

Research article

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Disease Progression Among Untreated HIV-Infected Patients in South Ethiopia: Implications for Patient Care

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Abstract

Context: The natural course of HIV disease progression among resource-poor patient populations has not been clearly defined.

Objective: To describe predictors of HIV disease progression as seen at an outpatient clinic in a resource-limited setting in rural Ethiopia.

Design: This prospective cohort study included all adult HIV patients who visited an outpatient clinic at Arba Minch hospital in South Ethiopia between January 30, 2003 and April 1, 2004. Clinical and hematologic measurements were done at baseline and every 12 weeks thereafter until the patient was transferred, put on antiretroviral therapy, was lost to follow-up, or died. Community agents reported patient status every month.

Setting: A district hospital with basic facilities for HIV testing and patient monitoring.

Main Outcome Measures: Death, diagnosis of tuberculosis, and change in disease stage.

Results: We followed 207 patients for a median duration of 19 weeks (range, 0-60 weeks). A total of 132 (64%) of them were in WHO stage III. The overall mortality rate was 46 per 100 person-years of observation (PYO). Mortality increased with advancing disease stage. Diarrhea, oral thrush, and low total lymphocyte count were significant markers of mortality. The incidence of tuberculosis was 9.9 per 100 PYO. Baseline history of easy fatigability and fever were strongly associated with subsequent development of tuberculosis.

Conclusion: The mortality rate and the incidence of tuberculosis in our cohort are among the highest ever reported in sub-Saharan Africa. We identified oral thrush, diarrhea, and total lymphocyte count as predictors of mortality, and easy fatigability and fever as predictors of tuberculosis. The findings have practical implications for patient care in resource-limited settings.

Introduction

Rates of disease progression in human immunodeficiency virus (HIV)-infected patients differ between populations due to differences in viral subtypes, host factors, or the environment.[1] However, our knowledge about the pat-

tern of disease progression in HIV infection in developing countries is limited.[2] The few studies done in Africa and other developing countries show that the rate of disease progression is faster among resource-poor patient populations.[3-6] A recent study from Uganda, however,

reported that the rate of disease progression is similar in developed and developing countries.[7] The pattern of disease progression among Ethiopian patients has not been studied.

Moreover, with the availability of highly active antiretroviral therapy (HAART), such studies became impossible for ethical reasons. In South Ethiopia, we started to treat HIV patients with HAART in August 2003. Prior to the start of HAART, HIV-infected patients were registered and followed as part of a clinic to treat opportunistic infections. Here, we present the results from a cohort of HIV patients from south Ethiopia who did not receive HAART. The objective of this study was to describe the natural course of HIV disease progression as seen at an outpatient clinic in a resource-limited setting in rural Ethiopia.

Methods

Background

This study was conducted at Arba Minch Hospital (AMH), located 500 km south of Addis Ababa. The hospital has 158 beds and serves a population of nearly 1.5 million.

AMH has been doing HIV counseling and testing since the early 1990s. Since January 2002, the HIV unit has been upgraded to serve as a clinic for opportunistic infections. Since August 2003, antiretroviral therapy (ART) has been given to the patients, following the World Health Organization (WHO) and national recommendations.[8,9]

Both rapid and enzyme-linked immunosorbent assay (ELISA) tests were used for HIV testing. We used an automated hematology analyzer (Sysmex Kx-21; Sysmex Corporation; Kobe, Japan) for the measurement of hematologic parameters. A semi-automatic photometer (Photometer 5010, Version 3.0; RIELE; Berlin, Germany) was used for the clinical chemistry tests.

Patients and Study Design

This was a prospective cohort study. Recruitment into the study began in January 30, 2003 and patients were followed through April 1, 2004. Although ART was introduced in August 2003, recruitment into the treatment was withheld until end of December 2003 when a guideline on the fee scheme was issued by the hospital management. All consenting HIV-positive patients older than 15 years of age and residing within the hospital's catchment area were eligible for the study. Initial assessment included basic sociodemographic variables, past medical history, presenting complaints, history of present illness, physical examination including weight and height, and complete blood cell count (CBC). Chest x-ray and acid-fast bacilli stain (AFB) were done per clinical indication. We defined and categorized tuberculosis according to the National Tuberculosis and Leprosy control manual of Ethiopia.[10]

Staging and Follow-up

We staged patients according to the WHO clinical staging system[11] before doing the laboratory investigations. Symptomatic patients were given treatment according to the specific diagnosis. We scheduled 12-weekly follow-up for all patients unless indicated otherwise. At each regular visit, we interviewed patients for new symptoms and examined for new clinical findings. We also did a CBC at each regular visit.

Community Agents

We employed 2 secondary school graduates with basic training on HIV counseling as community agents to follow the patients at the community level. We assigned each of them to the newly recruited patients with their contact details. The agents visited them monthly and offered home-based counseling and support.

Endpoints

Death, change in clinical stage (for stages I, II, and III), and diagnosis of tuberculosis were the main outcome variables. Death at community level was ascertained through community agents. The data clerk at the clinic reported hospital deaths on patient record. Patients who left the study area permanently were labeled as transferred. Patients were regarded as being in care if they had follow-up or initial visit within the previous 90 days before the end of the study and community agents reported that the patient was alive. Patients were regarded as lost to follow-up if they had not had a visit within the previous 90 days and the responsible community agent reported that the patient was lost. We closed the pre-ART follow-up period between January 1, 2004 and April 1, 2004. We followed 90 days into the ART period until we obtained endpoint measurements on all patients, including those on their 12-weekly appointments. Patients who were put on ART were censored at the date of treatment initiation.

Statistical Analysis

We used SPSS for Windows version 12.0 for data analysis. All completed patient data were entered into SPSS on the same day of examination. Follow-up data were also handled similarly. We evaluated the WHO clinical stage, oral candidiasis (oral thrush), diarrhea, body mass index (BMI), total lymphocyte count (TLC), and hemoglobin (Hgb) as predictors of death in our patients. The TLC was treated as a dichotomous variable at a cut-off value of 1200 cells/mL because of its clinical significance for the initiation of ART.[8] Similarly, we used the cut-off value 18.5 kg/m² for BMI.[12] Because we do not have normal values for Hgb in the study area, we used an arbitrary cut-off value of 10 g/dL for both men and women. This is the cut-off value below which treatment with zidovudine-containing regimen is not recommended.[8] All of the clinical symptoms were treated as dichotomous variables.

We used the Kaplan-Meier method to determine the event-free survival, and the log-rank test was used to assess the statistical significance. In order to determine the relative risk for death we used the Cox-regression method. The hazard ratio (HR) was used to determine the difference in the relative risk for death, and it was described as 95% confidence interval (95% CI). We calculated death rates as death per 100 PYO.[13]

A patient was considered to have progressed to the next highest WHO stage provided that he or she presented with a new stage-defining event[12] at 12 weeks or later following the initial examination. The date of staging was considered the date of progression. We estimated the rate of disease progression by the Kaplan-Meier method for patients in stages I, II, and III.

Tuberculosis incidence was calculated as number of tuberculosis cases per 100 PYO. We calculated 95% CIs of rates and rate ratios of tuberculosis incidence assuming Poisson distribution of tuberculosis occurrence. All patients were considered to be at risk of developing tuberculosis during follow-up. Patients already on treatment were also considered at risk because of the risk of reinfection. We evaluated fever, easy fatigability, cough, past history of tuberculosis, TLC 1200/mL, and WHO stage as possible predictors of tuberculosis by the Kaplan-Meier and Cox-regression methods as described above.

Proportions of relevant variables were compared using the chi-squared test. Statistical tests were considered significant if the 2-sided *P* value was < .05.

Ethical Considerations

The study protocol was approved by the National Ethics Review Committee in Ethiopia and by the Regional Committee for Medical Research Ethics in Western Norway. HIV testing was done after informed written consent following a pretest counseling session. Patients were offered the available treatment irrespective of their consent to participate in the study. It is not the Ethiopian policy to give isoniazid (INH) prophylaxis to adult HIV-infected patients.[11]

Results

Sociodemographic Characteristics

We enrolled and followed 207 patients between January 30, 2003 and April 1, 2004. A total of 191 (92%) patients came from urban areas, mostly (168 patients, 81%) from Arba Minch town. Their median age was 30 years (range, 17-75 years). More than one third of the patients were divorced, widowed, or separated. Almost one third were unemployed, and one third had no formal education. A quarter of them came with a letter of exemption from fee

for medical services, and their mean monthly income was about US\$26.

Clinical Characteristics at Initial Examination

In total, 132 (64%) patients were in WHO stage III at initial examination (Table 1). Cough was the most common presenting complaint (82 patients, 40%) followed by weight loss (73 patients, 35%) and diarrhea (69 patients, 33%). Silky hair (softening, straightening, and loss of scalp hair) was found in 21% of the patients. None of patients in stage I had silky hair but 7%, 27%, and 28% of patients in stages II, III and IV respectively had silky hair (chi-squared test for trend = 27, df = 3, *P* < .01). Dermatitis (68 patients, 33%), oral thrush (67 patients, 32%), and tuberculosis (55 patients, 27%) were the 3 most common additional diagnoses at initial examination. Kaposi's sarcoma (5 patients, 2.4%), esophageal candidiasis (3 patients, 1.5%), and *Pneumocystis carinii* pneumonia (1 patient, 0.5%) were rarely diagnosed.

Additionally, 45 (19%) patients had a past or present history of herpes zoster and 46 (22%) patients gave past history of at least 1 episode of tuberculosis. At enrolment, 55 (27%) patients either were on treatment for tuberculosis or were diagnosed to have tuberculosis. Smear-negative pulmonary tuberculosis (PTB-) was the most common type (30 of 55 patients, 54%), followed by smear-positive pulmonary tuberculosis (PTB+; 11 out of 55 patients, 20%), extrapulmonary tuberculosis (EPTB; 9 out of 55 patients, 16%), and unspecified in 5 out of 55 patients (9%).

Patient Follow-up

The median duration of follow-up was 19 weeks (range, 0-60 weeks). By the end of the study, 47 (23%) patients had died, 11 (5%) patients were lost to follow-up, 9 (4%) were transferred to another health institution, 51 (25%) were put on ART, and 89 (43%) were under regular follow-up and not yet put on ART.

Table 1: Distribution of Patients in Each WHO Stage at Presentation, Arba Minch Hospital, 2004

WHO Stage	Number of Patients	Percentage
I	22	11%
II	28	13%
III	132	64%
IV	25	12%
Total	207	100%

WHO = World Health Organization

Mortality Rates

A total of 47 patients died during follow-up, all due to HIV-related conditions. Thus, the overall rate of mortality was 46 per 100 PYO (47 deaths/101.3 person-years of observation). Mortality increased with advancing disease stage. At the end of the study period, the proportion of patients who died was 0%, 11%, 36%, and 40% in stages I, II, III, and IV, respectively (log-rank test; chi-squared = 18.5, $P < .001$) (Figure 1). Patients with diarrhea (chi-squared = 11.4, $P = .001$), oral thrush (chi-squared = 23.5, $P < .001$), low lymphocyte count (TLC 1200 cells/mL) [chi-squared = 10.2, $P = .001$], low body mass index (BMI $< 18.5 \text{ kg/m}^2$) [chi-squared = 8.2, $P = .004$], or anemia (Hgb 10 g/dL for both sexes) [chi-squared = 9.0, $P = .003$] had significantly higher mortality. Nevertheless, when stratified by disease stage, only diarrhea and oral thrush remained significant markers of death (Figure 2).

In the Cox-regression model that contained diarrhea, oral thrush, low TLC, low BMI, WHO stage III and IV, and anemia, only oral thrush and low TLC remained significant markers of mortality (HR [95% CI = 3.5 [1.86.7] and 3.5 [1.48.4] for oral thrush and for low TLC, respectively) (Table 2).

Incidence of Tuberculosis

Ten patients (5 men and 5 women) developed tuberculosis during follow-up. One patient developed PTB+, 2 developed EPTB, and the other 7 were PTB-cases. The

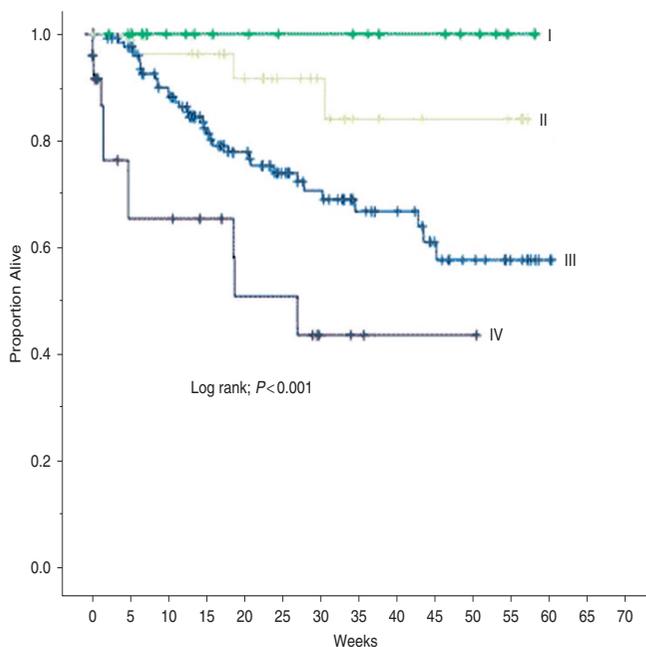


Figure 1
Survival according to initial WHO stage, Arba Minch Hospital, 2004.

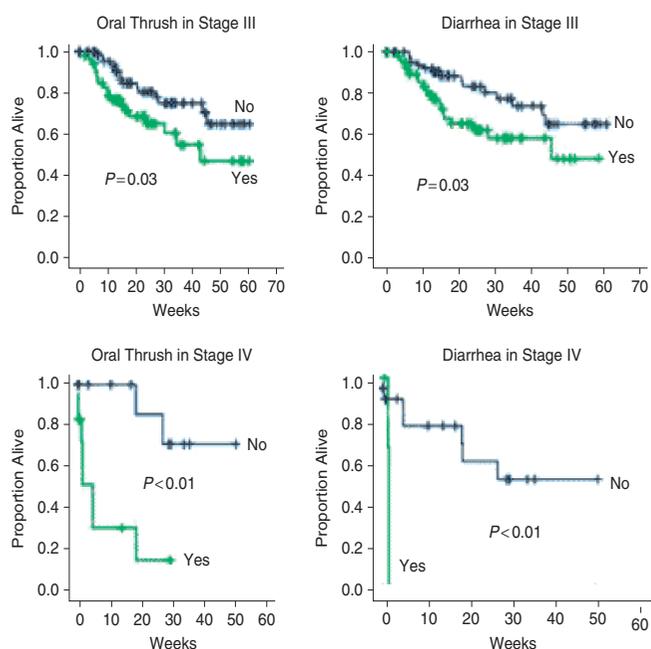


Figure 2
Kaplan-Meier estimates of survival in patients with and without history of diarrhea and oral thrush, Arba Minch Hospital, 2004.

overall incidence rate of tuberculosis was 10 cases/101.3 PYO = 9.9 cases per 100 PYO (95% CI, 8.112.0). The incidence rate was higher in patients with stage III and IV disease (8/70.5 PYO = 11.4 per 100 PYO) than stage I and II combined (2/30.9 PYO = 6.5 per 100 PYO), but the difference was not statistically significant (incidence rate ratio = 1.8; 95% CI = 0.48.2). Patients with baseline history of easy fatigability (chi-squared = 16.8, $P < .001$) and fever (chi-squared = 22.0, $P < .001$) were more likely to develop tuberculosis during follow-up. There was no significant association with past history of tuberculosis (chi-squared = 3.2, $P = .073$; log-rank test).

In the Cox-regression model that contained cough, fever, easy fatigability, and WHO stage III and IV, only fever (HR = 15.6, 95% CI = 2.887.5, $P = .002$) and easy fatigability (HR = 9.2, 95% CI = 1.944.5, $P = .006$) were significant predictors of tuberculosis (Table 3).

Change in Clinical Stages

Only 9 patients progressed to a higher disease stage during follow-up 5 from stage I to II, 2 from stage II to III, 1 from III to IV, and 1 progressed directly from stage I to III. Evidence for progression from stage I to II were weight loss between 5% and 10% of body weight in 4 cases, and repeated upper respiratory tract infection in 1 patient. Patients with initial stage I disease had the highest risk of

Table 2: Hazard Ratio (HR) of Death According to Different Cox-Regression Analyses, Arba Minch Hospital, 2004

	Univariate Analysis(HR [95% CI])	Multivariate Analysis(HR [95% CI])
Oral thrush (yes vs no)	3.8 (2.16.8)	3.5 (1.86.7)
TLC (< 1200/mL vs > 1200/mL)	3.0 (1.56.0)	3.5 (1.48.4)
Hgb (< 10 g/dL vs > 10 g/dL)	4.2 (1.511.8)	--
WHO stage (IIIIV vs III)	6.1 (2.019.2)	--
Diarrhea (yes vs no)	2.6 (1.54.7)	--
BMI (< 18.5 kg/m ² vs > 18.5 kg/m ²)	2.5 (1.34.9)	--

HR = hazard ratio; CI = confidence interval; TLC = total lymphocyte count; Hgb = hemoglobin; WHO = World Health Organization; BMI = body mass index

a new stage-defining event (log-rank test; chi-squared = 21, $P < .001$).

Discussion

In this study, we found a very high mortality rate and a very high incidence of tuberculosis. We identified oral thrush and low TLC as strong predictors of death among our patients. Baseline history of easy fatigability and fever predicted subsequent development of tuberculosis. The risk of new stage-defining event was highest among patients with stage I disease. Additionally, we identified silky hair as a sign of advanced HIV disease.

However, the findings should be interpreted cautiously because of some limitations in the study design. The short follow-up period did not allow us to measure the long-term disease progression pattern in our patients. Because of limited facilities, our diagnosis depended primarily on the clinical picture. We also did not attempt to determine the date of HIV infection in our patients, and hence it does not describe the full picture of the natural history of HIV infection. However, the findings of our study may be rep-

resentative of the actual situation in resource-limited settings as we followed patients during routine activities in the clinic. We also gathered reliable information about the outcome of our patients because of the community agents.

A mortality rate of 46 per 100 PYO in our cohort is probably among the highest ever reported in sub-Saharan Africa. The high proportion of patients with advanced disease, the high magnitude of comorbid clinical conditions, and the high death detection rate by community agents probably contributed to the high mortality rate. In other hospital-based studies from Africa, mortality in the absence of HAART ranged from 10 to 35 per 100 PYO.[2] As a comparison, a community-based study in south-central Ethiopia showed a crude mortality rate of 11.2 per 1000 PYO among adults.[14]

Most of the incidence data for TB come from developed countries.[15,16] From Africa, we have only limited data.[17] An incidence rate of 9.9 per 100 PYO in our study is about 10 times higher than that reported from a

Table 3: Hazard Ratio (HR) for Tuberculosis Incidence According to Different Cox-Regression Analyses, Arba Minch Hospital, 2004

	Univariate Analysis(HR [95% CI])	Multivariate Analysis(HR [95% CI])
Fever (yes vs no)	17.6 (3.589.4)	15.6 (2.887.5)
Weakness (yes vs no)	11.3 (2.748.9)	9.2 (1.944.5)
Cough (yes vs no)	4.3 (1.0417.4)	--
Past history of TB (yes vs no)	3.4 (0.814.6)	--
WHO stage (IIIIV vs III)	2.0 (0.49.5)	--

HR = hazard ratio; CI = confidence interval; TB = tuberculosis; WHO = World Health Organization

research clinic in Ethiopia.[18] Ours is in agreement with a report of 10.4 per 100 PYO from Cape Town.[17] Most of our patients came from low socioeconomic backgrounds where tuberculosis is rampant even without HIV. Because we used clinical criteria, overdiagnosis of PTB-cases could have contributed to the high incidence. However, because the data were collected under real-life situations at a district hospital, it is likely to represent the actual tuberculosis situation. Although easy fatigability and prolonged low-grade fever are often described as non-specific symptoms of tuberculosis,[10] patients with these symptoms may require more frequent monitoring for tuberculosis.

Presence of diarrhea remained a significant marker of death in patients with stages III and IV disease. Because diarrhea is an easily recognizable symptom, history of diarrhea should always be determined during clinical examinations even when other stage-defining events are present. Whether diarrhea could predict mortality in patients receiving ART needs further evaluation. Further studies should also attempt to identify definitive causes of diarrhea and their prognostic values in such settings.

Several authors have described the prognostic value of oral candidiasis, BMI, TLC, and anemia.[19-25] We further confirm the prognostic value of oral thrush and low TLC but not of BMI and hemoglobin levels in patients who are not receiving ART. Additionally, we found that the mortality rate was higher in patients with oral candidiasis within the same WHO stage. The WHO now recommends initiation of ART for all patients in stage III if there are no facilities for performing CD4+ cell counts.[8] In settings with scarce resources, priority should be given to patients with oral thrush.

Some authors reported silky hair (the "straight hair sign") as a sign of HIV infection, while others argued that it is not pathognomonic for HIV infection.[26-28] Its pathogenesis is not known but some reported it as being a manifestation of mitochondrial abnormality.[29] Although there are no published reports from Ethiopia, silky hair is included as a minor sign in the Ethiopian AIDS case definition.[30] This sign is not included in the WHO staging system.[11] Because more than a quarter of our patients with stage III and IV disease had silky hair, we suggest that it be included as a sign of advanced HIV infection in African patient populations. Whether the hair changes to its normal status with ART needs further investigation.

The apparent high risk for change in disease stage among asymptomatic patients could be due to the minor weight loss, which could occur with similar frequency in both HIV-positive and HIV-negative individuals as reported from Uganda.[6] Minor weight loss and pulmonary tuber-

culosis were the most commonly diagnosed conditions among HIV-positive individuals in Ethiopia.[31] In a multicountry study, no difference was found between stages I and II.[32,33] Moreover, the low risk for progression among patients in advanced stage could be due to the high mortality that probably occurred before any evidence of stage change.

Conclusion

In conclusion, we identified simple clinical and laboratory markers as predictors of death and tuberculosis occurrence. Identifying the specific stage-defining conditions could be of practical importance for patient counseling and for clinical decision-making in resource-limited settings. The prognostic value of these markers in patients receiving ART needs further investigation. History of easy fatigability and fever should be asked routinely in HIV-positive patients in order to identify patients at immediate risk of developing clinical tuberculosis. These symptoms could also identify patients who might benefit from tuberculosis prophylactic therapy. We recommend that INH prophylaxis be included as part of the standard package of care for Ethiopian HIV-infected patients.

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