

HIV infection in Haiti: natural history and disease progression

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Objective: A study was conducted to define the natural history and disease progression of HIV infection in a developing country.

Design: A prospective longitudinal cohort study.

Methods: Forty-two patients with documented dates of HIV seroconversion were followed in Port-au-Prince, Haiti. Patients were seen at 3 month intervals or when ill. Patients were treated for bacterial, mycobacterial, parasitic, and fungal infections, but antiretroviral therapy was not available. Patients were followed until death or until 1 January 2000; median follow-up was 66 months.

Results: By Kaplan–Meier analyses, the median time to symptomatic HIV disease (CDC category B or C) was 3.0 years [95% confidence interval (CI) 2.3–5.0 years]. The median time to AIDS (CDC category C) was 5.2 years (95% CI 4.7–6.5 years), and the median time to death was 7.4 years (95% CI 6.2–10.2 years). Community-acquired infections, including respiratory tract infections, acute diarrhea, and skin infections were common in the pre-AIDS period. AIDS-defining illnesses included tuberculosis, wasting syndrome, cryptosporidiosis, cyclosporiasis, candida esophagitis, toxoplasmosis, and cryptococcal meningitis. Rapid progression to death was associated with anemia at the time of seroconversion hazards ratio (HR) 4.1 (95% CI 1.1–15.0), age greater than 35 years at seroconversion HR 4.4 (95% CI 1.1–16.6), and lymphopenia at seroconversion HR 11.0 (95% CI 2.3–53.0).

Conclusion: This report documents rapid disease progression from HIV seroconversion until death among patients living in a developing country. Interventions, including nutritional support and prophylaxis of common community-acquired infections during the pre-AIDS period may slow disease progression and prolong life for HIV-infected individuals in less-developed countries. © 2000 Lippincott Williams & Wilkins

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Introduction

The natural history of HIV disease is complex and depends upon a variety of factors, including the mode of transmission, prevalent opportunistic infections, the availability of antiretroviral therapy, host genetics, and viral strain. Most of our know-

ledge of the natural history of HIV infection comes from developed countries, and data from developing countries are rare despite the fact that the Joint United Nations Programme on HIV/AIDS estimated that 95% of the people currently infected with HIV live in the developing world [1,2].

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The objective of this study was to understand the natural history of HIV infection from the time of seroconversion to the development of the first HIV-related illness, AIDS, and death in a group of patients in Port-au-Prince, Haiti.

Methods

The study was a longitudinal observational cohort study. Individuals with documented HIV seroconversion were recruited from September 1985 to September 1997 and followed at the Center of the Groupe Haitien d'Etude du Sarcome de Kaposi et des Infections Opportunistes (GHESKIO) in Port-au-Prince, Haiti. HIV seroconversion was documented when someone with a negative HIV antibody test by enzyme-linked immunosorbent assay (ELISA) subsequently developed a positive ELISA confirmed by a Western blot analysis. The study protocol and consent forms were approved by the Cornell University Medical College and GHESKIO Institutional Review Board (IRB).

The GHESKIO Center is the national HIV testing center in Haiti, providing voluntary HIV counselling and testing to a poor urban population. GHESKIO tests approximately 8000 new patients annually, with 30% testing HIV positive. HIV-positive individuals are offered ongoing counselling, medical care, home care, and nutritional support. Because of the cost of antiretroviral medications and the lack of a medical infrastructure required for drug monitoring and safe administration, antiretroviral therapy is not the standard of care in Haiti and is not available to patients at GHESKIO.

The cohort for the current study was recruited from two groups of individuals followed at GHESKIO, patients with sexually transmitted diseases (STD) and sexual partners of HIV-infected patients. All patients diagnosed with an STD at GHESKIO are provided treatment, HIV testing, counselling, condoms, and are told to return if they have recurrent symptoms. A group of patients who were HIV seronegative on initial testing returned at a future date with a second STD and were re-tested for HIV. The incidence of new HIV infection in this group was 18.9 per 100 person years [3]. STD patients with a documented seroconversion were asked to enrol in the current study. As part of a study of HIV transmission, HIV-discordant couples were provided frequent counselling, condoms, and STD treatment; and the seronegative partners were offered routine HIV testing. These efforts lowered HIV transmission rates to 1.6 per 100 years of follow-up [4]. Partners with documented HIV seroconversion were invited to participate in this study.

Individuals enrolled in the natural history cohort were asked to return for an evaluation by a physician every 3 months and sooner if symptomatic. Clinicians documented the medical evaluation on a structured form and ordered baseline laboratory tests at study entry and as clinically indicated. Complete blood counts were available for all patients from the beginning of the study. CD4 cell counts were measured starting in 1993 at 4–6 month intervals. If study participants were unable to attend clinic, a social worker visited them at home and recorded findings in the medical record. Patients were treated for bacterial, mycobacterial, fungal, and parasitic infections. After 1990, all patients with a positive purified protein derivative (PPD) test were provided with isoniazid prophylaxis for tuberculosis.

The definition of the acute retroviral syndrome followed previously published reports [5]. The seroconversion period was defined as the time interval between the last negative and the first positive HIV test; and the estimated seroconversion date was the midpoint of this period.

Participants were staged according to the United States Centers for Disease Control and Prevention (CDC) Classification System for HIV Infection. In 1993, the CDC revised this system, and therefore after 1993, patients were staged according to the Revised Classification System. Individuals were assigned to either category A (symptom-free disease), category B (HIV-related illness), or category C (AIDS) [6,7]. Symptomatic HIV disease refers to individuals in either category B or category C. CD4 cell counts were not available at our clinic until 1993; therefore we did not use a CD4 cell count of less than 200 as a clinical endpoint until after 1 January 1993.

The case definition of active tuberculosis was based upon the definition of the American Thoracic Society [8]. We required two of the following three criteria: (i) clinical symptoms of tuberculosis, (cough, fever, night sweats, etc.); (ii) acid-fast bacteria were visible in the sputum, or *Mycobacterium tuberculosis* was cultured from the sputum; (iii) the chest radiograph was independently interpreted as highly suggestive of tuberculosis. For patients without microbiological confirmation, we also required a clinical response to antituberculosis medications. For the diagnosis of other AIDS-defining illnesses, we relied upon the CDC's definitive and presumptive diagnostic guidelines, as presented in the 1993 Revised Classification System. We reported the cause of death as the illness immediately preceding death as determined by the physician caring for the patient at the time.

Laboratory

Serum HIV antibodies were detected by ELISA (Abbott Diagnostics, Abbott Park, IL, USA). Sera-reactive

by ELISA were confirmed by Western blot analysis (Dupont, Wilmington, DL, USA). Examination for acid-fast bacteria was performed by Ziehl-Neelsen staining, and culture for mycobacteria was performed in Lowenstein-Jensen medium. CD4 cell counts were measured in Haiti by the cytosphere manual method using a hemocytometer, and were validated by standardized flow cytometric measurements at the New York Hospital – Cornell Medical Center [9].

Analyses

Data were analysed using Epi Info 6 software (CDC, Atlanta, GA, USA) and SAS (SAS Institute, Carey, NC, USA). To determine a difference in two proportions, chi-square with Yates correction was used, and for expected cell values of less than five, Fisher’s exact test was used. Means and medians were compared with the use of Student’s *t*-test and the Wilcoxon rank sum test, respectively. Kaplan-Meier survival analyses were used to estimate progression times to clinical endpoints (HIV-related illness, AIDS, CD4 cell count < 200, tuberculosis, and death). Survival times were calculated from the estimated time of seroconversion to the date of the clinical endpoint; or for patients who did not reach the clinical endpoint, 1 January 2000. The log-rank test was used to compare survival times between different strata. Cox’s proportional hazards model was used for multivariate analysis.

Results

Between September 1985 and September 1997, 44 seroconversions were documented and 42 individuals agreed to participate in the current study. These 42 patients reported heterosexual intercourse as their only

HIV high-risk activity. The median time from the last negative HIV test to the first positive test was 7 months. The median age at seroconversion was 26.5 years for the 30 women in the cohort and 30.5 years for the 12 men. Of the 30 women, 12 (40%) were pregnant at the time of seroconversion. Of the 42 participants, five (12%) had a newly reactive syphilis serology at the time of seroconversion. Of the 32 individuals who had a PPD checked immediately after seroconversion, 21 (66%) were PPD positive. The median follow-up was 66 months.

Acute retroviral infection

Of the 42 study participants, 22 (52%) had symptoms of an acute retroviral infection. The symptoms were fever 64%, fatigue 36%, lymphadenopathy 32%, rash 14%, weight loss 14%, pharyngitis 14%, headache 9%, and diarrhea 5%. At the time of the first HIV-positive test, seven (17%) members of the cohort had an absolute lymphocyte count below 2000/mm³. Two individuals (5%) had herpes zoster lesions during the seroconversion period, and seven (17%) had a prolonged (> 1 year) lymphadenopathy syndrome after seroconversion.

Pre-AIDS community-acquired infections

Of the 42 participants, 36 (86%) had at least one community-acquired infection during the pre-AIDS time period. The percentage of the cohort affected and the incidence of these pre-AIDS infections are detailed in Table 1. The most common infections were respiratory tract infections, acute diarrhea, skin infections, and unexplained acute febrile episodes.

Symptomatic HIV disease

Among the 28 individuals who developed symptomatic HIV disease, 15 (54%) first presented with an HIV-

Table 1. Pre-AIDS community-acquired infections.

Infection	Patients affected (N = 42)		Incidence Cases/100 py (95% CI)
	No.	(%)	
Head and neck			
Purulent conjunctivitis	4	(9)	3.2 (1.3–6.2)
Sinusitis/otitis	4	(9)	1.8 (0.5–4.6)
Respiratory tract			
Bronchitis	16	(38)	16.1 (11.5–21.7)
Pneumonia	11	(26)	7.0 (4.0–11.1)
Gastrointestinal			
Acute diarrhea	16	(38)	15.2 (10.7–20.7)
Dermatological			
Impetigo	5	(12)	3.2 (1.3–6.2)
Furunculosis	5	(12)	2.3 (0.7–5.3)
Fungal skin infection	12	(29)	5.5 (2.9–9.5)
Severe scabies	7	(17)	4.6 (2.2–8.3)
Systemic			
Acute febrile episodes	8	(19)	5.1 (2.6–8.9)

CI, Confidence interval; py, person years.

related illness (CDC category B) and 13 (46%) presented with AIDS (CDC category C).

The first HIV-related illness was chronic diarrhea in four patients (14%), prurigo in three patients (10%), complicated herpes zoster in two patients (7%), and pelvic inflammatory disease, weight loss of greater than 10% body weight, oral thrush, chronic fever, chronic vaginal candidiasis, and seborrheic dermatitis, each in one patient (4%). Eight individuals (28%) presented with tuberculosis, two (7%) presented with wasting syndrome, two (7%) presented with a CD4 cell count of less than 200, and one (4%) presented with cryptococcal meningitis. Fifteen individuals subsequently developed other category B illnesses. Among the symptomatic individuals, 36% developed prurigo, 24% developed thrush, 20% developed complicated herpes zoster, and 16% had isolated weight loss. Among symptomatic women, 75% developed chronic vaginal candidiasis.

The Kaplan–Meier curve from seroconversion to symptomatic HIV disease (when individuals first developed a category B or C illness) is presented in Fig. 1a. The median time from seroconversion to the beginning

of symptomatic HIV disease was 3 years (95% CI 2.3–5.0 years). For the 19 patients in whom they were carried out, the median CD4 cell count at the time of symptomatic HIV disease was 340.

Among the 23 individuals who developed AIDS, the AIDS-defining illnesses were tuberculosis in nine (39%), wasting syndrome in seven (31%), a CD4 cell count of less than 200 in two (10%), cryptosporidiosis in one (4%), chronic cyclospora diarrhea in one (4%), cryptococcal meningitis in one (4%), candida esophagitis in one (4%), and toxoplasmosis in one (4%). Four people developed a second AIDS illness, including two cases of recurrent pneumonia, one case of candida esophagitis, and one case of wasting. The Kaplan–Meier curve of the time from seroconversion to AIDS is presented in Fig. 1b. The median time to AIDS was 5.2 years (95% CI 4.7–6.5 years). For the 16 people with CD4 cell data available at the time of AIDS diagnosis, the median CD4 cell count at the time of AIDS was 195.

Tuberculosis was both the most common presentation of symptomatic HIV disease and the most common AIDS-defining illness. The incidence of tuberculosis

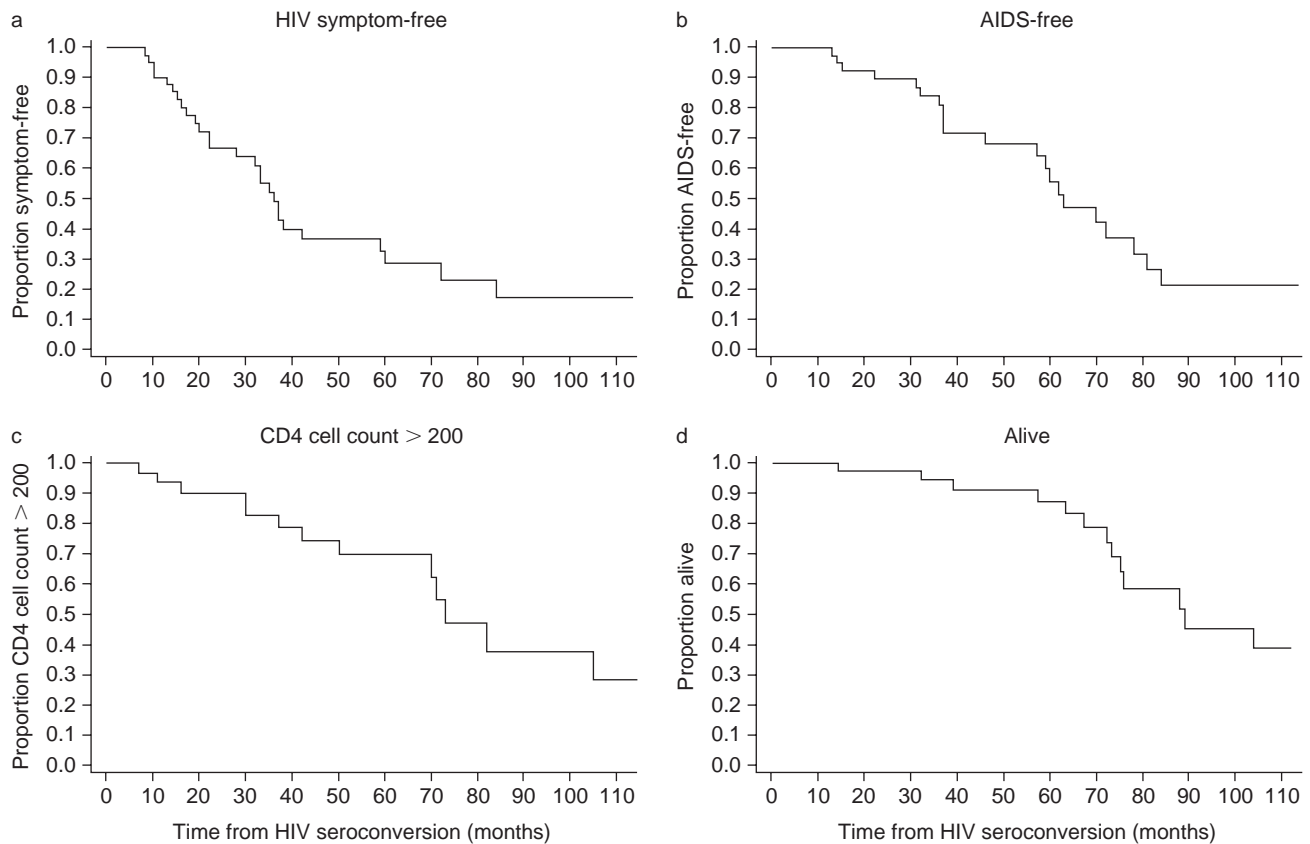


Fig. 1. Kaplan–Meier estimates of the proportion of the cohort (a) free of HIV symptoms; (b) free of AIDS; (c) with CD4 cell counts of less than 200; and (d) alive.

was 3.8 cases per 100 patient years. By survival analyses, 40% of the cohort developed tuberculosis at 6 years of follow-up. Eight cases were pulmonary tuberculosis and one case was extra-pulmonary. Of the nine individuals diagnosed with tuberculosis, four received isoniazid prophylaxis before diagnosis; however no one developed tuberculosis while on isoniazid prophylaxis. For the nine people with tuberculosis, the median time from seroconversion to the diagnosis of tuberculosis was 36 months.

CD4 cell count less than 200

CD4 cell counts were available for 33 study participants. One person who seroconverted in 1987 had a CD4 cell count of 130 in 1992 when CD4 cell testing first became available in Haiti. The CD4 cell counts of the other 32 people were greater than 200 upon first measurement. Among these 32, 13 subsequently had a CD4 cell count measured below 200. The Kaplan–Meier survival curve from the date of seroconversion to the time of a CD4 cell count of less than 200 is presented in Fig. 1c. The median time until the CD4 count dropped below 200 was 6.8 years (95% CI 4.1–8.3).

Death

Of the 42 participants, 15 (36%) have died. The cause of death was wasting syndrome in eight (53%), tuberculosis in two (13%), cryptococcal meningitis in one (7%), toxoplasmosis in one (7%), cryptosporidiosis in one (7%) and unknown in two (13%). The Kaplan–Meier curve showing survival from the time of seroconversion is shown in Fig. 1d. The median survival time from seroconversion to death for the entire cohort was 7.4 years (95% CI 6.2–10.2 years).

Predictors of disease progression

Predictors of disease progression present at the time of seroconversion are presented in Table 2. Of note is the fact that sex, pregnancy, PPD status, and rapid plasma reagin status did not influence disease progression in our cohort. Symptoms of the acute retroviral syndrome were not associated with disease progression, but lymphopenia at the time of seroconversion was. We did not have CD4 cell data at time of seroconversion

for the entire cohort; therefore these data were not used in the analysis of predictors of disease progression.

At the time of the first symptomatic HIV disease (CDC category B or C), weight loss greater than 10% of body weight carried a poor prognosis. The median survival for patients with weight loss at first HIV symptoms was 2.7 years compared with 5.3 years in patients without weight loss.

Long-term non-progressors

Among the 42 members of the cohort, four are symptom free (CDC category A) after more than 8 years of follow-up. The Kaplan–Meier curve of the proportion of the cohort free of symptomatic HIV disease plateaus at approximately 8 years because this proportion of the cohort has not progressed.

Discussion

HIV disease in Haiti progresses rapidly from initial infection to AIDS and to death. In our cohort, the median time from seroconversion to first HIV symptoms as defined by the CDC was 3 years, the median time to AIDS was 5.2 years, and the median time to death was 7.4 years. HIV destruction of the immune system progressed at a rapid pace, with 50% of the cohort's CD4 cell counts falling below 200 at 6.8 years. This is nearly twice as fast as the disease course in developed countries in the pre-antiretroviral era, in which the median time to AIDS was approximately 10 years and the median time to death was 12 years [10].

Previous reports [11,12] have shown that patients with HIV infection in developing countries progress rapidly to AIDS. Other studies [13–15] have shown that patients with AIDS in developing countries progress rapidly to death. However, the current report is the first to document the complete survival time from initial HIV infection to death in a developing country. The rapid disease course documented in this study has public health and policy implications. Models of the incidence of new HIV infections and of HIV-related

Table 2. Predictors of rapid HIV disease progression in Haiti.

Risk	Median survival (years)	Hazards ratio ^a		
		HR	(95% CI)	<i>P</i>
Anemia at time of seroconversion ^b	6.9	4.1	(1.1–15.0)	0.032
Age > 35 years at time of seroconversion	6.2	4.4	(1.1–16.6)	0.031
Lymphopenia at time of seroconversion ^c	5.2	11.0	(2.3–53.0)	0.002

^aHazards ratios (HR) adjusted for other variables in table.

^bAnemia defined as hemoglobin < 10 g/dl.

^cLymphopenia defined as an absolute lymphocyte count < 2000/ml. CI, Confidence interval.

mortality rely upon an estimate of the seroconversion to death survival time [16]. A shorter survival estimate will translate into higher HIV incidence and mortality projections for developing countries.

The reasons for this rapid progression are probably many, and may include poor nutrition, high rates of early community-acquired infections, and high rates of active tuberculosis.

In our cohort, individuals with anemia at the time of seroconversion died earlier than patients without anemia. Other studies [17–19] have suggested that anemia is associated with accelerated HIV disease progression. As a leading cause of anemia in developing countries is iron deficiency, one can postulate that anemia may be a marker for poor nutrition and micronutrient deficiency. Previous studies [20] have suggested that poor nutrition and micronutrient deficiency accelerate HIV disease.

Patients in our cohort had numerous debilitating illnesses before the onset of AIDS. This is similar to the results found in a cohort of HIV-positive patients followed in Uganda [21], who had a high incidence of community-acquired infections in the pre-AIDS time period. In our cohort, community-acquired infections, including respiratory tract infections, acute diarrhea, skin infections, and acute febrile episodes were common in the early years of HIV infection. All of these early infections, especially in a country where prompt treatment may not be available, may enhance viral replication and accelerate the course of HIV disease.

In our cohort, tuberculosis was the most common AIDS-defining illness. This is consistent with studies from other developing countries [2,22–24]. For most patients, tuberculosis was the first presentation of HIV infection occurring at a median of 36 months after seroconversion. Studies [25] suggest that active tuberculosis can increase HIV viral replication and accelerate the course of HIV disease. Therefore, active tuberculosis occurring frequently and early in the course of HIV disease is probably an important cause of rapid HIV disease progression in developing countries.

Data from this report suggest that events at the time of the acute retroviral syndrome are important determinants of the subsequent disease progression rate. Individuals with lymphopenia after acute HIV infection progressed rapidly to death. This is consistent with a growing body of literature [26,27] suggesting that the early depletion of T cell lines during acute HIV infection can lead to rapid immune dysfunction and death. One can postulate that a more virulent strain of HIV or host genetic factors in Haiti may predispose to a more virulent acute retroviral syndrome; however, the current study did not evaluate these possibilities and future studies are needed.

In our cohort, sex and pregnancy were not independently associated with rapid disease progression. However, anemia was associated with rapid progression in univariate and multivariate analysis. Because women, especially pregnant women in developing countries, are at high risk of iron-deficiency anemia and other micronutrient deficiency disorders, one can postulate a complex interplay between sex, pregnancy, malnutrition, and HIV disease progression.

The current study had several limitations. The sample size was small, and larger cohort studies are needed to confirm the findings of this report and to explore further the reasons for rapid HIV disease progression in developing countries. This study spanned 15 years, and advances in HIV disease diagnosis occurred during this time. This time lapse may have introduced some bias into our results.

Haiti is the poorest country in the western hemisphere and antiretroviral therapy is not presently the standard of care for HIV-infected adults. Current efforts by public and private institutions raise the hope that these drugs and the medical infrastructure to administer them safely may some day become available, even in the most impoverished nations.

In the interim, the current study suggests that simple interventions early in HIV disease may improve quality of life and prolong survival for HIV-infected adults in developing countries. Food, vitamin, and micronutrient supplements may improve patients' nutritional status and thereby slow HIV disease progression. Prompt treatment, oral rehydration, and prophylaxis of early infections, including community-acquired respiratory tract infections and diarrheal diseases, may decrease viral replication and slow disease progression. Studies in Cote d'Ivoire [28,29] have shown that early prophylaxis of HIV-infected adults with trimethoprim-sulphamethoxazole decreases morbidity and mortality. We have already shown that isoniazid prophylaxis prevents the occurrence of tuberculosis and slows the progression to AIDS and death [30]. As several patients in the current cohort developed tuberculosis after the completion of isoniazid prophylaxis, the question arises at to whether longer prophylaxis may be of additional benefit. These simple interventions may be possible in countries where triple-drug antiretroviral therapy is prohibitively expensive and may provide realistic hope for people with HIV in the developing world.

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