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The relationship between HIV seroconversion illness, HIV test interval and time to AIDS in a seroconverter cohort

F. TYRER, A. S. WALKER, J. GILLETT AND K. PORTER*, for the UK Register of HIV Seroconverters

MRC Clinical Trials Unit, London, UK

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SUMMARY

Seroconversion illness is known to be associated with more rapid HIV disease progression. However, symptoms are often subjective and prone to recall bias. We describe symptoms reported as seroconversion illness and examine the relationship between illness, HIV test interval (time between antibody-negative and anibody-positive test dates) and the effect of both on time to AIDS from seroconversion. We used a Cox model, adjusting for age, sex, exposure group and year of estimated seroconversion. Of 1820 individuals, information on seroconversion illness was available for 1244 of whom 423 (34%) reported symptomatic seroconversion. Persons with a short test interval ($\leqslant$2 months) were significantly more likely to report an illness than people with a longer interval (OR 6·76, 95% CI 4·75–9·62). Time to AIDS was significantly faster ($P=0{\cdot}01$) in those with a short test interval. The HIV test interval is a useful replacement for information on seroconversion illness in studies of HIV disease progression.

INTRODUCTION

The presence of seroconversion illness, typically characterized by ''flu-like' symptoms, including fever, malaise, night sweats, generalized lymphadenopathy, skin rashes and diarrhoea, in the course of HIV infection has been well documented [1–3]. Previous studies have reported an association between illness at the time of seroconversion and a more rapid disease progression [2, 4, 5]. However, the proportion of individuals who experience illness during primary infection is uncertain, because symptoms are neither sensitive nor specific enough to HIV infection, and are subject to recall bias at the time of the HIV-positive test. Lack of such information from clinical notes may mean either that the infected individual did not experience a seroconversion illness, or simply that such information was not sought and is, therefore, unknown.

* Author for correspondence: Dr K. Porter, MRC Clinical Trials Unit, 222 Euston Road, London NW1 2DA, UK.

Presence of symptoms may prompt some individuals, who believe they may recently have been exposed to HIV, to seek medical advice. If the clinician suspects seroconversion illness, an antibody test may be requested. If the individual is seroconverting to HIV at this time, the first test may be negative and clinicians are likely to follow up with a repeat test, which will be positive, a few weeks later. Alternatively, an individual who has regular HIV tests, may test positive for HIV when presenting to the clinician with a seroconversion illness. In both cases, the HIV test interval (time between last negative and first positive test dates) is likely to be shorter than that of patients without a seroconversion illness. Thus, the length of the HIV test interval may serve as a simple means of adjusting for seroconversion illness where illness is poorly recorded or information is not available. A recent study proposed using the HIV test interval as a proxy for seroconversion illness and reported that a short HIV test interval of $\leqslant$31 days was associated with a more rapid disease

progression [6]. However, information on seroconversion illness was not available in that study.

Here we describe reported symptoms compatible with HIV seroconversion and trends over time. We also investigate the relationship between reported seroconversion illness and HIV test interval and investigate the influence of both on the time between HIV seroconversion and AIDS.

METHODS

We used data from individuals enrolled on the UK Register of HIV Seroconverters reported by January 2002. The Register has been described in detail elsewhere [7, 8], but briefly, is a cohort of HIV-infected individuals aged 16 years or over with a history of a documented negative test within 3 years of a first positive test, or identified during the acute infection stage (based on strictly defined laboratory evidence of seroconversion). The date of seroconversion is taken as the date of laboratory evidence where known, otherwise it is the midpoint between the positive and negative test dates. Eligible subjects were enrolled from October 1994 and were identified both retrospectively and prospectively. Complete ascertainment of all eligible seroconverters was sought, including those who had died, transferred to other centres or become lost to follow up. All symptoms, described in the literature as suggestive of HIV seroconversion illness, were recorded in a standardized format [1–3].

We examined the relationship between the presence of illness and HIV test interval initially by examining the proportions of individuals reporting illness who have short and long test intervals and by then estimating the relative odds of reporting an illness in persons with a short test interval. We initially defined a test interval as short if it was less than 1 month and redefined it with increasingly longer lengths to explore any 'dose–response' relationship between the length of the test interval and HIV seroconversion illness.

We then used logistic regression models to investigate the association between the presence of seroconversion illness as the outcome variable and the HIV test interval, adjusting for sex, exposure category, age at seroconversion (16–19, 20–29, 30–39, 40+ years) and estimated year of seroconversion (1982–1989, 1990–1993, 1994–1997, 1998–2000).

Using log-rank methods and Cox proportional hazards models [9] we investigated the association between the presence of seroconversion illness, the HIV test interval and the time interval between HIV seroconversion and AIDS, also adjusting for the possible effects of sex, age at seroconversion (grouped as above), exposure category and calendar year at risk (as a time-dependent covariate) allowing for late entry [10]. AIDS was defined using the European case definition [11] and follow up was censored on the 31 December 2000. Persons not reported as AIDS to CDSC and SCIEH (the national AIDS reporting centres) by 31 December 2001 were assumed to be AIDS-free on 31 December 2000, thus allowing for a 1 year reporting delay. Persons who had moved abroad ($n=24$) or who had not been seen after January 1990 ($n=13$) were censored on the date they were last assessed in the clinic. Persons who died without AIDS ($n=116$) were censored on the date of death.

We repeated the analyses, restricting this to persons reported prospectively from 1994. We also carried out a sensitivity analysis, restricted to persons with a HIV test interval $\leqslant 12$ months, and measured time from the first positive date, rather than the midpoint.

RESULTS

Of 1820 seroconverters, 476 (26%) were diagnosed with AIDS and 424 (23%) died. The majority of seroconverters were men infected through sex between men (81%). Median year of estimated seroconversion was 1992 (range 1982–2000). Of 1244 individuals with information available on the presence (or absence) of illness at seroconversion, 423 (34%) reported symptoms suggestive of seroconversion illness.

As expected, completeness of reporting absence or presence of a seroconversion illness improved over time with information on illness known for 59% (643/1081) of seroconverters reported retrospectively, compared to 81% (601/739) of seroconverters reported prospectively (Table 1). General, non-specific symptoms accounted for approximately 90% of all events reported and varied little over time. Of interest, 8 (2%) individuals experienced more severe symptoms including AIDS-defining events.

Individuals with a short test interval were more likely to report a seroconversion illness than persons with a long test interval. We found that the shorter our definition of the test interval, the more likely was a seroconversion illness to have been reported compared to a long test interval (Fig. 1), the strongest association occurring at a test interval of $\leqslant 1$ month (OR 7·51, 95% CI 4·95–11·58) but with maximal discrimination of 2–3 months (OR 6·96, 95% CI

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Table 1. *Proportion of persons reporting symptoms compatible with HIV seroconversion illness over time and trends in reports of the most commonly reported symptoms*

	Collected retrospectively		Collected prospectively		
Estimated year of seroconversion …	1982–1990 *n* (%)	1990–1993 *n* (%)	1994–1997 *n* (%)	⩾1998 *n* (%)	Total *n* (%)
Number of individuals	490	591	460	279	1820
No information on seroconversion illness	237	201	118	20	576
Information on seroconversion illness	253	390	342	259	1244
No seroconversion illness reported	193 (76)	270 (69)	210 (61)	148 (57)	821 (66)
Seroconversion illness reported	60	120	132	111	423
Symptoms*	*n* (% of 60)	*n* (% of 120)	*n* (% of 132)	*n* (% of 111)	*n* (% of 423)
'Flu-like illness	12 (20)	29 (24)	35 (27)	40 (36)	116 (27)
Rash, erythema	15 (25)	24 (20)	31 (22)	44 (40)	114 (27)
Chills, fever, night sweats	15 (25)	32 (26)	36 (27)	30 (27)	113 (27)
Lymphadenopathy unspecified	11 (18)	19 (16)	16 (12)	23 (21)	69 (16)
Upper respiratory tract infection	13 (22)	23 (19)	17 (13)	13 (12)	66 (16)
Tiredness, lethargy	9 (15)	12 (10)	21 (16)	17 (15)	59 (14)
Nausea, vomiting, loss of appetite	6 (10)	8 (7)	9 (7)	19 (17)	42 (10)
Gastrointestinal problems	7 (12)	7 (6)	15 (11)	9 (8)	38 (9)
Weight loss, cachexia	6 (10)	8 (7)	6 (5)	3 (3)	23 (5)
Headache	2 (3)	4 (3)	7 (5)	7 (6)	20 (5)
Severe illness†	3 (5)	1 (1)	3 (2)	1 (1)	8 (2)

* Percentages relate to the number of individuals reporting presence of seroconversion illness citing these specific symptoms.
† Oesophageal candida ($n=3$), encephalitis ($n=2$), viral meningitis ($n=2$), bacterial meningitis ($n=1$).

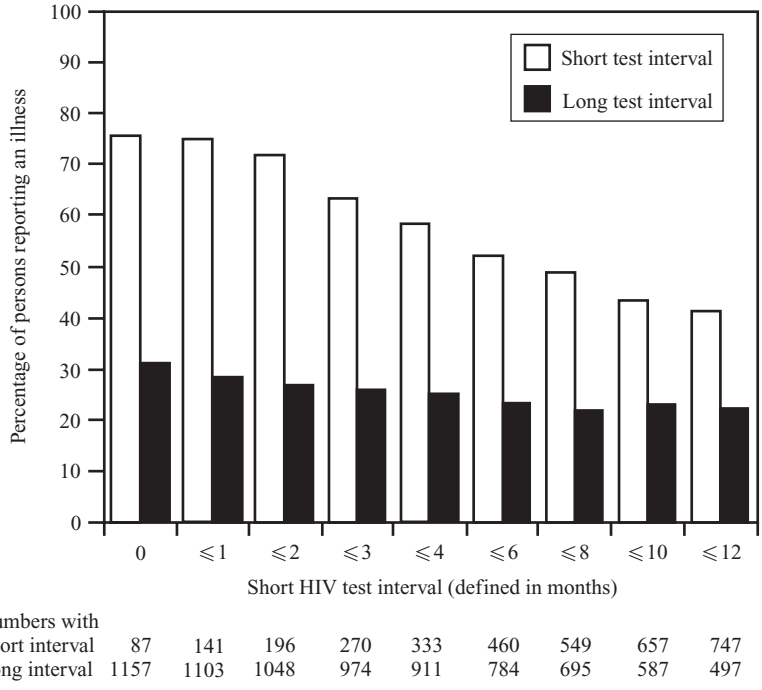

Fig. 1. Proportion of persons reporting an HIV seroconversion illness by varying lengths of HIV test interval ($n=1244$). (Test interval is the interval between the last antibody-negative and first antibody-positive test dates.)

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Table 2. *Factors associated with reporting a HIV seroconversion illness** (*n* = *1244*)

	Univariate			Multivariate*		
Variable	OR	95% CI	*P* value	OR	95% CI	*P* value
HIV test interval						
>2 months	1·00		<0·001	1·00		<0·001
⩽2 months	6·86	4·86–9·68		6·76	4·75–9·62	
Sex						
Male	1·00		0·44	1·00		0·33
Female	1·22	0·74–1·99		1·46	0·68–3·14	
Age group (years)						
16–19	0·56	0·24–1·31	0·002	0·53	0·21–1·30	0·04
20–29	1·00			1·00		
30–39	1·33	1·02–1·75		1·22	0·91–1·63	
40+	1·77	1·25–2·50		1·51	1·04–2·20	
Exposure category						
Sex between men	1·00		0·26	1·00		0·40
Injecting drug use	0·55	0·26–1·16		0·67	0·29–1·52	
Sex between men and women	1·23	0·81–1·86		1·39	0·73–2·64	
Other/unknown	1·30	0·36–4·63		0·71	0·17–2·89	
Year of seroconversion						
1982–1989	1·00		<0·001	1·00		<0·001
1990–1993	1·55	1·06–2·27		1·59	1·05–2·39	
1994–1997	2·16	1·48–3·17		2·10	1·39–3·16	
1998–2000	2·60	1·75–3·87		2·36	1·54–3·63	

* Adjusted for all other cofactors in the table.
OR, odds ratio; CI, confidence interval.

4·90–9·96, and OR 4·95, 95% CI 3·68–6·66 for lengths ⩽2 and ⩽3 months respectively). Thus we used a test interval of ⩽2 months to best approximate the presence of seroconversion illness.

We found that a HIV test interval of ⩽2 months was strongly independently associated with reporting a seroconversion illness after adjusting for other demographic factors (OR 6·76, 95% CI 4·75–9·62) (Table 2). Further, persons seroconverting in the latter periods were also more likely to report a seroconversion illness ($P<0·001$). We found evidence that older individuals were more likely to report an illness ($P=0·04$), but no evidence to suggest that sex or exposure category were associated with reporting a seroconversion illness ($P=0·33$ and 0·40 respectively).

Kaplan–Meier estimates showed that progression to AIDS appeared to be faster in those with a short HIV test interval compared to those with a long test interval (log-rank $P=0·02$). At 10 years following seroconversion we estimated an AIDS-free survival of 68·0 and 73·6% for those with short and long HIV test intervals respectively (Fig. 2).

In assessing the effect of covariates on the risk of AIDS, the HIV test interval was more prognostic than seroconversion illness. We found no evidence of an independent association between seroconversion illness and the risk of AIDS in our cohort ($P=0·82$) (Table 3). In contrast, we found that persons with a short HIV test interval were at a greater risk of AIDS than persons with a long test interval, both univariately [HR (hazards ratio) 1·37, 95% CI 1·04–1·81], and after adjustment for age, seroconversion illness, sex, exposure group and calendar year (HR 1·49, 95% CI 1·11–2·00). Older individuals ($P=0·03$), injecting drugs users (P heterogeneity $=0·04$) and those at risk in more recent calendar years ($P<0·001$) were also significantly associated with the progression to AIDS. Similar results were observed when we restricted the analysis to 739 individuals enrolled prospectively (HR 1·31 for AIDS, adjusted for age, sex, illness, exposure category and calendar year, 95% CI 0·51–3·35).

When we restricted analyses to persons with a HIV test interval of ⩽12 months, we found that persons

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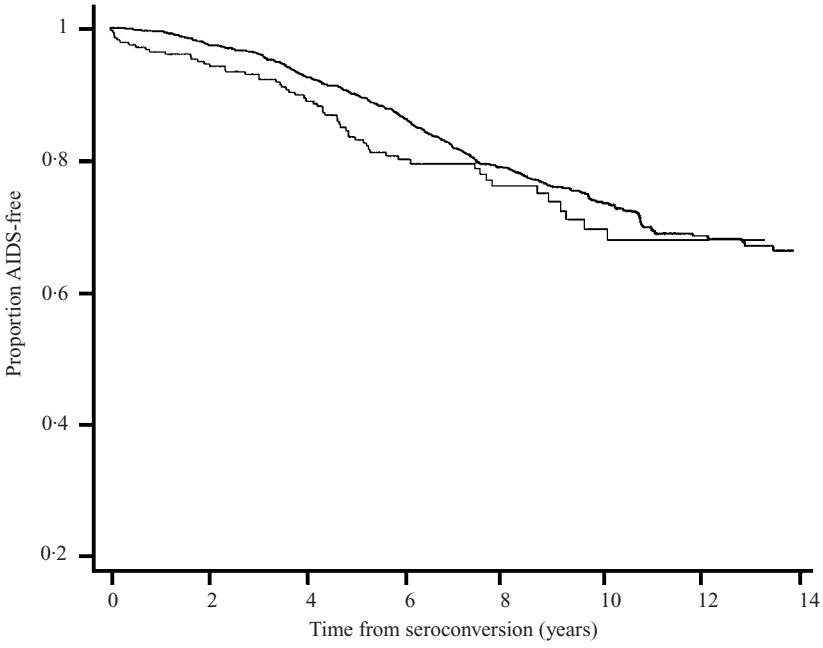
Table 3. *The relationship between seroconversion illness, HIV test interval and progression to AIDS* (n = 1820)*

	HIV test interval excluded from model			HIV test interval included in model		
Variable	HR	95% CI	*P* value	HR	95% CI	*P* value
HIV test interval						
>2 months				1·00		0·01
⩽2 months				1·49	1·11–2·00	
No seroconversion illness	1·00		0·82	1·00		0·98
Seroconversion illness	1·09	0·82–1·45		0·98	0·73–1·31	
Unknown seroconversion illness status	1·01	0·80–1·27		1·01	0·80–1·28	

* Adjusted for sex, age group, exposure category and calendar year at risk.
HR, hazards ratio; CI, confidence interval.



At risk

Interval > 2 months	1517	1291	1067	760	483	255	123	63 (upper line)
Interval ⩽ 2 months	237	176	134	88	54	28	11	6 (lower line)

Fig. 2. Kaplan–Meier graph of progression from seroconversion to AIDS by HIV test interval length, adjusted for age.

with a short test interval had a similarly increased risk of AIDS, whether time was measured from the positive date (HR 1·46, 95% CI 1·06–2·03) or the midpoint (HR 1·52, 95% CI 1·10–2·11).

DISCUSSION

We found a strong association between HIV test interval and the presence of seroconversion illness in persons enrolled on the UK Register, this was consistent with our hypothesis that persons with symptoms compatible with seroconversion illness are more likely to seek medical advice and/or request a repeat test closer to the negative test than usual. We also found that older individuals and those who seroconverted more recently were more likely to report an illness. This is likely to reflect a more heightened suspicion of HIV in older persons and those infected more recently, when they present with illness suggestive of HIV seroconversion. It may also be due to a more complete ascertainment of illness in recent years.

We also found that the length of the HIV test interval was associated with progression to AIDS.

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It seems likely that this association reflects the previously documented relationship between seroconversion illness and disease progression [2, 4, 5] and that using a HIV test interval of $\leqslant 2$ months best captures this relationship. We did not find an effect of seroconversion illness in our model, probably because of incomplete information on seroconversion illness in our cohort. As many as 41% of persons who seroconverted prior to 1994, before the study was established, had no information documented on illness. Further, even when data are collected prospectively, the report of symptoms is subject to recall bias for individuals at the time of a positive test. Symptoms reported were also general (e.g. ''flu-like' symptoms and rash) and non-specific, although they varied substantially between individuals but changed little over time. Furthermore, it may not simply be the presence or absence of illness, but its symptoms and duration, which influence disease progression. Pedersen et al. [4] reported that persons with an acute illness lasting 14 days or longer, progressed to AIDS more rapidly than those who were free of symptoms or had a mild illness. It is not possible to consider a link between severity of symptoms at seroconversion and progression to AIDS [4, 12] in terms of using the test interval as a proxy, because numbers with severe illness are too small (Table 1). The inability to account for specific symptoms, a level of detail that is not readily available in most centres, may have masked the effect of illness on disease progression.

In adjusting for late entry, we minimize bias and confounding from persons with short test intervals presenting earlier in infection. Clearly however, individuals with a short test interval are unlikely to have all presented due to the manifestations of symptomatic seroconversion. This population may also include people who are frequently tested because they perceive themselves at risk of HIV infection. If these individuals progress more rapidly to AIDS, for example due to co-infection with other sexually transmitted infections, the estimated effect of a HIV test interval of $\leqslant 2$ months could be an over-estimate of the effect of interest, namely the effect of seroconversion illness.

Furthermore, because individuals may be more likely to seek testing after a high risk event, seroconversion may have actually occurred closer to the date of the positive antibody test rather than the midpoint between negative and positive test dates. This may lead to an over-estimation of the time to AIDS for persons with a longer HIV test interval, and thus the association between test interval length and time to AIDS found here may be an artefact. This is unlikely, however, as results from the sensitivity analysis measuring time from the midpoint between tests were comparable to those measuring time from the first positive test date.

Conversely, patients with symptoms of acute primary infection may not have presented at a clinic immediately, for example, if symptoms were mild or if seroconversion illness was not initially thought to be HIV-related. An increased risk of progression to AIDS in this population would imply that the estimated effect of a short test interval could underestimate the true effect of seroconversion illness. Prospective studies have suggested that the relationship between seroconversion illness and faster disease progression may be due to higher or more variable HIV RNA levels [13, 14] or because the seroconversion illness itself is AIDS-defining [15]. We have not considered such explanatory pathways here.

Our findings highlight the difficulties in collecting information on seroconversion illness both retrospectively and prospectively. They also demonstrate that in the absence of well-recorded or complete information on seroconversion illness, the HIV test interval is an important factor for analyses of disease progression.

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REFERENCES

1. Cooper DA, Gold J, Maclean P, et al. Acute AIDS retrovirus infection. Definition of a clinical illness associated with seroconversion. Lancet 1985; **325**: 537–540.
2. Dorrucci M, Rezza G, Vlahov D, et al. Clinical characteristics and prognostic value of acute retroviral syndrome among injecting drug users. AIDS 1995; **9**: 597–604.
3. Kinloch-de Loës, de Saussure P, Saurat JH, et al. Symptomatic primary infection due to human immunodeficiency virus type 1: review of 31 cases. Clin Infect Dis 1993; **17**: 59–65.
4. Pedersen C, Lindhardt BO, Jensen BL, et al. Clinical course of primary HIV infection: consequences for subsequent course of infection. BMJ 1989; **299**: 154–157.
5. Lindback S, Brostrom C, Karlsson A, Gaines H. Does symptomatic primary HIV-1 infection accelerate

progression to CDC stage IV disease, CD4 count below 200×10^6/I, AIDS, and death from AIDS? BMJ 1994; **309**: 1535–1537.
6. CASCADE Collaboration. The relationships between HIV test interval, demographic factors and HIV disease progression. Epidemiol Infect 2001; **127**: 91–100.
7. UKRHS Steering Committee. The UK Register of HIV Seroconverters: methods and analytical issues. Epidemiol Infect 1996; **117**: 305–312.
8. UKRHS Steering Committee. The AIDS incubation period in the UK estimated from a national register of HIV Seroconverters. AIDS 1998; **12**: 659–667.
9. Cox DR, Oakes D. Analysis of survival data. London: Chapman and Hall, 1991.
10. Clayton C, Hills M. Statistical models in epidemiology. Oxford: Oxford University Press, 1993.
11. Ancelle-Park RA. European AIDS definition. Lancet 1992; **229**: 671.
12. Vanhems P, Lambert J, Cooper DA, et al. Severity and prognosis of acute immunodeficiency virus type I illness: a dose-response relationship. Clin Inf Dis 1998; **26**: 323–329.
13. Daar ES, Moudgil T, Meyer RD, Ho DD. Transient high levels of viremia in patients with primary human immunodeficiency type 1 infection. N Engl J Med 1991; **324**: 961–964.
14. Schacker TW, Hughes JP, Shea T, Coomb RW, Corey L. Biological and virological characteristics of primary infection. Ann Intern Med 1998; **128**: 613–620.
15. Vento S, Di Perri G, Garofano T, et al. Pneumocystis carinii pneumonia during primary HIV-1 infection. Lancet 1993; **342**: 24–25.