·0001
	Seroconversion illness	0·672	0·428 to 0·923	0·0001
	Other	−0·193	−0·247 to −0·138	0·0001
Calendar year of sc	⩽ 1985	0	—	—
	1986–7	0·144	0·050 to 0·179	0·0001
	1988–9	0·225	0·162 to 0·288	0·0001
	1990–1	0·223	0·608 to 0·813	0·0001
	1992–3	0·200	0·136 to 0·265	0·0001
	1994–5	0·114	0·046 to 0·181	0·001
	1996–8	−0·094	−0·166 to −0·021	0·01

* The overall estimate of the mean log (test interval) relates to a 20 year-old white male homosexual, infected prior to 1985, in whom the seroconversion date was based on laboratory evidence of seroconversion and the date of last negative test has been verified by the laboratory.

follow-up compared to other individuals ($P = 0{\cdot}002$). After adjusting for baseline demographic details, calendar period of follow-up and treatment uptake, this relative hazard dropped slightly (relative hazard [RH] 1·25, $P = 0{\cdot}05$). After further adjusting for the CD4 count as a time-updated covariate, the relative hazard remained similar (RH 1·30, $P = 0{\cdot}03$) suggesting that this effect of a short test interval could not be explained by a more rapid rate of CD4 loss in this group.

A total of 1339 (21·3%) individuals died over follow-up. In both univariable and multivariable analyses, there was no significant effect of a short test interval, although the relative hazard was consistently above one, suggesting that there may be a small but non-significant effect of a short test interval on survival.

Progression to a low CD4 count was considered only in those individuals whose baseline CD4 count (measured at least 9 months after seroconversion) was above 200 cells/mm^3. Thus, 5012 individuals were included in this analysis, of whom 1629 individuals (32·5%) experienced at least one CD4 count $<$ 200 cells/mm^3 over follow-up. Again, there were

Table 4. *Relationship between a short test interval and progression to AIDS, death and a CD4 count of 200 cells/mm³ or less*

	Progression to AIDS			Progression to death			Progression to CD4 < 200 cells/mm³		
	Relative hazard	95% CI	*P*-value	Relative hazard	95% CI	*P*-value	Relative hazard	95% CI	*P*-value
Effect of short test interval									
Unadjusted	1·42	(1·14–1·76)	0·002	1·12	(0·88–1·44)	0·35	1·14	(0·91–1·42)	0·25
Adjusted for baseline factors, calendar year of follow-up and treatment	1·25	(1·00–1·56)	0·05	1·16	(0·90–1·51)	0·26	1·02	(0·82–1·28)	0·84
Adjusted for above factors and CD4 count	1·30	(1·03–1·66)	0·03	1·20	(0·93–1·55)	0·16	—	—	—

no significant effects of a short test interval on progression rates, either unadjusted or after adjustment for demographic factors, calendar year of follow-up and treatment uptake.

One possible explanation for the association between a short test interval and progression to AIDS is that if the AIDS event occurred very soon after seroconversion it may have prompted the patient to request an HIV test. Thus, the development of AIDS would lead to a short test interval rather than the reverse. Seven patients in the cohort (one in the short test interval group) had a first AIDS diagnosis before the time of their first positive HIV test. However, exclusion of these patients had very little effect on the results of the analysis.

Analyses in which a short interval was defined as a 45 days or less ($n = 386$, 6·1%), gave very similar results for both AIDS (RH 1·25, 95% CI 1·00 to 1·56, $P = 0·05$) and death (RH 1·15, 95% CI 0·91 to 1·46, $P = 0·24$). In addition, exclusion of individuals whose last negative test report had not been verified by laboratory report, had little effect on the results (results not shown).

DISCUSSION

The CASCADE study includes almost 8800 infected individuals with known dates of seroconversion. As such, this study offers an ideal opportunity to explore the factors related to the HIV test interval in a group of individuals who represent all major risk, gender, ethnicity and age groups. Because of its size, the study also enables us to consider relationships between factors which may involve relatively small subgroups of the population, e.g. those with a short test interval.

The results from this study show large differences in the distributions of HIV test intervals between individuals from different risk groups for infection. In particular, compared to homo/bisexual men, haemophilic individuals tend to have very long test intervals, injecting drug users have slightly longer intervals and those from other/not stated risk groups tend to have much shorter test intervals. This is likely, in part, to be due to the increased awareness of HIV infection in homo/bisexual men, in whom regular HIV testing is more common. As haemophilic men were infected with HIV before a test became available, HIV tests were retrospectively performed on blood samples which had generally been stored at regular intervals. Thus, it may be expected that these test intervals were

less likely to be affected by the presence of a seroconversion illness. The longer test intervals in injecting drug users could reflect a more chaotic lifestyle and poorer access to care in this group [21]. Many cohorts did not collect information on ethnicity; thus the shorter test intervals in those in whom ethnicity was unknown should be interpreted cautiously. However, in those in whom ethnicity was known, black individuals tended to have longer test intervals than women, possibly reflecting poorer access to care in this group [22].

Test intervals were far longer in those cases where the last negative test result was reported by the subject, and in those in whom a history of a putative seroconversion illness was used to determine the date of seroconversion. Discussions with the cohorts involved in the study suggested that as most cohorts did not collect information on symptomatic infection, this was only likely to be used to determine seroconversion dates when the test interval was very long and was therefore thought to be particularly inaccurate. For this reason, these individuals were excluded from the analyses of progression to AIDS and death. Interestingly, there was an effect of calendar year of seroconversion on the test interval. Compared to those seroconverting before 1985, in whom the test interval was very short, those who seroconverted between 1986 and 1993 had significantly longer test intervals. Those seroconverting from 1996 onwards had much shorter test intervals. Clearly, in order to be recruited to a cohort study as a seroconverter after 1996, the last negative HIV test must have taken place relatively recently; because seroconversion dates were usually estimated using the midpoint method, anyone whose negative test occurred more than 2 years prior to 1996 would have had a seroconversion date before 1996. Thus, this effectively forces the test intervals in this group to be short.

We found a 42% increase in the hazard of AIDS in individuals with test intervals $\leqslant 31$ days. This effect was reduced slightly after adjustment for other demographic factors, calendar year of follow-up and receipt of antiretroviral treatment, but was not changed dramatically after adjusting for the changing CD4 count. Thus, it does not appear that this effect is explained by a more rapidly declining CD4 count in those with short test intervals. In addition, there was no suggestion that these individuals reached a low CD4 count more rapidly than those with longer test intervals. However, no effect of a short test interval was found for death, suggesting that this effect may be relatively short-lived. Once an individual develops AIDS, they are likely to receive antiretroviral treatment. Thus, any subsequent effect on death may be reduced.

One of the most likely explanations for our findings is that individuals with short test intervals are those who were prompted to present for medical care because of symptomatic infection. A number of studies have reported an association between acute seroconversion illness and HIV disease progression [5, 7–12]. It has been reported that individuals with symptomatic primary infection, also experience higher initial HIV-1 RNA levels at the time of seroconversion [14, 15]. One possible mechanism for an effect of a short test interval on progression is that individuals with acute seroconversion may have higher RNA 'set-point' levels which may translate into an increased risk of disease [23, 24]. Unfortunately, HIV-1 RNA data is not currently available for the CASCADE study, and so we cannot address this issue. However, again, it is likely that such an effect would also be apparent for survival, thus arguing against such an effect. A second possible explanation is that some of the events at the time of symptomatic primary infection were themselves AIDS-defining. Both *Pneumocystis carinii* pneumonia and oesophageal candida have been reported at the time of primary infection with HIV [25, 26]. Thus, this would clearly translate into a very rapid progression rate in these individuals, which probably would not be as apparent for death. However, in only seven cases, was the date of first AIDS disease prior to the first positive HIV test (including one individual with a short test interval), and exclusion of these individuals did not affect the results greatly.

Our findings suggest that it may be possible to use a short test interval as a proxy for seroconversion illness when performing an analysis of progression to AIDS. However, clearly a proportion of individuals with short test intervals are likely to be those who perceive themselves to be at high risk of infection, e.g. following unprotected sexual intercourse with a known HIV-positive partner, but who are asymptomatic. Furthermore, test intervals for those who request an HIV test as a result of a seroconversion illness will only be 'short' if they test during the window of infection (i.e. their first test is negative and this is followed by a repeat test which is positive). Individuals whose first test is just after seroconversion and is positive, will only have a short test interval if,

for some other reason, they had a negative test less than a month beforehand. Thus, a short test interval is likely to be an imperfect proxy for seroconversion illness, although it may be sufficient for most purposes.

The majority of the individuals included in the study had their date of seroconversion estimated using the mid-point method. There is the potential for bias to be introduced when using the mid-point method to estimate seroconversion dates if the probability of infection is not uniformly distributed over the test interval [17]. Thus, it may be that seroconversion dates are too early, leading to artificially longer times from seroconversion to AIDS in these patients. This bias will have least impact in those with the shortest test intervals; thus it may appear that these individuals experience more rapid disease progression than those with longer test intervals. However, such an effect would also be expected to manifest itself on progression to death, which is not the case in this study. It is also likely that the effect would be apparent for test intervals of differing lengths. In preliminary analyses (data not shown), there was no difference in progression rates according to whether the test interval was 1–2 months long or 1–2 years. Thus, we do not believe that this can explain our findings.

In summary, individuals with short test intervals ($\leqslant$ 31 days) appear to progress to AIDS more rapidly than those individuals with longer test intervals. If information on acute seroconversion illness is not available, then analyses of progression to AIDS could adjust for a short test interval as a proxy measure.

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