

## Four Years of Natural History of HIV-1 Infection in African Women: A Prospective Cohort Study in Kigali (Rwanda), 1988-1993

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**Summary:** Clinical features and mortality due to human immunodeficiency virus type-1 (HIV-1) infection in women are described as part of a prospective 4-year cohort study on perinatal transmission of HIV in Kigali, Rwanda. Two hundred fifteen HIV-seropositive (HIV+) and 216 HIV-seronegative (HIV-) pregnant women were enrolled at delivery between November 1988 and June 1989. Clinical information collected during systematic quarterly examinations was compared. HIV antibody tests were performed at delivery and CD4/CD8 lymphocyte counts at 15 days' postpartum. HIV- women who seroconverted during the follow-up period were excluded from the analysis of the comparison group starting at the date of seroconversion. At enrollment, all HIV+ women were asymptomatic for acquired immune deficiency syndrome (AIDS). Incidence of tuberculosis was 2.9 per 100 women-years (WY) after 4 years of follow-up in HIV+ women versus 0.2 per 100 WY among HIV- women (relative risk, 18.2; 95% confidence interval 2.4-137.0). Among HIV+ women, the incidence of AIDS (World Health Organization clinical AIDS definition) was 3.5 per 100 WY. The mortality rate was 4.4 per 100 WY among HIV+ women versus 0.5 per 100 WY among HIV- women. Clinical AIDS was present in only half of the fatalities. Tuberculosis was a major cause of morbidity and mortality in these HIV+ African women. An early diagnosis and an appropriate treatment or prevention of tuberculosis should improve the quality of life of HIV-infected patients in Africa. **Key Words:** HIV-1—Natural history—Tuberculosis—Women—Africa.

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Human immunodeficiency virus type 1 (HIV-1) infection is recognized as a major public health problem in sub-Saharan Africa (1,2). Most cases of acquired immune deficiency syndrome (AIDS) and HIV infection occur in adults contaminated by heterosexual contacts and in children infected by perinatal transmission (2,3).



In Africa, although the male-to-female sex ratio is close to 1:1 for AIDS cases, estimates of the HIV seroprevalence among young adults frequently give higher figures for women than men. In population-based HIV serosurveys performed in Uganda in 1989, women had an infection rate 1.4 times higher than that for men (4). Similar observations have been made in Rwanda (5).

The clinical aspects and the natural history of HIV infection among women have been primarily documented in Europe and in the United States (6-9). In these women, injecting drug use is the major risk factor for acquisition of HIV infection. It is conceivable that such observations cannot be extrapolated to African women who acquire HIV infection most likely by heterosexual intercourse, live in a very different socioeconomical and microbiological environment, and whose clinical management is also much more limited. At the present, few data are available on the specific characteristics of the natural history of HIV infection in African women (10).

The aim of this study is to describe events occurring over a 4-year prospective clinical follow-up in an already existing cohort of HIV-infected women after delivery in Kigali, Rwanda, in order to ultimately provide recommendations for improving the quality of care in this African environment.

## SUBJECTS AND METHODS

In an ongoing prospective cohort study on mother-to-child transmission of HIV-1, two groups of HIV-seropositive (HIV+) and seronegative (HIV-) women were enrolled at delivery at the maternity ward of the Centre Hospitalier de Kigali (CHK) and followed up. Details of the enrollment and follow-up procedures have been published elsewhere (11,12). Briefly, HIV testing was systematically offered between November 1988 and June 1989 to all women delivering in the maternity ward of the CHK and accepting the principles of the study. We enrolled consecutively those women who fulfilled the following inclusion criteria: delivering a live birth, living permanently within the city limits, and giving informed consent to participate. A group of HIV- women of comparable maternal age and parity was consecutively selected as a comparison group. Pretest information, objectives, constraints, and benefits of the study were related to each woman at delivery by a trained social worker. Posttest counselling was given to those who wanted to know their HIV serostatus or those of their children during the study period.

The women were systematically examined at 3-month intervals over the 4 years of follow-up by practitioners who were blinded to the HIV serostatus and focused on signs and symptoms of the World Health Organization (WHO) clinical case definition for AIDS in adults (13). A standardized questionnaire was applied during each consultation to collect data on symptoms

and hospitalizations occurring during the past trimester. Medical care was provided free of charge in both groups throughout the study period.

At delivery, a blood sample was collected from the mother and tested for HIV antibodies by a commercial enzyme linked immunosorbent assay (ELISA), Vironostika, Organon Teknika) and confirmed by a commercial Western blot (WB) technique (Du Pont de Nemours) with use of the Centers for Disease Control criteria of interpretation (14). All HIV- women were retested for HIV antibodies every 3 months during follow-up to detect possible seroconversions. Recent syphilis was diagnosed at delivery by dual positive nontreponemal test (VDRL, latex Wellcome) and treponemal test (TPHA, Wellcome). CD4 and CD8 lymphocyte counts were carried out by an indirect immunofluorescence technique at 2 weeks' postpartum. A CD4/CD8 ratio of <0.5 defined severe immunodeficiency (15).

Tuberculosis was confirmed if sputum smears stained by the Ziehl-Nielsen technique revealed typical alcohol acid-resistant bacilli or if *Mycobacterium tuberculosis* was obtained by culture of smears on Lowenstein medium, or isolated from pleural or lymph node biopsies. It was considered probable otherwise on the observation of a clinical improvement under tuberculosis treatment (three-drug regimen during 6 months).

HIV+ women were compared to HIV- women for morbidity and mortality. When a seroconversion occurred in an HIV- woman, she was excluded from the comparison group from the date of diagnosis of her seroconversion. Clinical outcomes were studied with use of available information collected by standardized follow-up questionnaires and hospital records (16). Incidence density rates of symptoms (expressed as rates per 100 women-years [WY]), clinical signs, and diseases such as tuberculosis were computed. A research of women lost to follow-up at four years was performed by a radio call in the city. Women who were known alive at that time but could not be examined contributed to the denominator for the survival analysis.

Chi-square test, Fisher's exact test, and Student's *t* test were used for comparisons, with a significance level of 0.05. Relative risks (RR) were computed to measure the strength of association for incidence density rates with their 95% confidence intervals (CI) according to the semi-exact method.

For HIV+ women, cumulative probabilities of survival and of remaining AIDS-free were computed according to the Kaplan-Meier product limit method and their 95% CI by Rothman's formula (17). Univariate analysis and the descendant stepwise logistic regression model were used to study the determinants of mortality in relation to maternal characteristics recorded at the time of delivery. The following variables were studied as potential risk factors: age <25 years, reproductive history with at least one spontaneous abortion, unstable sexual relationship, low income, presence of clinical signs and symptoms of HIV infection, and CD4/CD8 ratio <0.5.

## RESULTS

Details about the results obtained at enrollment in the study have been given elsewhere (11,12). In brief, the two groups of 215 HIV+ and 216 HIV- women gave 218 live births, respectively. The mean maternal age was 25.1 years (SD: 4.5 years) and the

total number of pregnancies was 2.7 (SD: 1.8). The proportion of women living in a stable relationship, legal marriage, or common-law union, tended to be lower in the HIV+ group (83%) than in the HIV- group (89%,  $p = 0.06$ ). HIV+ mothers did not differ from HIV- mothers in terms of occupation, monthly income, and place of origin. The HIV- mothers enrolled and those screened but not enrolled were similar in terms of socioeconomic status. Between delivery and day 15 postpartum, the drop-out rate in the HIV- group enrolled (16% of  $n = 257$ ) was not statistically different from that among the HIV+ group (21% of  $n = 273$ ). Predominant reasons for drop out were refusal of the husbands and false address given by the mothers.

Two weeks after delivery, no HIV+ woman fulfilled the WHO definition for clinical AIDS. The only differences between HIV+ and HIV- women were for chronic cough and history of herpes zoster, more frequently reported by HIV+ women than by HIV- women (6 vs. 3%,  $p = 0.08$ ; and 2 vs. 0%,  $p = 0.05$ , respectively). In contrast to the paucity of clinical signs and symptoms, 72.4% of the HIV+ women ( $n = 185$ ) had a CD4/CD8 ratio  $<1$  versus 10.1% of the HIV- women ( $n = 197$ ) ( $p < 0.001$ ). Profound immunosuppression was observed in 24.3% of the HIV+ women and in 3.0% of the HIV- women. There was no significant difference between the two groups for the presence of syphilis antibodies, with an overall prevalence of 13.3% ( $30/188 = 16\%$  in the HIV+ group, and  $19/181 = 10\%$  in the HIV- group).

Overall, the mean length of clinical follow-up was 34.9 months (SD = 16 months). HIV- women accounted for 594 WY of clinical follow-up, and HIV+ women for 637 WY (Table 1). Clinical follow-up data were obtained after 4 years for only 206 women. Loss to follow-up was primarily due to secondary settlement outside of the study area. When

taking into account the additional information provided by those women who died ( $n = 29$ ), seroconverted ( $n = 20$ ), or were lost to clinical follow-up before the end of the fourth year ( $n = 176$ ), 76% of the theoretical clinical follow-up of the cohort was available for the evaluation of the morbidity (Table 1). There were no significant differences in terms of demographic or clinical characteristics at time of inclusion of the women who were clinically followed up over the study period compared with those lost to follow-up (data not shown). After the radio call in the city, 299 women were known to be alive after 4 years, accounting for 690 WY of survival in HIV+ women and 727 WY in HIV- women (Table 1). These figures were used for the evaluation of mortality.

Over the entire follow-up period, there were statistically significant differences between HIV+ and HIV- women for the occurrence of each of the clinical signs and symptoms of the clinical AIDS case definition (Table 2). Weight loss, defined as the loss of 10% or more of the body weight measured at 3-month postpartum, generalized lymphadenopathy, generalized pruritis dermatitis, and persistent cough were the most frequently reported symptoms in the group of HIV+ women after 4 years of follow-up. However, herpes zoster was the sign most strongly associated with HIV infection (22 episodes) for a RR of 7.9 (Table 2).

Seventeen cases of tuberculosis (seven pulmonary, eight extrapulmonary, and two disseminated), of which 14 were confirmed bacteriologically, were diagnosed in HIV+ women versus one case of extrapulmonary tuberculosis confirmed in an HIV- woman. Overall, the incidence of tuberculosis was 2.86 per 100 WY in HIV+ women and 0.16 per 100 WY among HIV- women during the 48 months of follow-up (RR, 18.2; CI, 2.4-137.0).

The incidence density rate of hospitalizations was

TABLE 1. Four-year follow-up of a cohort of human immunodeficiency virus type 1 (HIV-1)-infected (HIV+) and uninfected (HIV-) women—Summary statistics (Kigali, Rwanda, 1988-1993)

	No. of women at inclusion	No. of seroconversions	No. of deaths	No. alive at 48 months <sup>a</sup>	Women-years of survival follow-up <sup>a</sup>	No. clinically followed up for 48 months	Women-years of clinical follow-up
HIV+ (%)	215 (100)	—	26 (12.1)	140 (65.1)	690	91 (42.3)	594
HIV- (%)	216 (100)	20 (9.3)	3 (1.3)	159 (73.6)	727	115 (53.2)	637
Total (%)	431 (100)	20 (4.6)	29 (6.7)	299 (69.4)	1417 (87.7) <sup>b</sup>	206 (47.8)	1231 (76.1) <sup>b</sup>

<sup>a</sup> Survival follow-up measured after a radio call in the city.

<sup>b</sup> Reference:  $4 \times 431 = 1,724$  women-years (WY) of follow-up minus 50 WY censored due to maternal death and 58 WY censored due to maternal seroconversion = 1,616 WY of theoretical follow-up.

TABLE 2. Incidence density rates per 100 women-years (WY) of signs and symptoms among human immunodeficiency virus type 1 (HIV-1)-infected (HIV+) and uninfected (HIV-) women during the first 48 months of follow-up (Kigali, Rwanda, 1988-1993)

Sign or symptom	HIV- women	HIV- women	Relative risk	95% Confidence interval	p Value <sup>a</sup>
Weight loss $\geq 10\%$ baseline <sup>b</sup>	12.6	5.9	2.1	1.4-3.1	0.0001
Prolonged fever ( $\geq 1$ month) <sup>b</sup>	6.1	2.2	2.8	1.5-5.1	0.0015
Chronic diarrhea ( $\geq 1$ month) <sup>b</sup>	5.4	1.7	3.2	1.6-6.2	0.0012
Generalized lymphadenopathy <sup>c</sup>	28.8	16.3	1.8	1.4-2.2	0.0001
Persistent cough ( $\geq 1$ month) <sup>c</sup>	9.1	4.1	2.2	1.4-3.6	0.0008
Generalized pruritis dermatitis <sup>c</sup>	10.1	4.1	2.4	1.6-3.9	0.0001
Herpes zoster <sup>c</sup>	3.7	0.4	7.9	2.4-26.3	0.0002
Oropharyngeal candidiasis <sup>c</sup>	5.2	1.3	4.2	1.9-9.0	0.0002
AIDS (WHO case definition) <sup>d</sup>	3.5	—	—	—	—

AIDS, acquired immune deficiency syndrome; WHO, World Health Organization.

<sup>a</sup> Chi-square test.

<sup>b</sup> Major sign of the WHO AIDS case definition.

<sup>c</sup> Minor sign of the WHO AIDS case definition.

<sup>d</sup> See definition in text.

13.9 per 100 WY among HIV+ women versus 9.5 per 100 WY in the HIV- group ( $p=0.01$ ) (Table 3).

Twenty-one women developed clinical AIDS during follow-up, all in the HIV+ group (3.5 per 100 WY). The cumulative probability of remaining AIDS-free among HIV+ women was 97.4% after 12 months of follow-up (CI, 94-99%), 95.5% after 24 months (CI, 91-98%), and 85.9% after 48 months (CI, 79-91%) (Fig. 1).

Although the occurrence of AIDS was rare in these HIV+ women, 26 of them (12.1%) died over the 4-year period versus three among HIV- women (1.4%). Women known to be alive after 4 years accounted for 87.7% of the theoretical follow-up for survival analysis (Table 1). The mortality rate was 4.4 per 100 WY among HIV+ women versus 0.5 per 100 WY among HIV- women (RR, 9.3; CI, 2.8-30.7). The cumulative probability of survival for HIV+ women was 98.6% at 12 months (CI, 95.7-99.5%), 93.6% at 24 months (CI, 89.0-96.3%), and 85.5% at 48 months (CI, 79.1-90.2%) (Fig. 2). The causes of death among HIV+ women were identified in 24 out of the 26 cases (92%): tuberculosis (8), persistent diarrhea (6), pneumonia (3), sepsis (3), malaria (2), encephalitis (1), and surgical complications (1). Only 12 of these 26 deaths (46%) were in women presenting with clinical AIDS at the time of death, but 22 were possibly HIV related. In HIV- women, one died of surgical complications during the early postpartum period, one of epileptic fit, and the last one of an encephalitis of unknown etiology.

Among the 16 maternal variables studied by univariate analysis, persistent cough at inclusion was the only symptom associated with mortality (Table

4). Nine of these variables were introduced in the multivariate logistic regression model. The only parameter significantly associated with 4-year mortality in HIV+ women was the presence of persistent cough ( $p = 0.048$ ; odds ratio, 2.66; CI, 1.01-7.01).

## DISCUSSION

Although women are estimated to represent more than half of the population of HIV-infected people worldwide (2), very few data are available on the natural history of HIV infection in women. The present study is an attempt to partially fill this gap in an African setting, providing long-term follow-up information. Our evaluation of the natural history of HIV infection had to suffer, however, a major constraint because of its prevalent cohort design (18). Indeed, the ideal way to describe the natural history of HIV infection is to follow incident cohorts. Such groups are difficult to identify and enroll, particularly in Africa. The main objective of our cohort study was the evaluation of the mother-to-child transmission rate of HIV. The women participating in our study, however, had just completed a pregnancy, were mostly asymptomatic at enrollment, but had an unknown duration of HIV infection. Our clinical observations collected prospectively in a systematic fashion with a comparison group of HIV- women may be used to approximate the "true" natural history of HIV infection in this population. The follow-up rate was high enough and comparable between the two groups to guarantee that unbiased conclusions were drawn from this analysis (16).

In our study, the cumulative probability of reach-

TABLE 3. Number and causes of hospitalizations in the two groups of human immunodeficiency virus type 1 (HIV-1)-infected (HIV+) and uninfected (HIV-) women (Kigali, Rwanda, 1988-1993)

Diagnosis	HIV+ women	HIV- women
Malaria	15	19
Diarrhea	8	0
Pneumonia	5	1
Tuberculosis	4	0
Meningitis	2	0
Breast abscess	2	2
Other infections <sup>a</sup>	4	0
Subsequent delivery or gynecological disorders	26	22
Postsurgery complications	14	9
Other causes	3	8
No. of hospital admissions	83	61

<sup>a</sup> Other infections: oropharyngeal candidiasis (1), herpes zoster (1), septicemia (2).

ing the AIDS stage is 4.5% after 2 years of follow-up and 14.5% after 4 years in HIV+ women. These figures are consistent with those described by Lindan and co-workers in another prevalent cohort of Rwandan women followed for 2 years (10). In addition, when comparing our study with those performed in other population groups in industrialized countries, our figure falls within the range of values already obtained, the cumulative probability of de-

veloping AIDS varying between 17.5% after 4 years among European women (7) and 21% among women after an index delivery (9). Although these studies used various definitions of AIDS and were also prevalent studies, this comparison suggests that the course of the HIV infection is not dramatically different in populations of women from industrialized countries compared with those from Africa.

After four years of follow-up, the mortality rate among HIV+ women was nine times higher than in HIV- women. These figures are lower than those obtained in a Ugandan rural adult population where the annual mortality rate was 11.6% (19,20). This difference may be explained by the lack of medical care in this rural population in contrast to our cohort or by the prevalent design. More than half of the deaths among the HIV-infected group occurred in women not fulfilling the clinical definition of AIDS in our study. This suggests that the life-threatening manifestations of HIV infection in African women are much broader than those strictly included in the AIDS case definition, as suggested earlier (10,20). Thus, the clinical definition of AIDS proposed in Bangui in 1986 may be seen as a tool of limited value for the evaluation of HIV-related mortality (13,21).

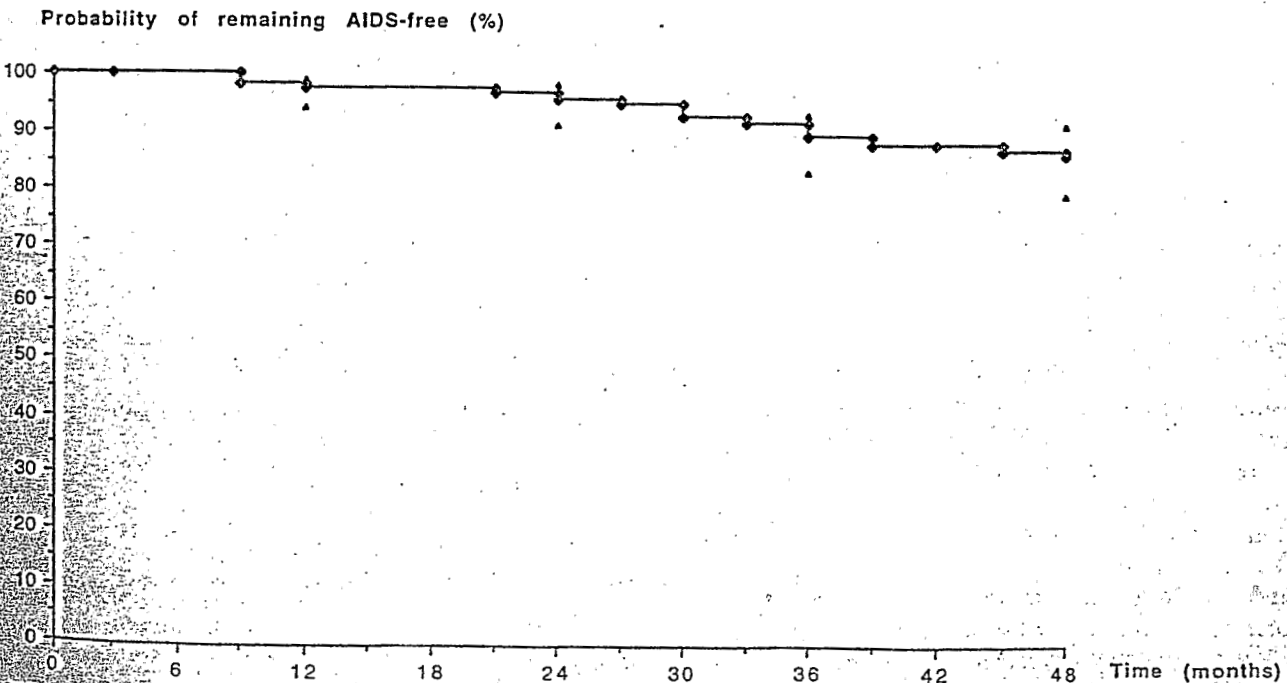


FIG. 1. Probability of remaining free of acquired immune deficiency syndrome (AIDS) among human immunodeficiency virus type 1-infected women (n = 215): Kaplan-Meier product limit method (Kigali, Rwanda, 1988-1993).

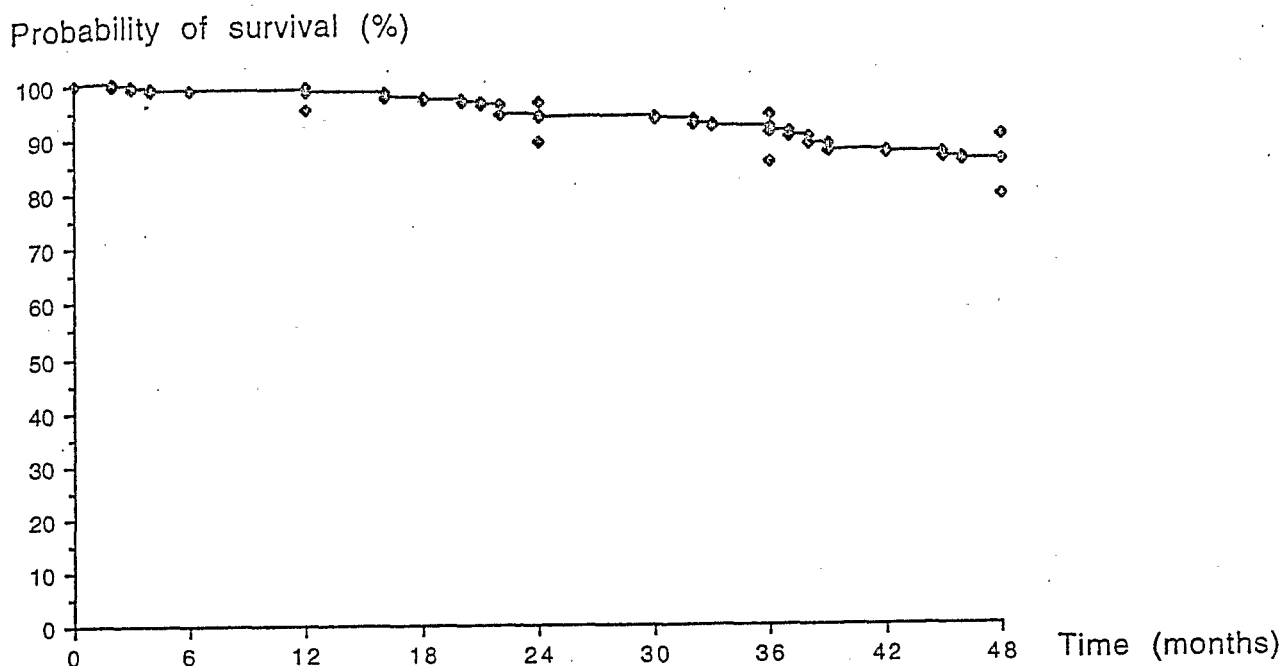


FIG. 2. Probability of survival among human immunodeficiency virus type 1-infected women ( $n = 215$ ): Kaplan-Meier product limit method (Kigali, Rwanda, 1988-1993).

In our study, each of the clinical signs and symptoms included in the WHO definition of AIDS was observed with increased frequency among HIV+ women as compared with HIV- women. One of the diseases most frequently encountered among HIV+ women and also frequently identified as a major cause of death was tuberculosis. Indeed, the risk of developing tuberculosis was 18 times higher for HIV+ women than for HIV- women. This fig-

TABLE 4. Univariate analysis—maternal variables at inclusion studied as possible determinants of 4-year mortality (Kigali, Rwanda, 1988-1993)

Variables at inclusion	% Decreased (n = 26)	Odds ratio	p Value
Age <25 years	35	1.9	0.11 <sup>a</sup>
Educational level >5 years	46	0.6	0.31 <sup>a</sup>
Low income <5 000 FRW (35 S)	12	1.7	0.27 <sup>a</sup>
Parity $\geq 2$	69	0.6	0.62
One or more abortion	31	1.4	0.23 <sup>a</sup>
Diarrhea ( $\geq 1$ month)	4	0.7	0.68
Prolonged fever ( $\geq 1$ month)	4	0.8	0.83
Weight <50 kg	18	0.9	0.25 <sup>a</sup>
Herpes zoster	4	0.9	0.92
Oropharyngeal candidiasis	4	3.7	0.24 <sup>a</sup>
Generalized pruritis dermatitis	4	1.0	0.97
Generalized lymphadenopathy	0	—	0.45
Persistent cough ( $\geq 1$ month)	27	2.6	0.05 <sup>a</sup>
CD4/CD8 ratio <0.5	19	0.9	0.82 <sup>a</sup>

<sup>a</sup> These variables were included in the multivariate analysis (logistic regression model).

ure is consistent with those found in other cohort studies in Africa (22,23). At any stage of HIV infection, subjects are at increased risk of reactivating a latent *M. tuberculosis* infection and probably also to acquire primary infection (24,25). Thus, the HIV epidemic has a striking effect, particularly in Africa, on the magnitude of the tuberculosis burden (26,27). It is noteworthy that in our multivariate analysis of risk factors of death in HIV+ women, the only clinical sign predictive of death is chronic cough at enrollment. This suggests that chronic cough should be considered as an early marker of a pejorative evolution of HIV infection in relation to tuberculosis or other pulmonary complications. The fact that profound immunosuppression was not predictive of mortality does not imply that this epidemiological association does not exist.

Tuberculosis as well as common bacterial complications of HIV infection such as pneumococcal infection are readily treatable by appropriate chemotherapy, making early clinical management of HIV-infected individuals feasible even in the developing world (28). In addition, in Africa, the evaluation of pragmatic approaches designed to prevent or treat early tuberculosis in HIV-infected patients should be considered of utmost priority. In the context of implementing programs for clinical and psychosocial management of HIV infection, women of

childbearing age should be targeted as they already pay a heavy tribute to the HIV pandemic.

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