Susceptibility to AIDS progression appears early in HIV infection

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To investigate whether predictors of AIDS progression are operative very early in the natural history of HIV infection, we conducted a nested case-control study within a cohort of 119 subjects who seroconverted while under observation in a prospective study of homosexual men. For each of the 18 cases who have progressed to AIDS, we randomly selected three controls who had seroconverted within 3 months of the case but who have remained AIDS-free. Cases and controls were compared with regard to laboratory and clinical parameters obtained at the time of the earliest HIV-positive result. The median duration between the estimated date of seroconversion and this first positive result was 4 months for cases and 6 months for controls. Cases exhibited lower CD4 counts (657 versus 774 × 10^6/l; $P = 0.037$), lower CD4:CD8 ratios (0.98 versus 1.39; $P = 0.003$), higher immune complex levels (C1q binding: 25 versus 15%; $P = 0.002$), lower hemaglobin concentrations (14.8 versus 15.2 g/l; $P = 0.011$), higher immunoglobulin (Ig) A levels (272 versus 184 mg/dl; $P = 0.003$), and higher IgG levels (1530 versus 1300 mg/dl; $P = 0.037$) than controls. Cases exhibited higher CD8 counts of marginal statistical significance (732 versus 597 × 10^6/l; $P = 0.059$). No differences were observed with respect to IgM levels, total lymphocyte or white blood cell counts, or the frequency of generalized lymphadenopathy. A total of 27.8% of cases but only 11.5% of controls reported one or more symptoms during the 6-month period preceding the first positive visit ($P = 0.027$). We conclude that laboratory and clinical abnormalities which are predictive of more rapid progression to AIDS may appear very early in HIV infection. This suggests that some of the factors responsible for more rapid disease progression are present in the host prior to or shortly after infection occurs.

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Introduction

A clearer picture of the natural history of infection with HIV-1 has recently begun to emerge. The rate at which infected people progress to AIDS has now been modelled in several populations [1–4]. Moreover, several markers associated with an increased risk of AIDS progression have now been identified and confirmed in a range of settings [5–8]. Clearly, the ability to identify those infected people at highest risk of developing AIDS within a given time period has important implications not only for individual patient management but for the design of clinical trials of agents aimed at preventing or deterring disease progression. Unfortunately, most of the data regarding these predictors have been derived from so-called 'seroprevalent' populations whose members have been

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infected for an unknown duration of time. As a result, in addition to other methodological problems, these data have shed little light on whether these predictors are operative at early stages of HIV infection. We have followed a seroincident cohort of 119 homosexual men, that is a group who seroconverted while under observation in our prospective study. We report here data indicating that an increased susceptibility to more rapid progression to AIDS begins to appear very early in the natural history of HIV infection.

Methods

A total of 729 homosexual men were recruited from the existing patient rolls of six general practitioners in central Vancouver between November 1982 and December 1984. Between enrolment and September 1986, subjects returned to their physicians approximately every 6 months and thereafter annually. Each visit included a self-administered questionnaire, a complete physical examination, and immunological and HIV-antibody testing. Subjects may also have had HIV-antibody testing between study visits at the discretion of their physician.

As of July 1989, we have documented a total of 119 seroconversions in 477 subjects who were seronegative at enrolment. These 119 subjects comprise the 'seroincident' cohort which forms the basis for this report. The date of seroconversion for these 119 subjects was estimated using the mid-point between their last negative and first positive HIV antibody test result. Cases of AIDS in this cohort were diagnosed according to Centers for Disease Control (CDC) criteria and reported by their physicians. In addition, for complete case ascertainment, a manual record linkage was undertaken with the Canadian Federal Centre for AIDS national registry. The cumulative progression to AIDS in the seroincident cohort was plotted using Kaplan–Meier methods [9].

Three members of the seroincident cohort who had not progressed to AIDS as of July 1989, denoted controls, were matched to each case on the basis of date of seroconversion to within 3 months. The selection of controls for each case was carried out randomly from all those who met the matching criteria. Laboratory and clinical data for the cases and controls were obtained from the first positive visit following seroconversion. Data regarding symptoms pertained to self-reported symptoms in the 6-month period prior to the first positive visit. The presence of generalized lymphadenopathy, defined as the presence of nodes >1 cm in diameter at two or more non-inguinal sites, was determined by the physician at the first positive visit. Comparisons of laboratory variables between cases and controls were carried out using a paired t-test in which each case was compared with the mean of the corresponding controls [10]. Data regarding generalized lymphadenopathy and symptoms were analyzed using Mantel–Haenszel methods for matched data [11]. Matched sets which did not contain three controls due to missing data for a variable of interest were excluded from analyses involving that variable. All reported P values are one-sided as the direction of the association with each parameter was prespecified based on available evidence.

Results

As of July 1989, a total of 18 cases of AIDS had been diagnosed in the seroincident cohort. The manual linkage with the federal registry confirmed all 18 cases and revealed no additional cases in this cohort not already known to us. The 18 cases consisted of 10 cases of *Pneumocystis carinii* pneumonia, three cases of Kaposi's sarcoma, three cases of other opportunistic infections, and one case of lymphoma. Figure 1 shows the Kaplan–Meier curve for progression to AIDS in the seroincident cohort. The estimate for the cumulative progression to AIDS at 76 months following seroconversion is 36.6% (±15.0). As seen in Fig. 1, the diagnosis of AIDS in the 18 cases ranged from 19 to 73 months following seroconversion with a median of 40 months.

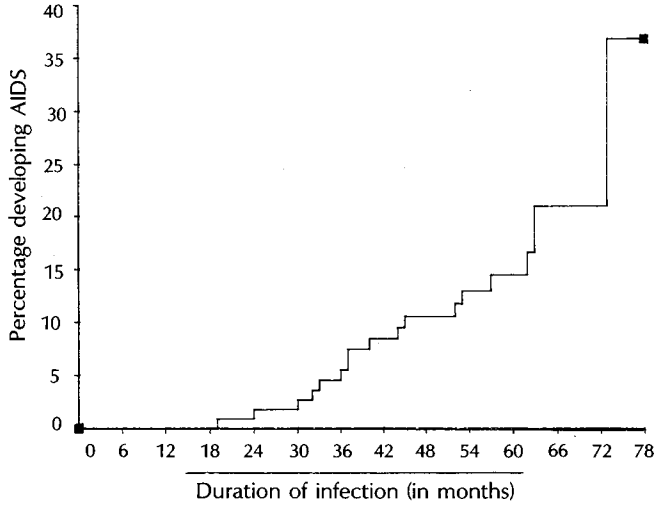

Fig. 1. Kaplan–Meier curve for progression to AIDS by months following seroconversion in a subgroup of 119 seroconverters within a cohort of homosexual men.

Accordingly, these 18 cases and 54 controls were included in the comparative analysis. The median duration between the estimated date of seroconversion and the first positive result was 4.0 months for cases (range:1–18) and 6.0 months for controls (range:1–23) with this difference being non-significant ($P = 0.44$). Laboratory and clinical data from the first positive visit were obtained a median of 34 months (range:16–60) prior to diagnosis for the cases. Controls were AIDS-free for a median of

57 months (range:11–74) from the date of the first positive result to July 1989.

Table 1 presents a comparison between cases and controls with respect to lymphocyte subset results obtained at the first positive visit. Differences were observed with respect to CD4 counts and CD4:CD8 ratios. In particular, cases had a mean CD4 count of 657 × 10^6/l compared to 774 × 10^6/l in the controls ($P = 0.037$). Similarly, mean CD4:CD8 ratios were significantly lower in the cases (0.98 versus 1.39; $P = 0.003$). Cases exhibited higher CD8 counts than controls (732 versus 597) but this difference was only of marginal statistical significance ($P = 0.059$). No differences were observed with respect to total lymphocyte or white blood cell counts.

As seen in Table 2, cases had significantly higher immune complex levels than did controls (C1q binding: 25 versus 15%; $P = 0.002$) and exhibited significantly lower hemoglobin concentrations (14.8 versus 15.2; $P = 0.011$). Cases also had significantly higher immunoglobulin (Ig)A (272 versus 184 mg/dl; $P = 0.003$) and IgG levels (1530 versus 1300 mg/dl; $P = 0.037$). No differences were observed with respect to IgM levels.

Table 3 summarizes the results of analyses for generalized lymphadenopathy and symptoms. Similar proportions, namely 61.1% of cases and 60.4% of controls, were found to have had generalized lymphadenopathy at the first positive visit ($P = 0.352$). There was evidence, however, of increased risk associated with symptoms in the 6-month period prior to the first positive visit. A total of 27.8% of cases, but only 11.5% of controls, reported one or more symptoms during this period ($P = 0.027$), giving rise to an odds ratio of 3.7. No single symptom attained statistical significance but the individual prevalences were low.

Table 3. Comparison of clinical parameters from earliest seropositive visit in 18 seroincident cases and 54 seroincident controls.

Cases (%)	Controls (%)	Odds ratio*	P†
Generalized lymphadenopathy			
11/18 (61.1%)	32/53 (60.4%)	2.0	0.352
One or more symptoms‡			
5/18 (27.8%)	6/52 (11.5%)	3.7	0.027

*Mantel–Haenszel estimate based on 1:3 matching with dichotomous exposure. P† value based on Mantel–Haenszel chi-square statistic for matched data with correction for continuity. ‡Includes fatigue, fever, night sweats, unintentional weight loss, diarrhea, arthralgia, cough (unrelated to smoking), shortness of breath, oral thrush and herpes zoster.

Discussion

The evidence is mounting that in the absence of therapy the proportion of HIV-infected people who will ultimately progress to develop AIDS is close to 100% and that the median time from infection to diagnosis is in the region of 8–10 years [1,6]. If the proportion progressing is truly that high, then clinical prediction must confine itself not to delineating those who will progress to AIDS from those who will not, but rather to delineating those who will demonstrate more rapid progression from

Table 1. Comparisons of lymphocyte subset results from earliest seropositive visit in 18 seroincident cases and 54 seroincident controls.

	Cases		Controls		
Variable	Mean	s.d.	Mean	s.d.	P value*
CD4 count (10^6/l)	657	158	774	186	0.037
CD8 count (10^6/l)	732	304	597	155	0.059
CD4:CD8 (ratio)	0.9	0.33	1.3	0.30	0.003
Lymphocytes (10^6/l)	2126	444	2105	437	0.445
White blood cells (10^6/l)	5700	976	6040	1109	0.210

*P value (one-sided) based on paired t-test.

Table 2. Comparison of other laboratory parameters from earliest seropositive visit in 18 seroincident cases and 54 seroincident controls.

	Cases		Controls		
Variable	Mean	s.d.	Mean	s.d.	P value*
Immune complexes (C1q%)	25	9	15	9	0.002
Hemoglobin (g/l)	14.8	7.4	15.2	3.3	0.011
IgA (mg/dl)	272	104	184	35	0.003
IgG (mg/dl)	1530	323	1300	262	0.037
IgM (mg/dl)	150	71	137	29	0.266

*P value (one-sided) based on paired t-test. Ig, immunoglobulin.

those who will progress more slowly. Similarly, attempts to detect host susceptibility factors and disease cofactors may be confined to the identification of variables associated not with disease itself but simply with a proclivity to more rapid disease progression. However, the question of universal progression might never be satisfactorily clarified. The ultimate proportion and rate of AIDS progression may no longer be observable in the natural state with the advent of therapies which are being utilized at earlier stages of HIV infection and which are already delaying clinical deterioration and altering progression rates [12]. In the absence of a definitive answer, the terms predictors, susceptibility factors, and cofactors will refer to variables associated with more rapid disease progression which might therefore be utilized to identify people at higher risk of developing AIDS within a given time interval.

While the natural history of HIV infection remains the subject of considerable current interest, our understanding of the full course of this infection has been hindered by the lack of complete data on various infected populations that have been studied. Cohorts in which the time of infection is known for each subject, denoted seroincident cohorts, have provided the best data on the rate of progression to AIDS [3,4], but laboratory and clinical data to identify predictors are often lacking in such groups. On the other hand, seroprevalent cohorts, in whom duration of infection is unknown, have provided the best data regarding clinical predictors of AIDS progression. Decreases in the CD4 cell count and the related CD4:CD8 ratio have now been established in numerous reports as the hallmark predictors of AIDS progression [5–8, 13–15]. Among numerous other poor prognostic indications that have also been reported are the presence of HIV antigenemia [5,6,13], loss of anti-p24 antibody [13,16], human T-lymphotropic virus coinfection [17], lowered hemoglobin concentration [5–7,14,18], decreased platelet count [5,7,14], and elevations in IgG [7], IgA [5–7,19,20], CD8 count [5], serum beta$_2$-microglobulin (β_2-M) [6,21,22], cytomegalovirus antibody titer [5], serum and urine neopterin [23–25] and erythrocyte sedimentation rate [6,18].

Although these different laboratory markers have been associated with progression to AIDS in cross-sectional studies or, at best, in longitudinal studies of seroprevalent populations, two fundamental questions remain unanswered. The first is whether a given marker is truly indicative of an increased host susceptibility to AIDS or is simply acting as a surrogate for duration of infection. Indeed, any laboratory marker which changes predictably with time will automatically demonstrate predictive value for progression to AIDS in populations whose duration of infection is unknown and varied. A related question is whether the predictive value of a given marker is truly independent or whether it arises simply by virtue of correlation with established predictors. These questions have been partially addressed in the past using multivariate analyses. In such analyses, the predictive value of a given laboratory marker is adjusted by other predictors including a known time-dependent variable such as the CD4 count which is taken to act as a surrogate for duration of infection [5–7]. Such analyses provide partial assurance of a direct predictive association, but the present data provide more compelling evidence of a true host susceptibility by confirming associations between classical markers and increased progression to AIDS in a population in which time since seroconversion has been controlled.

The second question not addressed in most previous studies concerns how early in the course of HIV infection a laboratory marker becomes predictive. The associations we detected between AIDS progression and alterations in CD4 cell count, CD4:CD8 ratio, hemaglobin, immune complexes, IgG, and IgA are consistent with previous reports from seroprevalent populations [5–7,13–15,19,20]. However, the present findings also suggest that as early as 4 months after the estimated date of seroconversion, these laboratory markers may already be predictive of more rapid progression to AIDS. It is noteworthy, although of marginal statistical significance, that we found elevated CD8 counts to be associated with progression. A similar association has been found in some studies [5,6] but not in others, including our own seroprevalent cohort [7,26]. It is also of note that generalized lymphadenopathy did not appear to be associated with progression to AIDS as has been the case in most large prospective studies to date [5–7]. This calls into question whether generalized lymphadenopathy should be regarded as a poor prognostic sign, and whether it should be incorporated into HIV staging systems such as the current CDC classification.

Additionally, we have found that the occurrence of symptoms around the time of seroconversion is associated with an increased rate of progression to AIDS. The timing and nature of our questionnaires do not allow a definitive characterization of these early symptoms as a seroconversion illness. Nevertheless, our data are consistent with a recent report from Denmark [27], suggesting that those individuals who experienced an acute illness associated with seroconversion have a more rapid progression to AIDS than those who did not.

One important caveat in this and many other studies concerns the use of time of seroconversion to approximate the time of infection. Recent studies have suggested that long latency periods between infection and seroconversion can occur in an appreciable proportion of people [28,29]. Although we matched our cases and controls with respect to time of seroconversion, it is conceivable that the cases were actually infected longer than the controls by virtue of having had longer latency periods. If so, then we have not adequately controlled for duration of infection and our observed associations might still be confounded by this time factor. Even so, this would not deny the practical observation that early laboratory markers are present soon after seroconversion. Moreover, one would have to postulate that longer latency periods are associated with an increased risk of early progression to AIDS. If so, then failure to seroconvert soon after infection would in turn itself represent a marker of host sus-

ceptibility to AIDS already present by the time of serconversion.

Based on our data, we hypothesize that at least some of the factors responsible for more rapid disease progression are present in the host prior to or shortly after HIV infection. This conflicts somewhat with the concept that risk of more rapid progression to AIDS is determined primarily by cofactors that operate well after HIV infection has been established. These pre-existing or early cofactors could be related to genetics [30,31], to high initial viral 'load' [32], and/or to biological properties of the HIV variants involved [33] among others.

We recognize that the predictive value of the early markers we have identified must await prospective evaluation. However, the present data provide the possibility of using laboratory markers shortly after seroconversion to identify hosts who are at increased risk of more rapid progression to AIDS. This has clear implications for the design of inevitable future clinical trials involving subjects in the earliest stages of HIV infection, and for future management strategies involving the immediate or early initiation of therapy in such recently infected high-risk people.

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