Cause-Specific Mortality and the Contribution of Immune Reconstitution Inflammatory Syndrome in the First 3 Years after Antiretroviral Therapy Initiation in an Urban African Cohort

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Background. Although many studies have reported high early mortality among patients enrolled in antiretroviral therapy (ART) programs in sub-Saharan Africa—particularly among those individuals with advanced immunodeficiency—few studies have reported the most common causes of these early deaths

Methods. We determined cause-specific mortality and the contribution of immune reconstitution inflammatory syndrome (IRIS) in a well-characterized patient cohort in Kampala, Uganda, over a 36-month period of ART.

Results. In a cohort of patients who initiated antiretroviral therapy in Uganda, we observed a high early mortality rate among patients with advanced disease. The most common causes of death were tuberculosis and cryptococcal meningitis. The contribution of immune reconstitution inflammatory syndrome to mortality was limited.

Conclusions. We show a significant early mortality in our ART cohort in resource-limited settings that is driven by advanced human immunodeficiency virus disease and characterized by low CD4 cell counts. In our experience, the contribution of IRIS to this observed early mortality is limited.

The dramatic reduction in morbidity and mortality among human immunodeficiency virus (HIV)–infected individuals who initiated antiretroviral therapy (ART) in resource-limited settings has mirrored reductions in morbidity and mortality among such patients in developed countries [1–4]. However, the considerable gains that have been made by HIV treatment programs in resource-limited settings have been tempered by ongoing reports of high early mortality and high rates of loss to follow up among individuals receiving ART [5–10]. Investigations involving patients who have been lost to follow up have revealed that a high proportion of such individuals are lost to follow up as a result of death [6, 11–13]. Therefore, previous mortality estimates for ART rollout programs in sub-Saharan Africa are likely to have underestimated true HIV-related and ART-related mortality [14, 15].

Although many studies have reported high early mortality among patients enrolled in ART programs in sub-Saharan Africa—particularly among those individuals with advanced immunodeficiency—few studies have reported the most common causes of these early deaths [9]. It has become increasingly recognized that immune reconstitution can precipitate the unmasking of subclinical infections [16, 17]. A proportion of patients with these unmasked cases may develop signs of immune reconstitution inflammatory syndrome (IRIS), an exaggerated inflammatory response that was first described in patients with treated opportunistic infections that paradoxically worsened with ART initiation [18]. Although it was anticipated that IRIS would be a major problem in ART rollout programs in resource-limited settings because of low CD4 cell counts at ART

initiation and a high underlying prevalence of *Mycobacterium tuberculosis* and *Cryptococcus neoformans* infection, the contribution of both types of IRIS events (unmasking and paradoxical) to the early mortality seen in HIV treatment cohorts in resource-limited settings is still unclear. In this study, we determined cause-specific mortality and the contribution of IRIS in a well-characterized patient cohort in Kampala, Uganda, over a 36-month period of ART.

PATIENTS AND METHODS

Study setting and population. The Infectious Diseases Institute of Makerere University (Kampala, Uganda) is a center of excellence in the delivery of HIV clinical care and training, with >20,000 patients enrolled and >6000 patients actively receiving ART. A nested research cohort was established in 2004, with a prospective enrollment of 559 ART-naive patients initiating ART from April 2004 through April 2005. A more detailed description of the study procedures and data collection, as well as clinical, immunological, and virological outcomes in this cohort at 12 months of ART, has been described elsewhere [19].

In brief, ART-eligible adults (≥18 years of age) were enrolled in the study if they fulfilled all of the following eligibility criteria: (1) confirmed HIV type 1 infection; (2) regular attendance at clinic visits, based on at least 2 clinic visits within the previous 6 months; (3) stable residence within a 20-km radius of Kampala; (4) willingness to be followed up at the Infectious Diseases Institute for at least 2 years; and (5) eligibility for ART according to the World Health Organization (WHO) 2003 and Uganda Ministry of Health guidelines (ie, a CD4 cell count ≤200 cells/ μL or WHO stage IV), and (6) provision of written informed consent. The first-line ART regimen prescribed was stavudine or zidovudine plus lamivudine and either nevirapine or efavirenz. Daily trimethoprim-sulfamethoxazole prophylaxis was provided to all participants regardless of CD4 cell count, and those individuals who were allergic to trimethoprim-sulfamethoxazole were given dapsone. In general, ART initiation in patients who are co-infected with tuberculosis is delayed until after completion of the intensive phase. The study was approved by the Makerere University Faculty of Medicine Research and Ethics Committee and the Uganda National Council for Science and Technology (no. MV 853). At enrollment, a study physician conducted a clinical evaluation, including a full medical history and a physical examination. Tuberculosis symptoms were assessed, and patients were referred for laboratory testing or radiological examination on the clinicians' discretion. Asymptomatic patient sputum samples are not routinely screened for tuberculosis. *Cryptococcus* antigenemia was measured at ART initiation regardless of the presence of symptoms.

Laboratory testing was performed every 3 months and included a full blood count (Beckman Coulter ACT diff 2), a CD4 cell count by FACS Count (Becton Dickinson), HIV type 1 viral load measurement (Roche Amplicor) with a detection limit of 400 copies/mL, and measurement of serum aspartate transaminase and creatinine levels. Clinical and laboratory data were captured in a structured questionnaire and entered into an Oracle software database, version 9.0. Patient outcome data, including death, transfers, and loss to follow-up, are updated on an ongoing basis.

Ascertainment of death. We recorded all deaths in the cohort over the initial 3 years after ART initiation. The cause of death was determined by one of the study physicians (B.C.) from a combination of source documents, including review of outpatient medical records, such as laboratory results, inpatient hospital records, and a structured interview with the patient's next of kin ("verbal autopsy"). Patients who missed a scheduled visit were first contacted by telephone or, if this was unsuccessful, through a home visit. Therefore, the rate of loss to follow-up is low (13, 8, and 2 patients in the first, second, and third years, respectively), and most causes of death are ascertained. Pathological autopsies were not performed in this cohort.

Deaths were classified as either HIV related (if they were due to known or suspected HIV-associated opportunistic infections or malignancies), due to ART toxicity, or due to other medical conditions. We further determined whether any HIV-related death was due to an underlying IRIS. IRIS was defined as a new onset with atypical presentation (unmasking) of an opportunistic infection or worsening of a known treated infection (paradoxical) within 6 months after ART initiation, using modified criteria from 2 existing published case definitions [20, 21]: (1) atypical presentation; (2) exaggerated inflammatory response (eg, very high-grade fever); (3) worsening of symptoms (for paradoxical IRIS); and (4) increase in CD4 cell count and/ or a decrease in HIV RNA load > 1 log when these parameters were available. We also included a negative microbial culture result as an additional criterion in the case of paradoxical IRIS events. Two investigators (A.K. and B.C.) independently reviewed the cohort charts of patients with suspected IRIS events, and a third investigator (Y.M.) arbitrated in any cases in which there was a lack of consensus.

Statistical analysis. The primary outcome of this study is death during the first 36 months after ART initiation. The mortality rate was ascertained for the following time periods: 1–3 months, 4–6 months, 7–12 months, 13–18 months, 19–24 months, 25–30 months, and 31–36 months after ART initiation. The causes of death were also described. Secondary outcomes included the risk factors for death during the first 36 months of ART. Univariate and multivariate Cox proportional hazards models were used to examine baseline clinical and laboratory predictors of all-cause mortality. Factors that were found to be associated with mortality with a *P* value <.2 in a univariate model were considered as potential covariates in the multi-

variate models. All *P* values were 2-sided. We performed survival analysis, including Kaplan-Meier estimates, to evaluate the cumulative probability of death over a 36-month period of ART according to baseline CD4 cell count. All statistical analyses were performed with Stata software, version 9.2 (Stata).

RESULTS

Baseline characteristics of the study population. Of the 559 patients who initiated ART from April 2004 through April 2005, 386 (69%) were female; their median age was 38 years (interquartile range [IQR], 33–44 years). At ART initiation, the majority of the patients had advanced immunosuppression, with 89% of the patients having disease classified as WHO stage 3 or 4, a median CD4 cell count at the time of ART initiation of 98 cells/μL (IQR, 21–163 cells/μL), and a median log viral load of 5.4 copies/mL (IQR, 5.0–5.8 copies/mL). Specific ART regimens included stavudine-lamivudine-nevirapine, administered to 413 (74%) of the patients; zidovudine-lamivudine-efavirenz , administered to 144 (26%); and stavudine-lamivudine-efavirenz, administered to 2 (0.5%). Thirty-one percent of the patients had a body mass index (BMI; defined as the patient's weight in kilograms divided by the square of their height in meters) <18. One hundred and seventy patients (31%) had a hemoglobin level of 8–11 g/dL, and 26 (5%) had a hemoglobin level of <8 g/dL. Seventy-seven patients (14%) were receiving antituberculosis treatment, and 17 (3%) were being treated for cryptococcal meningitis.

All-cause and cause-specific mortality. Figure 1 shows the incidence of death (per 100 person-years) during the first 36 months of ART, and table 1 shows baseline predictors of HIV-related mortality after 144 weeks of ART. A total of 99 patients (17%) died over the 36-month period; 80 (14%) died during the first 12 months (58 [73%] of these 80 patients died during the first 3 months of treatment). Fifteen (3%) of the patients died during the second year, and 4 (1%) died during year 3 of ART. The overall mortality rate was 12.2 deaths per 100 person-years at risk (95% confidence interval [CI], 6.6–9.8). When the follow-up period was divided into 1-year time bands (from ART initiation through 1 year, from 1 year through 2 years, and from 2 years though 3 years), the mortality rates were 17.9 deaths per 100 person-years at risk (95% CI, 14.5–22.1), 2.3 deaths per 100 person-years at risk (95% CI, 1.2–4.3), and 1.2 deaths per 100 person-years at risk (95% CI, 0.5–3.3), respectively.

Of the 80 deaths that occurred during the first year, 69 (86%) were HIV related (of which 4 were attributed to IRIS), 3 (4%) were due to ART toxicity (2 to hepatotoxicity and 1 to lactic acidosis), and 8 (10%) were due to other medical conditions. During the second year, 4 deaths (27%) were HIV related, 4 (27%) were due to ART toxicity (1 to hepatotoxicity, 2 to lactic acidosis, and 1 to pancreatitis), and 7 (46%) were due to other
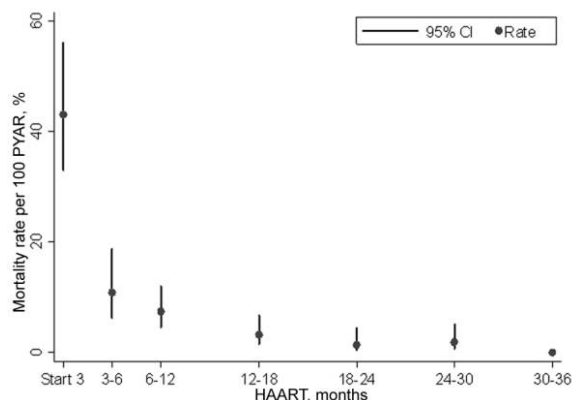

Figure 1. All-cause mortality incidence rates (95% confidence interval [CI]) during the first 36 months of antiretroviral treatment, showing highest rates per 100 person-years at risk (PYAR) during the first 3 months after highly active antiretroviral therapy (HAART) initiation.

medical conditions. Of the 4 deaths that occurred in the third year, 3 were HIV related (figure 2).

Of the 76 HIV-related deaths, 18 (25%) were due to central nervous system infections (11 cases of *Cryptococcus neoformans* meningitis, 4 cases of *Toxoplasma gondii* encephalitis, 2 cases of *Herpes zoster* meningitis, and 1 case involving a cerebral mass), 13 (16%) were due to active tuberculosis, 7 (10%) were due to Kaposi sarcoma, 5 (7%) were due to *Pneumocystis jiroveci* pneumonia, 4 (5%) were due to chronic diarrhea, 5 (7%) were due to severe HIV-related anemia, and 2 (3%) were due to cervical cancer. Eighteen patients (23%) had undiagnosed infections, and there were 4 patients with other conditions (1 case each of lymphoblastic lymphoma, pulmonary aspergillosis, bacterial pneumonia, and septicemia).

Among the 54 patients with HIV-related deaths that occurred during the first 3 months of ART, we identified only 4 (7%) in whom death could be attributed to IRIS. All cases were "unmasking" events, and they included 1 case of *Cryptococcus* meningitis, 1 case of extrapulmonary tuberculosis, 1 case of tuberculosis meningitis, and 1 case of an intracerebral mass (table 2).

Mycobacterium tuberculosis and *Cryptococcus neoformans* were the 2 most common pathogens responsible for death. Of interest, 8 (62%) of the 13 deaths from tuberculosis occurred in patients who experienced clinical symptoms prior to or at the initiation of ART. Of these, 5 (62%) of 8 did not receive treatment before ART initiation; the remaining 5 patients were asymptomatic at the time of ART initiation and subsequently experienced unmasked tuberculosis disease (2 of these patients had tuberculosis IRIS). Eleven patients died of cryptococcal meningitis. Eight of the 11 patients who died had cryptococcal antigenemia at baseline.

Risk factors for all-cause and HIV-associated death. The baseline characteristics that were statistically significantly

Table 1. Baseline Predictors of Human Immunodeficiency Virus (HIV)–Related Mortality after 144 Weeks of Antiretroviral Therapy (ART)

Variable	Univariate analysis	P	Multivariate analysis	P
Age, years				
<35	1.00			
≥35	1.23 (0.78–1.94)	.368		
Male sex	1.16 (0.72–1.87)	.528		
WHO disease stage				
1 and 2	1.00		1.00	
3 and 4	2.46 (0.89–6.73)	.080	1.40 (0.50–3.95)	.523
CD4 cell count	1.00			
≥100 cells/μL	1.54 (0.75–3.15)		1.00	
50–99 cells/μL	1.14 (0.43–2.99)	.242	1.27 (0.62–2.62)	.513
25–50 cells/μL	3.33 (1.98–5.63)	.795	0.84 (0.32–2.25)	.737
<25 cells/μL		<.001	2.49 (1.43–4.34)	<.001
HIV RNA level				
<5 log copies μ/L	1.00		1.00	
≥5 log copies μ/L	1.64 (0.84–3.19)	.146	1.21 (0.69–2.11)	.69
ART regimen				
Stavudine, lamivudine, and nevirapine	1.00			
Zidovudine, lamivudine, and efavirenz	1.01 (0.61–1.69)	.964		
BMI				
≥18	1.00		1.00	
<18	2.32 (01.47–3.67)	<.001	1.76 (1.09–2.85)	.021
Hemoglobin level				
≥8 g/dL	1.00		1.00	
<8 g/dL	4.05 (2.14–7.69)	<.001	3.49 (1.81–6.73)	<.001
Cryptococcal antigen positive	2.47 (1.36–4.50)	.003	1.60 (0.86–2.96)	.137

NOTE. BMI, body mass index defined as the weight in kilograms divided by the square of the height in meters; WHO, World Health Organization.

associated with all-cause death in the univariate analysis included stage 3 or 4 WHO classification (odds ratio [OR], 2.59; 95% CI, 1.05–6.37), a CD4 cell count <25 cell/uL (OR, 2.86; 95% CI, 1.79–4.56); BMI <18 (OR, 1.94; 95% CI, 1.29–2.91), and a hemoglobin level <8 g/dL (OR, 3.70; 95% CI, 2.07–6.64).

In the multivariate model, independent risk factors for death were CD4 cell count <25 cells/uL (OR, 2.17; 95% CI, 1.35–3.48), BMI <18 (OR, 1.62; 95% CI, 1.06–2.50), and hemoglobin levels <8 g/dL (OR, 3.41; 95% CI, 1.88–6.16). Among the 45 patients who had at least 1 other CD4 cell count measurement,
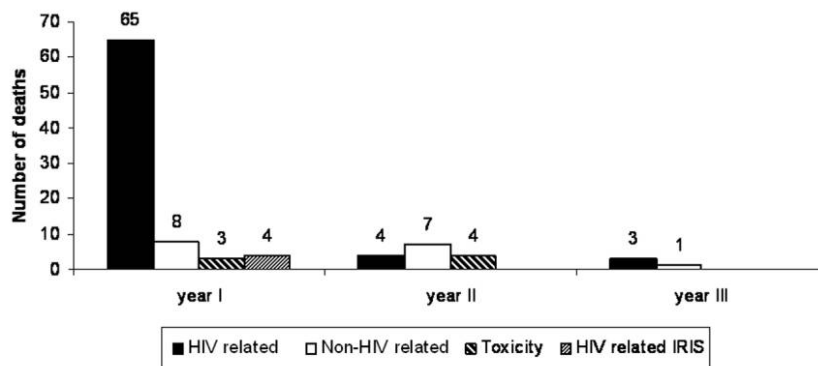

Figure 2. Cause-specific mortality during the first 3 years of antiretroviral treatment. HIV, human immunodeficiency virus; IRIS, immune reconstitution inflammatory syndrome.

Table 2. Characteristics of Patients with Death that Was Attributed to Immune Reconstitution Inflammatory Syndrome

Patient	Atypical presentation	Exaggerated inflammatory response	Signs and symptoms	CD4 cell count increase	Decrease in viral load >1 log copies/mL	Opportunistic infection	Weeks from initiation of ART to diagnosis	Weeks from initiation of ART to death
1	Yes	Yes	Fever, anemia, hepatosplenomegaly, wasting, dehydration	NA	NA	Extrapulmonary TB	3	4
2	Yes	Yes	Convulsions, nystagmus, blurred vision, intermittent delirium	From 204 cells/μL to 504 cells/μL	From 5.8 log copies/mL to 2.6 log copies/mL	Intracerebral mass	20	24
3	Yes	Yes	High fever, severe headache, loss in vision, convulsions	From 316 cells/μL to 720 cells/μL	From 5.8 log copies/mL to 2.6 log copies/mL	TB meningitis	15	16
4	Yes	Yes	High intracranial pressure, fever, confusion, severe headache	NA	NA	Cryptococcus meningitis	4	4

NOTE. ART, antiretroviral therapy; NA, not applicable; TB, tuberculosis.
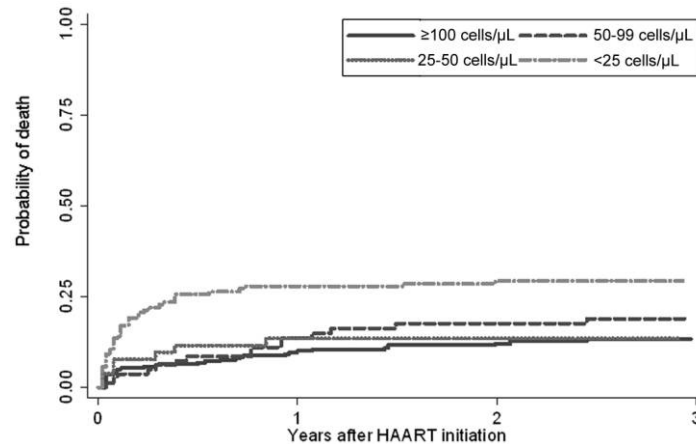
Figure 3. Cumulative probability of death over a 36-month period of highly active antiretroviral therapy (HAART) according to CD4 cell count stratum, with the highest mortality rates realized in those individuals with CD4 cell counts <25 cells/μL.

we observed a smaller mean increase in CD4 cell counts among patients who died than we did among patients who remained alive (83 vs 253 cells/uL).

The baseline characteristics associated with HIV-related death in univariate and multivariate analysis are similar to those for all-cause mortality (table 1); cyrptococcal antigenemia was also included in the model and was a predictor of HIV-related death in the univariate analysis but was not statistically significant in the multivariate model.

Figure 3 shows a Kaplan-Meier curve depicting the probability of death over the 3-year period of observation according to CD4 cell count stratum. The log-rank test ($P < .001$) indicates that the probability of death was statistically significantly different among the different CD4 cell count strata, with the lowest survival among patients who initiated ART with a CD4 cell count <25 cells/uL. When baseline CD4 cell count is separated into quartiles, the same trend is observed, with a statistically significant association with death for patients in the lowest quartile.

DISCUSSION

In this well-characterized cohort of patients who initiated ART at an urban clinic in 2004, we observed a high mortality rate of 14% during the first year of therapy, particularly during the first 3 months. The study highlights the high early mortality in ART cohorts in resource-limited settings that has been observed by other groups in similar settings [9, 22, 23]. Over a 3-year period of follow-up in our cohort, 80 (81%) of 99 deaths occurred during the first year of treatment, whereas 58% of all the deaths occurred during just the first 3 months of ART.

We were able to ascertain the cause of death for the majority of our patients and found that in the first year of ART, 80% of the deaths were associated with an HIV-related infection. The main causes of the high HIV-related mortality in the first year were central nervous system infection and mycobacterial disease in association with severe immunodeficiency. Tuberculosis and cryptococcal disease accounted for at least one-third of all HIV-related deaths, although this is likely to be an underestimate, because one-quarter of the patients died with an undiagnosed infection. Our findings concur with the previously published leading causes of early mortality in sub-Saharan Africa, which include tuberculosis, cryptococcosis, acute sepsis, malignancies, and invasive bacterial disease [4, 7, 8]. These findings are also similar to those of a study from Senegal, which found that 18.5% of deaths were due to mycobacterial infection, 18.5% were due to neurological disorders (one-third of which were *Cryptococcus* infection), and 18.5% were due to unspecified infectious diseases [7].

Our study also shows that a large number of deaths may have been preventable if the infrastructure for opportunistic infection screening was routinely available and patients were given prophylaxis or treatment prior to ART initiation. Five of 8 patients who experienced symptoms of tuberculosis before or at ART initiation did not receive treatment for tuberculosis. During study enrollment, patients underwent a standardized symptom screening and physical examination (including a tuberculosis screening), but the decision to initiate antituberculosis therapy is at the discretion of the attending clinician at our center. Atypical clinical, radiological, and laboratory presentation of tuberculosis in patients with HIV infection could have been the cause of delayed treatment in these subjects.

Of the 11 patients who died of cryptococcal meningitis, 8 had asymptomatic cryptococcal antigenemia at baseline, whereas 3 had previously received a diagnosis of and treatment for cryptococcal meningitis. Our data are similar to those of Liechty et al [24], who showed that asymptomatic cryptocccal antigenemia was an independent predictor of death. In another cohort from South Africa, antigenemia (dilutional titer >1:8)

was 100% sensitive and 96% specific for predicting the development of cryptococcal meningitis during the first year of ART, and cryptococcal antigenemia was an independent predictor of mortality (adjusted hazard ratio, 3.2; 95% CI, 1.5–6.6) [25]. Taken together, these data suggest that cryptococcal antigen screening in patients with CD4 cell counts <100 cells/μL can be used to predict those patients who will develop cryptococcal meningitis after ART initiation and who may therefore benefit from fluconazole prophylaxis. In our general clinic, patients are not screened routinely for cryptococcal antigenemia.

Although the phenomenon of IRIS has been extensively described, this study specifically addresses IRIS-related deaths. We observed 4 deaths that could be attributed to IRIS, of which 3 were attributable to central nervous system syndromes. Two patients who were asymptomatic at the time of ART initiation subsequently developed unmasked tuberculosis IRIS. The overall contribution of IRIS events to mortality in this cohort was <7%, which is similar to the IRIS-attributable mortality of 4.5% reported from an ART clinic in Johannesburg, South Africa [26]. These observations support the view that, in most cases, IRIS is a self-limited clinical entity. The IRIS deaths primarily involved the central nervous system, suggesting that central nervous system manifestations may not be as well tolerated as manifestations in other body compartments and may require more-urgent attention [27]. If, as a result of the difficulty in distinguishing between unmasking tuberculosis and unmasking tuberculosis IRIS, we had considered all cases of tuberculosis in the first 3 months of ART to be cases of tuberculosis IRIS, such cases would still have accounted for only 11% of the deaths during first 3 months of ART.

In contrast to the mortality in year 1, the mortality during years 2 and 3 was low (3%), indicating that, once patients have survived the initial ART period of 6 months, their prognosis is good. In the second and third year, other medical conditions and ART-related toxicities emerged as the leading causes of mortality. More than 70% of the patients were receiving a stavudine-based regimen, and these toxicity-related deaths may be related to the inclusion of stavudine in the first-line regimens in resource-limited settings, which can result in fatal lactic acidosis [28, 29].

Consistent with the findings of previous reports, we showed that a CD4 cell count <25 cells/μL was a risk factor for mortality [1, 3, 22, 30, 31]. Ensuring ready access to HIV testing and earlier initiation of ART, in addition to optimal treatment of underlying opportunistic infections, are important strategies for reducing early mortality. As other investigators have shown, a hemoglobin level <8 mg/dL was also an independent risk factor for death [23, 32]. The association between a low hemoglobin level and mortality may be attributable to underlying undiagnosed infections.

Our study has several potential limitations. The generalizability of our findings may be limited, because we describe an urban research cohort in Uganda. The degree to which our study findings correlated with those of studies conducted in other resource-limited settings was reassuring in this regard. Second, the ability to diagnose the etiologic agent of death is limited in our setting, and 23% of the infectious deaths in our cohort had causes that were not ascertained. Finally, because some of the patients with asymptomatic cryptococcal antigenemia were treated with high-dose fluconazole, there may have been higher IRIS-related mortality from unmasked cryptococcal disease among patients who received ART.

In conclusion, we show a significant early mortality in our ART cohort in resource-limited settings that is driven by advanced HIV disease and characterized by low CD4 cell counts. In our experience, the contribution of IRIS to this observed early mortality is limited. Furthermore, our data suggest that many of the HIV-related deaths could have been prevented if more-stringent screening strategies, combined with treatment or prophylaxis, were implemented more effectively. Mass HIV testing strategies should be implemented to target otherwise-healthy HIV-infected individuals to avoid late presentation to HIV treatment facilities. A strategy of early ascertainment and linkages to care, combined with vigilant screening and treatment for opportunistic infections, may be an effective strategy to reduce early mortality.

Acknowledgments

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