Impact of opportunistic diseases on chronic mortality in HIV-infected adults in Côte d'Ivoire

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Objective. To estimate incidence rates of opportunistic diseases (ODs) and mortality for patients with and without a history of OD among HIV-infected patients in Côte d'Ivoire.

Methods. Using incidence density analysis, we estimated rates of ODs and chronic mortality by CD4 count in patients in a co-trimoxazole prophylaxis trial in Abidjan before the highly active antiretroviral therapy (HAART) era. Chronic mortality was defined as death without a history of OD or death more than 30 days after an OD diagnosis. We used Poisson's regression to examine the effect of OD history on chronic mortality after adjusting for age, gender, and current CD4 count.

Results. Two hundred and seventy patients (40% male, mean age 33 years, median baseline CD4 count 261 cells/µl) were followed up for a median of 9.5 months. Bacterial infections and tuberculosis were the most common severe ODs. Of 47 patients who died, 9 (19%) died within 30 days of an OD, 26 (55%) died more than 30 days after an OD, and 12 (26%) died with no OD history. The chronic mortality rate was 31.0/100 person-years for those with an OD history, and 11.1/100 person-years for those with no OD history (rate ratio (RR) 2.81, 95% confidence interval (CI): 1.43 - 5.54). Multivariate analysis revealed that OD history remained an independent predictor of mortality (RR 2.15, 95% CI: 1.07 - 4.33) after adjusting for CD4 count, age and gender.

Conclusions. Before the HAART era, a history of OD was associated with increased chronic HIV mortality in Côte d'Ivoire, even after adjusting for CD4 count. These results provide further evidence supporting OD prophylaxis in HIV-infected patients.

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It has been estimated that in sub-Saharan Africa, 25 million adults and children were living with HIV/AIDS and approximately 2.2 million died of HIV-related causes in 2003 alone.[1] In this region most deaths among HIV-infected people are related to treatable and preventable opportunistic diseases (ODs).

Efforts to ramp up antiretroviral therapy (ART) delivery to resource-limited settings have met with a relative imbalance of efforts to implement OD prophylaxis. In the absence of current widespread ART use, mortality still occurs because of preventable acute ODs. Experience in the developed world has also proved that having a previous OD increases long-term mortality, even when controlling for CD4 cell count.[2] While this has not yet been demonstrated in Africa, proving the so-called 'chronic mortality' effects of an OD suggests an even greater need for OD prevention. Our objective was to estimate the incidence rates for ODs and mortality for patients with and without a history of OD in different stages of HIV infection in Côte d'Ivoire. We hypothesised that a history of OD would increase mortality in HIV-infected adults in Côte d'Ivoire, even after adjusting for age, gender and CD4 cell count.

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Methods

Study sample

The study sample consisted of the placebo arm of a randomised controlled trial of early chemoprophylaxis with co-trimoxazole for HIV-infected adults in Abidjan, Côte d'Ivoire (ANRS 059).[3] HIV-infected patients (N = 270) in the placebo arm of the trial were followed between April 1996 and March 1998, with a median follow-up time of 9.5 months. CD4 cell counts were assayed every 6 months. Details of the trial have been published elsewhere.[3]

Opportunistic diseases under consideration

For the purposes of this analysis, ODs were first sorted into 11 groups: severe bacterial infections, mild bacterial infections, severe fungal infections, mild fungal infections, tuberculosis, malaria, isosporiasis, toxoplasmic encephalitis, non-tuberculous mycobacteriosis, other severe illnesses, and other mild illnesses. Infectious diagnoses were grouped according to the causative micro-organism. Second, ODs were assigned to one of two categories (mild or severe) to reflect either a greater or lesser effect on acute OD-related mortality. The diagnostic criteria used by the trial team event documentation committee have been reported previously.[4]

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CD4 cell count

The OD incidence and mortality rate analyses were performed within three clinically relevant CD4 cell count strata: > 200/µl, 51 - 200/µl, and ≤ 50/µl. CD4 cell counts at the time of diagnosis of an OD were estimated by linear interpolation between two consecutive CD4 cell count measures. Sensitivity analyses were performed to examine whether results were sensitive to the assumption underlying the modelling of CD4 cell counts at the time of OD diagnosis.

Mortality

We defined two types of HIV-related mortality: (*i*) 'acute' mortality, defined as a death within the first 30 days of an OD diagnosis; and (*ii*) 'chronic' mortality, defined as death occurring in the absence of any OD, or death more than 30 days after an OD diagnosis.

Statistical analyses

We conducted both crude and adjusted analyses. The crude analysis estimated the OD incidence density and mortality rates with and without a history of OD using an incidence density approach.[5] We built a Poisson's regression model, adjusting for multiple observations within the same person, to examine the linear trend of OD incidence rates across CD4 strata.[6] We developed a second Poisson's regression model to estimate the effect of a history of OD after adjusting for CD4 cell count strata (≤ 50/µl, 51 - 200/µl, and ≥ 201/µl), age at enrolment (< 31 years or ≥ 31 years), and gender.

For the mortality analyses, the time at risk within each CD4 cell count stratum was divided into the time before and after the first OD occurrence. We performed an additional analysis to determine if CD4 cell count modified the relationship between OD history and chronic HIV mortality. We conducted a test of homogeneity by comparing the relative risks for chronic HIV mortality for those with and without an OD history across CD4 cell count strata.[6] All analyses were performed using SAS 8.2 (SAS Institute, NC).

Results

Incidence of opportunistic diseases within clinically relevant CD4 cell count strata

The incidence rates of severe ODs varied substantially across CD4 cell count strata. After 'other severe diseases', bacterial infections were the most common OD and toxoplasmosis was the least common. For nearly all severe ODs, with the exceptions of malaria and isosporiasis, there was an increase in incidence rate as CD4 cell counts fell to ≤ 50/µl. The linear trend was significant for severe bacterial infections, non-tuberculous mycobacteriosis, and other severe ODs (*p*-value for trend < 0.05). Among patients with CD4 cell counts ≤ 50/µl, the incidence rate was highest for 'other severe diseases', followed by severe bacterial infections, and non-tuberculous mycobacteriosis. The incidence rates per 100 person-years for any mild OD were 66, 107, and 188 for the CD4 cell count strata > 200/µl, 50 - 200/µl, and ≤ 50/µl, respectively. For any severe OD, the incidence rates per 100 person-years were 65, 139, and 159 for the strata > 200/µl, 50 - 200/µl, and ≤ 50/µl (Fig. 1).

Mild ODs occurred more frequently than severe ODs across all CD4 cell count strata. There also was a linear trend of increasing incidence of mild ODs as CD4 cell count decreased for mild bacterial and mild fungal ODs (*p*-value for trend < 0.05).

Chronic mortality

Overall, 47 of 270 participants (17%) died during the course of the trial. Of these, 9 (19%) died within 30 days of an OD diagnosis; their deaths were classified as 'acute'. The remaining 38 deaths were defined as 'chronic' as these patients either did not have a history of OD (*N* = 12) or survived more than 30 days after their OD diagnosis (*N* = 26). The estimated crude chronic mortality rate was 19.8 per 100 person-years. Patients with an OD history had a higher chronic mortality rate (31.0 per 100 person-years) than patients without an OD history (11.1 per 100 person-years) (Fig. 1). Current CD4 cell count was strongly associated with chronic mortality (Table I). Results of multivariate analyses showed that after adjusting for age, gender, and current CD4 cell count, patients with an OD history were more than twice as likely to die as patients without an OD history (rate ratio (RR) 2.15) (Table I).

The results of the analysis examining whether the effect of OD history on chronic mortality was similar within different CD4 cell count strata indicated lack of effect for patients with CD4 cell counts ≤ 50/µl (RR 0.86, 95% confidence interval (CI): 0.29 - 2.55). The effect of OD history was the highest for the CD4 cell count stratum 51 - 200/µl (RR 4.89, 95% CI: 1.42 - 16.88). For CD4 cell count > 200/µl, there was a trend towards an increase in chronic mortality (RR 2.07, 95% CI: 0.46 - 9.26). The *p*-value for the test of heterogeneity of the effect of OD history on chronic mortality by CD4 cell count was 0.1005. The results were robust to the method of estimation of CD4 cell count at the time of OD.

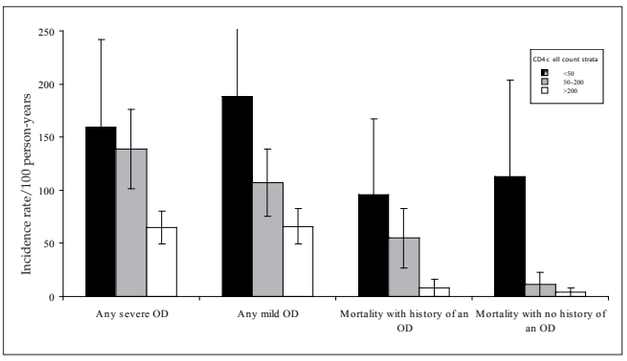

Fig. 1. Incidence rates per 100 person-years for any severe OD, any mild OD, mortality with a history of an OD, and mortality with no history of an OD, each stratified by CD4 cell count.

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Table I. Chronic HIV mortality rates: crude and adjusted hazard rate ratios by history of opportunistic disease (OD), CD4 stratum and age, Abidjan, Côte d'Ivoire

Risk factor	Chronic deaths (*N*)	Time at risk (years)	Incidence rate per 100 PY	Crude rate ratio (95% CI)	Adjusted rate ratio (95% CI)
Overall	38	192	19.8	—	—
History of OD					
Yes	26	84	31.0	2.81 (1.43 - 5.54)	2.15 (1.07 - 4.33)
No	12	109	11.1	1.00	1.00
CD4 stratum (cells/µl)					
> 200	7	126	5.6	1.00	1.00
51 - 200	18	54	33.5	6.01 (2.54 - 14.25)	4.73 (1.97 - 11.39)
≤ 50	13	13	103.2	18.60 (7.62 - 45.41)	16.57 (6.14 - 44.71)
Gender					
Male	19	80	23.7	1.40 (0.74 - 2.65)	0.73 (0.36 - 1.50)
Female	19	112	17.0	1.00	1.00
Age at enrolment (yrs)					
≥ 31	27	91	30.0	2.76 (1.37 - 5.56)	1.97 (0.98 - 3.97)
< 31	11	102	10.8	1.00	1.00

CI = confidence interval; PY = person-years.

Discussion

This study estimated the incidence rates of ODs and chronic mortality rates for HIV-infected patients in Côte d'Ivoire with and without a history of OD, stratified by CD4 cell count. Eighty-one per cent of patients who died during the course of the trial died either with no history of OD or more than 30 days after an OD diagnosis, with the rate ratio for chronic mortality twice as high for patients with a history of OD as for those with no OD history. This increased risk of mortality in patients with a history of OD has not been reported for sub-Saharan Africa, although it has been seen in the USA.[2] These findings highlight the fact that OD prophylaxis not only can prevent acute mortality but may also decrease later HIV-associated mortality, and suggest that treating ODs after they occur may be less effective in the long run than preventing them.

The spectrum of morbidity that we describe is congruent with the literature on HIV disease in sub-Saharan Africa.[7,8] We found that invasive bacterial infections were the most frequent severe ODs (after the 'other severe diseases' category) in all CD4 cell count strata, and that tuberculosis was the second most frequent OD in almost all CD4 strata with the exception of the < 50/µl stratum. However, the results of this analysis were not indicative of an association between CD4 cell count and incidence of malaria, which contrasts with the results of Whitworth *et al*.[9] from Uganda. Methodological and diagnostic differences make a direct comparison between the findings of these two studies difficult.

Our results also differ from those of several other studies, which showed that non-tuberculous mycobacteriosis was found infrequently in the most severely ill HIV patients.[9] While relatively uncommon in our overall population, non-tuberculous mycobacteriosis was the second most frequent cause of severe morbidity among patients with CD4 cell counts ≤ 50/µl. Direct comparison of these results with previous results in the literature was difficult because most of the studies focused on the prevalence of non-tuberculous mycobacteriosis in Africa, not the incidence.

The estimates of OD incidence presented here extend and complement the analysis of Attia *et al*.[4] by accounting for the availability of longitudinal CD4 cell count measures and describing the incidence of ODs and mortality within several clinically important CD4 cell count strata. Other studies[10,11] have also emphasised that knowledge of the current state of surrogate markers may provide better guidance for subsequent steps in HIV management.

Current, rather than baseline, CD4 cell count-specific OD incidence may be more appropriate to use in models aimed at assessing both the most efficient CD4-based initiation criteria for OD prophylaxis and ART.[12] Modelling of this type can also inform critical questions of disease management requiring immediate action when data are sparse.

This study has several limitations. First, the short time frame of the trial may have limited the presentation of less common ODs. Second, the population enrolled in the trial may not accurately represent the general population of HIV-infected patients in Côte d'Ivoire. However, the more rigorous diagnostic capabilities within the trial may lend better insight into the true incidence of ODs and the chronic mortality that is attributable to them. Third, geographical variation may

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affect the ability to generalise these results to other regions of sub-Saharan Africa.[7,10] The development of rational clinical guidelines to assist in patient care decision making should ideally be based on region-specific data.[7]

In summary, this is the first study of HIV-infected patients in Côte d'Ivoire focusing on the relationship between a history of ODs and chronic mortality. In sub-Saharan Africa, co-trimoxazole prophylaxis has been shown to reduce short-term mortality in HIV-infected adults.[11,13] The association between a history of OD and chronic mortality suggests that OD prophylaxis could also have implications for long-term mortality. Since most of the important ODs were preventable within this trial, it is critical to ensure adequate access to OD prophylaxis for all HIV-infected patients in sub-Saharan Africa. Despite the effort put into increasing the availability of ART in these populations, many HIV-infected patients do not have access to such treatment, and there may be substantial benefit to also including a focus on OD prophylaxis as part of the comprehensive package of care.

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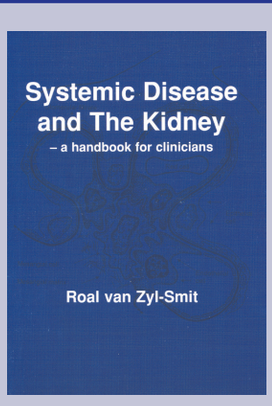

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