# Papers

## Progression to symptomatic disease in people infected with HIV-1 in rural Uganda: prospective cohort study

Dilys Morgan, Cedric Mahe, Billy Mayanja, James A G Whitworth

## Abstract

**Objectives** To estimate the rate of progression from seroconversion to symptomatic disease in adults infected with HIV-1, and to establish whether the background level of signs and symptoms commonly associated with HIV-1 in uninfected controls are likely to affect progression rates.

**Design** Longitudinal, prospective cohort study of people infected with HIV-1 and randomly selected subjects negative for HIV-1 antibodies identified during population studies.

**Setting** Study clinic with basic medical care in rural Uganda.

**Subjects** 275 patients infected with HIV-1 (107 prevalent cases and 168 incident cases) and 246 controls negative for HIV-1 antibodies.

**Main outcome measures** Signs and symptoms of HIV disease, as determined by stages 2 and 3 of the World Health Organization clinical staging system.

**Results** The median time from seroconversion to WHO stage 2 was 25.4 months and to stage 3 was 45.5 months. 43% of the participants infected with HIV-1 had signs or symptoms by two years after seroconversion. The most common clinical conditions used to define progression of disease were weight loss, mucocutaneous manifestations, bacterial infections, chronic fever, and chronic diarrhoea. Although the rates of these conditions (apart from minor weight loss) were significantly higher in the participants infected with HIV-1, they were also relatively frequent in the control group. Herpes zoster, oral candidiasis, and pulmonary tuberculosis were not common events in the control group and therefore were more indicative of infection with HIV-1.

**Conclusions** Disease progression associated with infection with HIV-1 seems to be rapid in rural Uganda. This is most likely due to the high prevalence of conditions in the general population that could be taken as symptoms and signs of infection with HIV-1.

## Introduction

Although some studies have found that progression of disease in patients infected with HIV-1 is more rapid in African people living in sub-Saharan Africa,[1–4] most studies have found rates of progression similar to those in rich countries.[5–9] However, in Africa it is rare to find cohorts for whom tests negative for HIV-1 antibody and positive HIV-1 tests (and hence an estimated date of seroconversion) are documented.

We report rates of, and reasons for progression to, early symptomatic disease in adults for whom estimated dates of HIV-1 seroconversion were available in a cohort in rural Uganda. We also assessed the rates of conditions commonly associated with HIV-1 infection in participants infected with HIV-1 before they developed AIDS compared with those in participants not infected with HIV-1.

## Methods

### Participants and design

We established a clinical cohort in rural south western Uganda in 1990 by recruiting participants from a large study that followed the dynamics of HIV-1 infection with annual HIV-1 serosurveys of the general population.[10] The cohort comprised prevalent cases of HIV-1 infection diagnosed in 1989 and 1990 and incident cases detected during annual serosurveys; we used randomly selected people who were negative for HIV-1 antibodies, as controls.[11] The estimated date of seroconversion for the incident cases was taken as the midpoint between the last test negative result and first positive result for antibodies to HIV-1.

All participants gave informed written consent (signature or thumbprint), and they were reviewed by a study doctor every three months. The participants were asked about their medical history, were given a full physical examination, and underwent basic laboratory investigations. Any complaints or medical findings were investigated and treated with drugs from the World Health Organization's list of essential drugs. Participants could also attend the clinic at any time when they were ill during the study. At each routine visit, participants infected with HIV-1 were categorised according to the clinical and performance scale of the staging system for patients infected with HIV-1 proposed by the WHO (see box).[12]

The staff at the clinic were not aware of the HIV status of the participants. This ensured confidentiality and reduced the risk of bias in the reports. All participants were strongly encouraged to attend the HIV counselling sessions and testing facilities that were provided as part of the study.

Medical Research Council Programme on AIDS, Uganda Virus Research Institute, PO Box 49, Entebbe, Uganda
Dilys Morgan
*clinical epidemiologist*
Cedric Mahe
*statistician*
Billy Mayanja
*medical officer*
James A G Whitworth
*head of programme*

Correspondence to:
D Morgan, Public Health Laboratory Service Communicable Disease Surveillance Centre, London NW9 5EQ
dmorgan@phls.org.uk

### Statistical analysis

To minimise the number of missed events when the median time from seroconversion to symptomatic disease, represented by WHO stages 2 and 3, was estimated, we included only incident cases seen within two years of their estimated date of seroconversion.



Cumulative probability (95% confidence intervals) of remaining symptom-free from time of seroconversion (Kaplan-Meier plot)

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**Proposed WHO staging system for patients infected with HIV-1**[12]

**Stage 1:**
- Asymptomatic
- Persistent generalised lymphadenopathy

**Stage 2:**
- Weight loss between 5% and 10% of body weight
- Minor mucocutaneous manifestations (seborrhoeic dermatitis, prurigo, fungal nail infections, recurrent oral ulcerations, angular stomatitis)
- Herpes zoster within the past five years
- Recurrent upper respiratory tract infections (for example, bacterial sinusitis)

*And/or*
- Performance scale 2: symptomatic, normal activity

**Stage 3:**
- Weight loss >10% body weight
- Unexplained chronic diarrhoea for longer than one month
- Unexplained prolonged fever (intermittent or constant) for longer than one month
- Oral candidiasis
- Oral hairy leukoplakia
- Pulmonary tuberculosis within last year
- Severe bacterial infections (for example, pneumonia, pyomyositis)

*And/or*
- Performance scale 3: bedridden for less than 50% of the day during the last month

**Clinical stage 4 (AIDS):**
- HIV wasting syndrome*
- *Pneumocystis carinii* pneumonia
- Toxoplasmosis of the brain
- Cryptosporidiosis with diarrhoea for more than one month
- *Cryptococcus*, extrapulmonary
- Cytomegalovirus infection of an organ other than liver, spleen, or lymph nodes
- Herpes simplex virus infection—mucocutaneous for more than 1 month or visceral of any duration
- Progressive multifocal leukoencephalopathy
- Any disseminated endemic mycosis
- Candidiasis of the oesophagus, trachea, bronchi, or lungs
- Atypical mycobacteriosis, disseminated
- Non-typhoidal salmonella septicaemia
- Extrapulmonary tuberculosis
- Lymphoma
- Kaposi's sarcoma
- HIV encephalopathy†

*And/or*
- Performance scale 4: bedridden for more than 50% of the day during last month

*Defined by the Centers for Disease Control and Prevention as weight loss of greater than 10% body weight, plus either unexplained chronic diarrhoea (greater than 1 month) or chronic weakness and unexplained prolonged fever (greater than 1 month). †Defined by the Centers for Disease Control and Prevention as clinical findings of disabling cognitive dysfunction and/or motor dysfunction, interfering with activities of daily living, progressing over weeks to months in the absence of a concurrent illness or condition other than infection with HIV that could explain the findings.
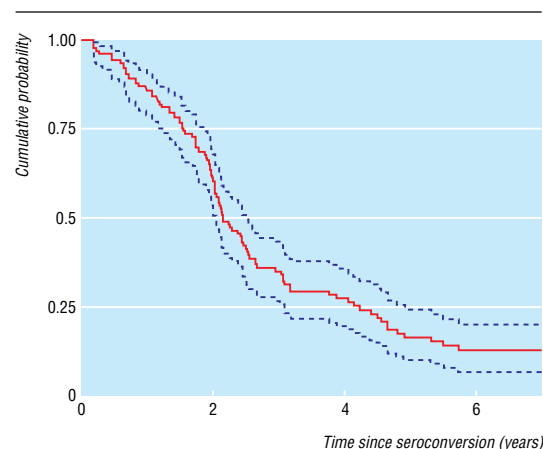
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The WHO staging system is hierarchical—it is assumed that once individuals have moved to a given stage, they have passed though all previous stages. Participants who had symptoms at enrolment or who progressed directly to a higher stage were considered to be left censored (the event that defined the move to the next stage happened before the date of recording). This left censoring tends to overestimates of the time from seroconversion to a given stage. We provide the proportion of individuals who were left censored for each stage so that the degree of bias can be assessed. The date of the routine appointment at which a participant was first seen with an event that defined a WHO stage was used to estimate the time between seroconversion and the patient developing symptoms.

Kaplan-Meier survival methods were used to estimate the median probabilities (and interquartile ranges) and cumulative probabilities (95% confidence intervals by Greenwood's method) for times to the various endpoints. To estimate the background level of stage defining conditions in this population, we compared the rates of conditions during follow up—from the first visit to the last visit before the patient was classified as having AIDS—for all incident cases, prevalent cases and controls by using the Mantel-Haenszel test. All analyses were performed with the STATA 6.0 statistical package. This paper reports data from 1990 to the end of 2000.

## Results

By the end of 2000, 275 patients infected with HIV-1 (107 prevalent cases and 168 incident cases) and 246 controls who tested negative for HIV-1 infection had been enrolled. We enrolled more than 80% of individuals identified for selection from the large population study into the clinical cohort, and over 92% of participants living in the area were seen during 2000. Compliance rates remained high.

In total, 142 incident cases were seen within two years of their estimated date of seroconversion (table 1). Figure 1 shows the cumulative probabilities of remaining symptom free after seroconversion.

The most common clinical conditions associated with disease progression were weight loss, mucocutaneous manifestations, bacterial infections, chronic

fever, and chronic diarrhoea (table 1). The number of events and the rates of these and other conditions defining a WHO stage (prior to AIDS) in all participants are shown in table 2. With the exception of minor weight loss, the rates of these conditions were significantly higher in participants infected with HIV-1 than in controls, although the conditions were also relatively frequent in the control group. Herpes zoster, oral candidiasis, and pulmonary tuberculosis were not common events in the control participants, as shown by their higher rate ratios.

## Discussion

Early manifestations and progression rates of disease in patients infected with HIV-1 are particularly difficult to assess in Africa. Most reports of clinical manifestations have been in patients admitted to hospital or attending clinics; these patients are not representative of the general population, because patients tend to present late and few make it to referral centres.

### Time between seroconversion and appearance of symptoms

Symptoms of infection with HIV-1 seem to developed quickly in incident cases seen within two years of their estimated date of seroconversion: only 17% of participants remained symptom-free five years after seroconversion. The median time to WHO stage 2 (25.4 months) was probably overestimated due to the effects of left censoring, but the bias for time to WHO stage 3 (45.5 months) should be negligible. Other studies in Kenya and Haiti have also reported rapid progression from seroconversion to symptomatic disease.[13] [14] Progression times in industrialised countries are much longer, with 78%-85% of patients infected with HIV remaining asymptomatic five years after seroconversion.[15] [16]

### Recognising progression to symptomatic disease

The most common single reason for recognising progression to symptomatic disease in our cohort was minor weight loss, but this was as common in controls who tested negative for HIV-1 antibodies as in participants infected with HIV-1. Minor mucocutaneous

**Table 1** Enrolment characteristics of the incident cases infected with HIV-1, used for estimating progression times, median time from seroconversion to WHO stages 2 and 3 and reasons for progression

| Characteristic | Value |
|---|---|
| No of participants seen within two years of seroconversion | 142 |
| Men | 70 |
| Women | 72 |
| Median (IQR) age (years) | 30 (24-38) |
| Median (IQR) time between tests negative and positive for HIV antibodies (months) | 12.1 (9.8-18.0) |
| Median (IQR) time from seroconversion to enrolment (months) | 10.6 (7.3-16.8) |
| Median (IQR) follow up from seroconversion to last visit (years) | 4.2 (2.3-6.6) |
| No of patients in each WHO stage on enrolment: | |
| 1 (asymptomatic) | 123 |
| 2 (mild disease) | 12 |
| 3 (moderate disease) | 6 |
| 4 (AIDS) | 1 |
| Median (95% CI) time from seroconversion to stage 2 (months)* | 25.4 (23.9 to 29.6) |
| No (%) of patients in WHO stage 2 | 63 |
| Reasons for progression:** | |
| Minor weight loss (5-10% baseline weight) | 38 (61) |
| Minor mucocutaneous manifestations | 16 (25) |
| Herpes zoster | 9 (14) |
| Median (95% CI) time from seroconversion to stage 3 (months)† | 45.5 (36.2 to 51.3) |
| No (%) of patients in WHO stage 3 | 72 |
| Reasons for progression:** | |
| Major weight loss (>10%) | 24 (33) |
| Severe bacterial infection | 23 (32) |
| Chronic diarrhoea | 13 (18) |
| Chronic fever | 10 (14) |
| Pulmonary tuberculosis | 3 (4) |
| Oral candidiasis | 2 (3) |
| Oral hairy leukoplakia | 1 (1) |

IQR=interquartile range.
*Using 104 subjects in stage 2: 51 progressed from stage 1; 12 were in stage 2 and 7 were in higher stages on enrolment; and 34 went straight to stages 3 or 4. Thus 53 (51%) were left censored.
**Each participant could have more than one reason for progression.
†Using 80 subjects in stage 3: 66 progressed from stages 1 or 2; 6 in stage 3 and 1 in stage 4 on enrolment; and 7 went straight to stage 4. Thus 14 (18%) were left censored.

problems, severe bacterial infections, chronic fever, and chronic diarrhoea were also common clinical complaints that occurred before a patient was classified as having AIDS. Although participants infected with HIV-1 had significantly higher rates of these conditions, they were also frequent in the controls (see table 2). However, in agreement with other African studies,[17] [18] we found that herpes zoster, oral candidia-

**Table 2** Rates of visits to study clinic by patients with conditions defining WHO stages (pre-AIDS) in participants infected with HIV-1 compared with controls negative for HIV-1 antibodies

| | Infected with HIV (total PYO=1120.2) | | Negative for HIV antibodies (total PYO=1336.5) | | | |
|---|---|---|---|---|---|---|
| | No of patients | Rate (per 100 PYO) | No of patients | Rate (per 100 PYO) | Rate ratio* (95% CI) | P value† |
| WHO stage 2: | | | | | | |
| Weight loss (5%-10%) | 521 | 46.5 | 551 | 41.2 | 1.1 (1.0 to 1.3) | 0.045 |
| Minor mucocutaneous disease | 197 | 17.6 | 58 | 4.3 | 4.1 (3.0 to 5.4) | <0.001 |
| Herpes zoster | 51 | 4.6 | 6 | 0.5 | 10.1 (4.4 to 28.9) | <0.001 |
| Recurrent upper respiratory tract infection | 21 | 1.9 | 7 | 0.5 | 3.6 (1.5 to 8.4) | 0.002 |
| WHO stage 3: | | | | | | |
| Weight loss >10% | 232 | 20.7 | 98 | 7.3 | 2.8 (2.2 to 3.6) | <0.001 |
| Chronic diarrhoea | 60 | 5.4 | 22 | 1.6 | 3.3 (2.0 to 5.3) | <0.001 |
| Prolonged fever | 56 | 5.0 | 37 | 2.8 | 1.8 (1.2 to 2.7) | 0.005 |
| Oral candidiasis | 43 | 3.8 | 1 | 0.08 | 51.3 (7.1 to 372) | <0.001 |
| Oral hairy leukoplakia | 6 | 0.5 | 1 | 0.08 | 7.2 (0.9 to 59.5) | 0.033 |
| Pulmonary tuberculosis | 24 | 2.1 | 2 | 0.08 | 28.6 (3.9 to 212) | <0.001 |
| Severe bacterial infection | 126 | 11.3 | 47 | 3.5 | 3.2 (2.3 to 4.5) | <0.001 |

PYO=person years of observation.
*Rate in patients infected with HIV-1 divided by rate in participants negative for HIV-1 antibodies.
†Comparison of rate ratios using Mantel-Haenszel test.

CHALASANI/REX

**What is already known on this topic**

The few studies that have reported time from seroconversion to HIV-1 symptomatic disease in poor countries suggest that this interval is shorter than in rich countries

**What this study adds**

Progression from seroconversion to symptomatic disease seems to be rapid in rural Africa

The apparent rapid disease progression in rural Africa is most likely to be due to the high prevalence of what could be taken as symptoms and signs of HIV-1 in the general population

sis, and pulmonary tuberculosis were highly predictive for infection with HIV-1. The small number of participants may have affected our results, but a study of women in Rwanda reported similar rates of weight loss, mucocutaneous conditions, chronic fever, and diarrhoea in groups whose test results were positive and negative for HIV-1 antibodies.[6] In rich countries, the rates of these conditions, and the rate ratios, were considerably lower in groups testing positive and negative for HIV-1 antibodies.[19 20]

### Background levels of other conditions

Most of the population in rural Uganda lives in poverty; food is often in limited supply, there is no electricity, and there is poor access to any, let alone clean, water. Malaria is endemic, and infections other than HIV, especially bacterial infections, are common. The shorter interval from seroconversion to symptomatic disease in African populations probably reflects the high background level of these conditions, rather than rapid disease progression.

### Conclusions

The progression of disease in patients infected with HIV-1 in Africa seems to be rapid; this is most likely to be due to the high prevalence of what could be taken as symptoms and signs of infection with HIV-1 in the general population. Studies that showed rapid progression of disease in patients infected with HIV in Africa could have led to the belief that HIV disease progresses more rapidly in Africa than elsewhere.

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*Endpiece*
## The danger of health books

Be careful of reading health books, you may die of a misprint.

Mark Twain

Submitted by Peter Teichman, assistant professor, Department of Family Medicine, West Virginia University

# Commentary: Virus, host, or environment?

Peter H Kilmarx

Morgan et al present data from a fruitful, long running body of research that looked at the clinical manifestations of infection with HIV-1 in a cohort in rural Uganda. Their key finding was that symptoms suggestive of infection with HIV-1 develop relatively rapidly—the median time from seroconversion to symptomatic disease (WHO stage 2) was only 25.4 months. In contrast, most patients in rich countries are asymptomatic even five years after acquiring infection.

Does disease associated with infection with HIV-1 progress more quickly in African populations? This is a crucial issue. Knowing the rate of disease progression allows us to give a prognosis to individual patients. At the population level, it helps us to understand the broader impact of the epidemic on population characteristics, the workforce, and healthcare needs. Rates of disease progression might differ between populations for three reasons: variations in the pathogenicity of the subtypes of HIV-1 that cause infections, variations in host characteristics, and the presence or absence of certain environmental factors—such as the presence of coexistent *Mycobacterium tuberculosis* or the availability of adequate medical treatment. These factors are difficult to disentangle, but in developed countries, rates of disease progression do not seem to be associated with the viral subtype or the patient's country of origin.[1] Data from poor countries are sparse and conflicting, but some show that the progression of disease in these settings is more rapid than in rich parts of the world.[2] [3] More recently, the use of highly active antiretroviral drugs has become the overwhelming factor that has affected disease progression. In 2001 the estimated number of deaths from HIV and AIDS in North America, western Europe, Australia, and New Zealand was 75 500 (out of a total population of about 731 million); this compares with 2.3 million deaths in sub-Saharan Africa (total population about 596 million).[4]

This report from Morgan et al indicates a key reason for the apparently rapid development of symptoms in people in rural Uganda: many of the study's participants who were negative for HIV-1 antibodies also had symptoms suggestive of infection with HIV-1. The most commonly reported condition—loss of 5-10% of body weight—occurred at a rate of more than 40 per 100 person years of follow up whether or not participants were infected with HIV-1. Other symptoms, such as prolonged fever, were more common in the people infected with HIV-1, but they were also common among those who were negative for HIV-1 antibodies. The rapid development of symptoms among rural Ugandans infected with HIV-1 is, at least in part, unrelated to infection, but it is linked to the poor background health status of this population.

This study underscores two points. Firstly, the presence of symptoms is a poor guide for staging disease associated with HIV-1 infection. "Harder" outcomes, such as CD4 T lymphocyte count, blood concentration of HIV RNA, and death, are better endpoints on which to base epidemiological studies of disease progression. However, these laboratory tests are expensive and not available for patients in poor settings. Accurate, low cost assays to monitor disease activity and progression are needed urgently.[5] Secondly, the health status of rural Africans is generally poor. Further research is needed to determine the role of the environment in the progression of disease associated with infection with HIV-1 in poor settings. Meanwhile, it is appropriate that initiatives to provide antiretroviral treatment, which are much needed, also aim to improve basic health care and control other infectious diseases, such as malaria and tuberculosis.

Competing interests: None declared.

Thailand
MOPH-US CDC
Collaboration,
Ministry of Public
Health, Nonthaburi
11000, Thailand
Peter H Kilmarx
*associate director for science*

pbk4@cdc.gov

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*One hundred years ago*
## Is the lady doctor a failure?

This question has recently been asked in America and in one important quarter at least has been answered in the affirmative. This is all the more remarkable, since America is not only the country which witnessed the new birth of the lady doctor in modern times, but that in which she has hitherto appeared most to flourish. Miss Elizabeth Blackwell, who was the first, graduated in 1849. Three years later there were six in Philadelphia. In 1889 there were 3,000 lady doctors in the United States; in 1896 there were 4,555, and now there are probably 6,000, some of whom have very lucrative practices. But these would seem to be the exception. From Chicago comes the news that Princess Bamha Dhuleep Singh, daughter of the late Maharajah Dhuleep Singh, and seventy other young women, who were studying medicine at the North-Western University, will have to seek another school. After thirty two years' trial the trustees of the University have come to the conclusion that women are not a success as doctors. The school is to be abolished and the property sold. One of the trustees, Mr. Raymond, goes so far as to say that it is impossible to make a doctor of a woman, He adds: "We have run the Women's Medical School at a loss of £5,000 a year. Women cannot grasp chemical laboratory work or the intricacies of surgery. Fifteen years ago the graduating class of men and women signed a memorial saying that coeducation was a failure. Then we conducted the college exclusively for women, and it has been worse than a failure."

(*BMJ* 1902;i:287)

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