Clinical course of primary HIV infection: consequences for subsequent course of infection

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Abstract

***Objective*—To investigate the impact of the clinical course of the primary HIV infection on the subsequent course of the infection.**

***Design*—Prospective documenting of seroconversion, follow up at six month intervals, and analysis of disease progression by life tables.**

***Patients*—86 Men in whom seroconversion occurred within 12 months.**

***Primary outcome measure*—Progression of HIV infection, defined as CD4 lymphocyte count $<0{\cdot}5\times10^9$/l, recurrence of HIV antigenaemia, or progression to Centers for Disease Control group IV.**

***Main results*—Median follow up was 670 (range 45-1506) days. An acute illness like glandular fever occurred in 46 (53%) subjects. Three year progression rates to Centers for Disease Control group IV was 78% at three years for those who had longlasting illnesses (duration $\geqslant$14 days) during seroconversion as compared with 10% for those who were free of symptoms or had mild illness. All six patients who developed AIDS had had longlasting primary illnesses. Three year progression rates to a CD4 lymphocyte count $<0{\cdot}5\times10^9$/l and to recurrence of HIV antigenaemia were significantly higher for those who had longlasting primary illnesses than those who had no symptoms or mild illness (75% *v* 42% and 55% *v* 14%, respectively).**

***Conclusion*—The course of primary infection may determine the subsequent course of the infection.**

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Introduction

The clinical course of HIV infection with respect to factors that may predispose to or promote the development of symptoms is largely unknown. Several factors, including immunological and virological variables, have been reported to predict disease progression.[1-7] Most of these variables seem to be consequences of infection or markers of the duration of infection rather than determinants of disease progression, and it should be emphasised that cofactors for disease progression have not yet been found.

Most cohort studies so far have been performed with patients positive for HIV but without known time of seroconversion whereas longitudinal studies of those with known dates of seroconversion are scarce. We report on the clinical course of HIV infection in 86 men in whom the time of becoming positive for HIV antibody was known and relate disease progression to the clinical course of the primary infection.

Patients and methods

The study population was a group of 86 men seen at AIDS screening clinics in Copenhagen who became positive for HIV antibody within 12 months. All had had a negative test for HIV antibody followed by a confirmed positive test for HIV antibody. Seventy six were homosexual men, four were intravenous drug abusers, two were haemophiliacs, and four were heterosexuals. The median age was 30 (range 14-59) years.

Seroconversion was documented prospectively through repetitive HIV testing at the screening clinics in the period November 1984 to August 1988.[8] Everyone had a physical examination and was given a standardised questionnaire by an interviewer that sought information on illnesses within the previous three months.[9] The result of the antibody test was not known at the time of the interview. The study group made up about 15% of all subjects positive for HIV followed at the Copenhagen AIDS screening clinics; it included all known to have become seropositive within 12 months.

The date of seroconversion was calculated as the midpoint of the dates of the last test result negative for HIV and the first confirmed positive result or, when possible, taken as the date of the serum sample positive for HIV antigen and negative for HIV antibody or the sample positive for p24 antibody and negative for HIV antibody on enzyme linked immunosorbent assay (ELISA). The median interval between the last negative and the first positive test for HIV antibody was 108 (range 6-392) days. For one subject the interval exceeded 12 months, but a serum sample positive for HIV antigen was available from the intervening period. Three patients became positive for HIV antibody in 1984, 35 in 1985, 22 in 1986, 18 in 1987, and eight in 1988.

Antibody to HIV was determined by ELISA and serum samples were confirmed as positive by an immunoblot method.[10] When available, stored serum samples were tested for HIV antigen.[11] All subjects had serological tests for syphilis, cytomegalovirus infection, and hepatitis B. T cell subsets were determined about every six months with monoclonal antibodies.[5]

During follow up the subjects were seen about every six months. At each visit they were interviewed about symptoms related to infection with HIV and given a physical examination.

Disease was classified according to the Centers for Disease Control classification system for HIV infection,[12] and AIDS was defined according to the Centers for Disease Control revised surveillance definition.[13] Generalised lymphadenopathy was defined as the presence of lymph nodes with a diameter >1 cm at two or more extrainguinal sites. Clinical signs of immune deficiency during the acute HIV infection (oral thrush, oesophageal candidiasis, or herpes zoster) were regarded as part of the acute illness (Centers for Disease Control group I).

A primary illness was defined as an acute onset febrile illness lasting for at least three days in association with seroconversion. A longlasting illness was arbitrarily defined as an illness with fever lasting 14 days or more. The following were chosen as criteria of progression of HIV infection: CD4 lymphocyte count $<0{\cdot}5\times10^9$/l, recurrence of HIV antigenaemia, or progression to Centers for Disease Control group IV.

Life tables were used to analyse progression, in-

cluding progression to a CD4 lymphocyte count $<0{\cdot}5\times10^9$/l and recurrence of HIV antigenaemia, and were compared by the log rank test.[14] Within subject changes in CD4 lymphocyte counts were analysed by the Wilcoxon one sample rank sum test. All significance levels correspond to those for two tailed tests.

Results

Median follow up from estimated date of seroconversion was 670 (range 45-1506) days. Eight (9%) of the 86 subjects were lost to follow up a median of 269 (range 47-833) days after the estimated date of seroconversion.

ACUTE CLINICAL ILLNESS

Forty six (53%) subjects had an acute clinical illness associated with seroconversion, and of these 27 had a longlasting primary illness. The symptoms and clinical signs are presented in table I. The median duration of acute illness was 16 (range 4-56) days. Twenty two (44%) of 50 subjects who were examined for HIV antigen at seroconversion were temporarily positive for HIV antigen. There was no significant difference between subjects with longlasting primary illnesses and those with mild illness or no symptoms in regard to HIV antigenaemia at seroconversion (50% and 41% respectively). No subject had serological evidence of syphilis, recent infection with hepatitis B virus, or cytomegalovirus.

TABLE I—*Clinical signs and symptoms associated with primary HIV infection in 86 men who became positive for HIV antibody*

	No (%) with symptom	Median (range) duration of symptom (days)
No primary illness	40 (47)	
Primary illness	46 (53)	16 (4-56)
Fever	46 (53)	16 (4-56)
Generalised lymphadenopathy	36 (42)	
Trunk rash	21 (24)	9 (5-40)
Sore throat	31 (36)	10 (4-32)
Oral thrush	9 (10)	14 (7-30)
Dry cough	19 (22)	8 (3-14)
Arthralgia or myalgia	16 (19)	14 (3-28)
Weight loss	11 (13)	21 (14-30)
Diarrhoea	9 (10)	7 (2-21)
Encephalitis	4 (5)	10 (3-21)
Oesophageal candidiasis	2 (2)	
Herpes zoster	1 (1)	
Glomerulonephritis	1 (1)	
Pneumonitis	2 (1)	
Anal ulceration	1 (1)	

CHANGES IN T CELL SUBSETS AND RECURRENCE OF HIV ANTIGENAEMIA

T cell subset counts were available for 84 subjects. Of these, 17 (20%; 95% confidence interval 11% to 35%) had progressed to a CD4 lymphocyte count $<0{\cdot}5\times10^9$/l at one year, 29 (35%; 22% to 48%) at two years, and 47 (56%; 35% to 77%) at three years. Stored serum samples collected during follow up were available from 70 subjects, and HIV antigenaemia recurred in five (7%; 0% to 13%) at one year, 14 (20%; 8% to 32%) at two years, and 18 (26%; 9% to 44%) at three years. Both recurrence of HIV antigenaemia and progression to CD4 lymphocyte count $<0{\cdot}5\times10^9$/l were significantly associated with a longlasting primary illness (table II).

We also compared changes in the absolute number of CD4 lymphocytes after seroconversion (fig 1). At baseline and at six month follow up there was no significant difference in the CD4 cell count between the groups, but during the second year after seroconversion the CD4 cell count decreased significantly in the group with longlasting illness in association with seroconversion whereas it remained stable in those who had mild illness or no symptoms during seroconversion.

TABLE II—*Progression to CD4 lymphocyte count $<0{\cdot}5\times10^9$/l and recurrence of HIV antigenaemia related to clinical course of primary infection*

Duration of primary illness (days)	Three year progression* (95% confidence interval)	Significance†
	CD4 lymphocyte count $<0{\cdot}5\times10^9$/l	
≥14 days (n=26)	75% (45% to 100%)	
<14 days (n=58)	42% (23% to 73%)	p=0·009
	Recurrence of HIV antigenaemia	
≥14 days (n=24)	55% (25% to 84%)	
<14 days (n=46)	14% (0% to 31%)	p=0·036

*Analysed by life tables.
†Log rank test.

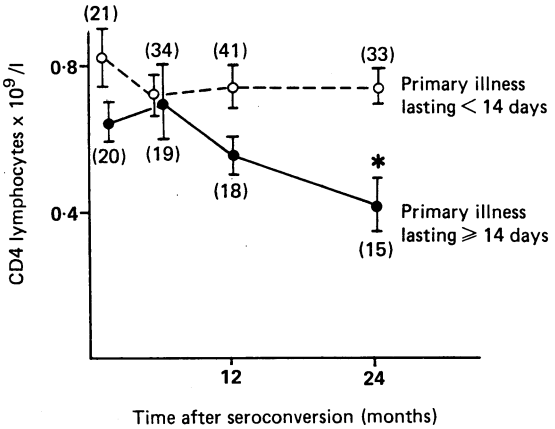

FIG 1—*Changes in CD4 lymphocyte count during 24 months of follow up related to clinical course of primary infection. Bars show mean and standard error; number of analyses is shown in parentheses. Asterisk indicates significant difference compared with baseline values ($p<0{\cdot}05$)*

DISEASE PROGRESSION TO CENTERS FOR DISEASE CONTROL GROUP IV

Eighteen (21%) of the patients progressed to Centers for Disease Control group IV. Disease was manifested by constitutional symptoms in two patients, minor opportunistic infections in 11 (seven with oral thrush, one with hairy leucoplakia, three with herpes zoster), and AIDS associated opportunistic infections in five (four with *Pneumocystis carinii* pneumonia, one with oesophageal candidiasis). The overall actuarial progression rate to group IV was 35% (95% confidence interval 13% to 58%) at three years.

Disease progression was significantly associated with the duration of symptoms during seroconversion ($p<0{\cdot}001$) (fig 2). The three year progression rate was 78% (52% to 100%) for subjects with longlasting

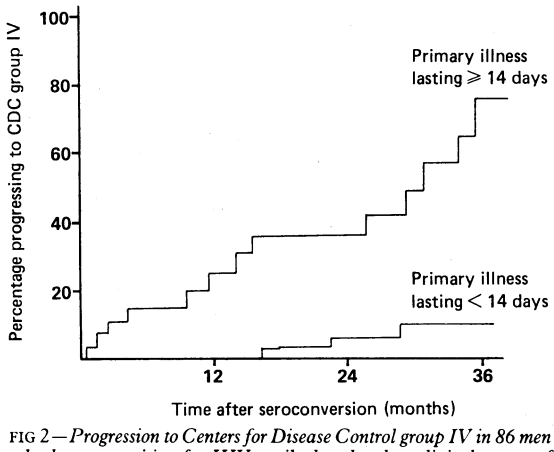

FIG 2—*Progression to Centers for Disease Control group IV in 86 men who became positive for HIV antibody related to clinical course of primary infection. Life tables were used to analyse disease progression and were compared by log rank test*

primary illnesses compared with 10% (0% to 28%) for those who were symptom free or had mild illness during seroconversion.

Six (7%) patients developed AIDS, which was manifested as *Pneumocystis carinii* pneumonia in five and oesophageal candidiasis in one. All of the patients who developed AIDS had longlasting primary illnesses associated with seroconversion.

Discussion

This study found a significant relation between the course of the primary HIV infection and the long term outcome of the infection. The risk of developing AIDS related disease (Centers for Disease Control group IV) within three years of seroconversion was eight times higher for subjects with a longlasting acute illness during seroconversion than for those who were symptom free or had only mild symptoms during seroconversion (78% *v* 10%).

This is the first report to describe an association between the severity of the primary infection and the subsequent course of the HIV infection. It is therefore crucial to consider if any factors may have biased this observation. Our study population was not chosen from a well defined cohort of subjects initially negative for HIV antibody, which means that subjects with symptoms related to HIV (primary illness or generalised lymphadenopathy) probably made up a fairly large proportion of the group. As all participants were in Centers for Disease Control groups I-III at entry, and as information about primary symptoms was obtained near the time of seroconversion, the comparison of clinical outcome in subjects with or without a symptomatic primary illness was not biased by our study design.

A longlasting primary illness was defined as an illness with a duration of at least 14 days. This time limit was chosen arbitrarily, but it must be emphasised that the relation between the severity of the primary illness and the subsequent risk of developing other symptoms related to HIV remained significant no matter what point between 0 and 14 days was chosen to distinguish between a longlasting and a mild primary illness (results not shown). This relation between the course of the primary HIV infection and the long term outcome of the infection indicates that the factors that determine the clinical response to the primary infection also determine the subsequent course of the infection.

During the initial phase of the infection many types of cells are infected, including monocytes, macrophages, microglial cells, and CD4 lymphocytes. The infection with HIV is persistent and life long, and it is believed that progressive disease is a consequence of a gradual rise in viral replication (from macrophages and monocytes) with a resultant increase in the number of latently infected CD4 lymphocytes, which on activation produce large amounts of virus and are subsequently killed.[15] If this model for progressive disease is valid, both the kind of tissues infected and the number of cells infected during the initial phase may influence the subsequent course of the infection. Factors that could determine viral spread during the primary infection include the viral inoculum, the route of infection, the immune state of the person who is exposed, and the host response to the primary infection. A severe primary illness could reflect the elicitation of a vigorous humoral or cellular immune response, or both, directed against HIV and the resultant formation of antigen-antibody complexes and release of lymphokines. Such an activation of the immune system could create a fertile ground for HIV replication.[15]

Conversely, a severe primary illness could be related to an early and extensive spread of the virus owing to a defective host immune response. One of our patients was treated with prednisolone at the time of seroconversion and developed AIDS two months after seroconversion. This case, which has been reported elsewhere,[16] and reports on disease progression in children,[17] in elderly patients who received blood transfusions,[1] and in people who were immunocompromised at exposure[18] indicate that immune state may influence the subsequent outcome of the HIV infection.

The primary infection with HIV has been reported to occur both symptomatically[19-21] and asymptomatically.[22,23] In our study 46 (53%) subjects reported an acute illness during the interval between negative and positive results on tests for HIV antibody. This high incidence of clinical illness associated with seroconversion is in accordance with an Australian and a Dutch series[21,24] but not with series from the United Kingdom and Canada.[22,23] We may have overestimated the incidence as patients with an acute disease may have been more likely to seek medical advice. On the other hand, their failure to recall trivial symptoms may have resulted in underreporting of mild primary illnesses. In contrast with other series, a fairly large proportion of our subjects who became positive for HIV antibody had clinical signs of immune deficiency such as oral thrush and oesophageal candidiasis.[25] These manifestations were not persistent and probably reflect a transient immune suppression, as is seen on infection by other lymphocytopathic viruses.[26]

At three years of follow up over half the subjects had developed immune deficiency (defined as CD4 lymphocyte count $<0{\cdot}5\times10^9$/l), and more than a quarter had recurrence of HIV antigenaemia. Although HIV infection may persist for years with minimal or no symptoms, this early depletion of CD4 lymphocytes and the recurrence of HIV antigenaemia indicate that for a considerable proportion of those infected the disease is already active early in the chronic infection. This might have implications for starting antiviral treatment.

In conclusion, we found a strong association between a longlasting symptomatic primary HIV infection and the subsequent risk of developing other symptoms related to HIV. Future studies should focus on the pathogenesis of acute HIV infection as a delineation of the crucial early events may provide the basis for a better understanding of progressive immunodeficiency during HIV infection.

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Poor response to treatment of renal anaemia with erythropoietin corrected by iron given intravenously

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Recombinant human erythropoietin is being used increasingly to treat renal anaemia in patients receiving haemodialysis and continuous ambulatory peritoneal dialysis. Its efficacy is undisputed; nevertheless, several centres have reported that some patients have responded poorly, slowly, or not at all. We report on five patients who responded poorly to such treatment until they were given iron intravenously.

Case reports

The five patients we describe participated in a study assessing the effect of erythropoietin on renal anaemia in 11 patients who were receiving regular haemodialysis. All five were treated with erythropoietin (Boehringer Mannheim) 240 U/kg/week intravenously and started prophylactic oral iron supplementation (ferrous gluconate 300 mg/day; 35 mg elemental iron) two weeks before the treatment with erythropoietin. Each patient had a normal serum ferritin concentration before treatment (51, 40, 44, 34, and 37 μg/l; normal range 15-300 μg/l). Serum iron concentration and total iron binding capacity were monitored and the percentage saturation with transferrin calculated (serum iron concentration (μmol/l)÷total iron binding capacity (μmol/l)×100%).

The mean (SD) increase in haemoglobin concentration in the five patients was 25 (13) g/l over the first eight weeks of treatment with erythropoietin compared with 45 (20) g/l in six other patients in the study (all of whom had serum ferritin concentrations >400 μg/l and transferrin saturations >30% before treatment). Each of the five patients had an initial rise in haemoglobin concentration, which was not sustained; they were then given iron dextran intravenously (Imferon; 50 mg elemental iron/ml) 1 ml twice weekly during the last hour of dialysis.

The mean weekly rise in haemoglobin concentration during the four weeks before intravenous treatment with iron was 2·0 g/l; this rose to 5·3 g/l after the treatment was started ($p<0·005$, paired t test), indicating more effective erythropoiesis even though the dose of erythropoietin was the same (table). Four of the patients had normal serum ferritin concentrations immediately before treatment with iron, suggesting adequate stores of iron in marrow; the remaining patient had a concentration at the lower limit of the normal range. In contrast, all five patients had low transferrin saturations (<20%).

Comment

Our data show a retarded response of haemoglobin concentration to erythropoietin, which was corrected by giving iron intravenously. Eschbach *et al* also reported on a patient in whom the response of the packed cell volume declined in the presence of an ample serum ferritin concentration (518 μg/l) but low transferrin saturation (13%); this patient also responded to intravenous treatment with iron dextran.[1]

Erythropoietin seems to stimulate erythropoiesis to such an extent that the demand for iron can exceed the body's ability to release it from stores. This may lead to a functional iron deficiency, which can occur when serum ferritin concentrations are normal and iron can be detected in the marrow by staining.

Previous studies have suggested that stores of iron are adequate for erythropoiesis only if for every 50 g/l rise in haemoglobin concentration a serum ferritin concentration of ⩾100 μg/l is present.[2] Patients who are particularly likely to develop functional iron deficiency, therefore, are those with serum ferritin

Clinical measurements in five patients receiving dialysis and treatment with erythropoietin before and after intravenous treatment with iron. Figures in parentheses are percentage transferrin saturations

Case No	Age (years)	Sex	No of weeks of treatment with erythropoietin when response was poor	Before intravenous treatment with iron: Weekly increase in haemoglobin (g/l)*	Serum ferritin (μg/l)†	Serum iron (μmol/l)/ total iron binding capacity (μmol/l)†	After intravenous treatment with iron: Weekly increase in haemoglobin (g/l)‡	Serum ferritin (μg/l)§	Serum iron (μmol/l)/ total iron binding capacity (μmol/l)§
1	26	M	5-7	2·3	16	4·8/54·0 (8·9)	8·0	17	23·2/59·8 (38·8)
2	51	F	4-8	1·8	35	5·0/57·5 (8·7)	3·5	56	20·0/53·3 (37·5)
3	22	M	2-6	0·3	32	7·8/44·4 (17·6)	3·8	21	47·0/53·3 (88·2)
4	53	M	3-6	2·3	14	6·7/54·0 (12·4)	4·8	30	17·5/56·5 (31·0)
5	52	M	2-6	3·3	31	8·5/50·6 (16·8)	6·3	16	14·0/57·2 (24·5)

*During four weeks before treatment with iron. †Immediately before treatment with iron was started. ‡During four weeks after treatment with iron was started. §After four weeks of treatment with iron.