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RISK FACTORS FOR DEATH IN HIV - INFECTED ADULT AFRICAN PATIENTS RECEIVING ANTI - RETROVIRAL THERAPY

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RISK FACTORS FOR DEATH IN HIV-INFECTED ADULT AFRICAN PATIENTS RECEIVING ANTI - RETROVIRAL THERAPY

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ABSTRACT

***Objective*: To determine risk factors for death in HIV-infected African patients on anti-retroviral therapy (ART).**

***Design*: Retrospective Case-control study.**

***Setting*: The MOH-USAID-AMPATH Partnership ambulatory HIV-care clinics in western Kenya.**

***Results*: Between November 2001 and December 2005 demographic, clinical and laboratory data from 527 deceased and 1054 living patients receiving ART were compared to determine independent risk factors for death. Median age at ART initiation was 38 versus 36 years for the deceased and living patients respectively ($p<0.0148$). Median time from enrollment at AMPATH to initiation of ART was two weeks for both groups while median time on ART was eight weeks for the deceased and fourty two weeks for the living ($p<0.0001$). Patients with CD4 cell counts <100/mm^3 were more likely to die than those with counts >100/mm^3 (HR=1.553. 95% CI (1.156, 2.087), $p<0.003$). Patients attending rural clinics had threefold higher risk of dying compared to patients attending clinic at a tertiary referral hospital ($p<0.0001$). Two years after initiating treatment fifty percent of non-adherent patients were alive compared to 75% of adherent patients. Male gender, WHO Stage and haemoglobin level <10 grams% were associated with time to death while age, marital status, educational level, employment status and weight were not.**

***Conclusion*: Profoundly immunosuppressed patients were more likely to die early in the course of treatment. Also, patients receiving care in rural clinics were at greater risk of dying than those receiving care in the tertiary referral hospital.**

INTRODUCTION

Introduction of anti-retroviral therapy (ART) into middle and low-income countries through programmes such as the World Health organisation's (WHO) "3 by 5" Initiative and President's Emergency Programme for AIDS Relief (PEPFAR) has brought a glimmer of hope to Africa, the continent most ravaged by the HIV pandemic (1-3). Through these and other initiatives, the number of people receiving ART in middle and low-income countries reached over three million people by the end at 2007 (2-4). Success at these initiatives is largely due to provision of funds for the purchase of medications (anti-retroviral drugs and antibiotics for treatment of opportunistic infections), laboratory equipment and supplies, training of health workers and establishment and/or strengthening of healthcare delivery systems (5). In spite of such commendable progress, an estimated two million people die annually from HIV related complications worldwide (4, 6).

The effectiveness at ART in decreasing HIV RNA levels, increasing CD4 cell counts and restoring immunity in treatment-naive HIV infected African patients has been previously reported in treatment initiatives from Kenya, Senegal, Uganda and South Africa (7-10). In a cohort of patients receiving ART in western Kenya, Wools-Kaloustian *et al* found that mean CD4 cell counts rose by 160,225 and 295/mm^3 at 12,24 and 36 months respectively. This study also documented a mortality rate of 5.4% and a loss to following-up rate of 24.5%, much of which was attributed to death (7). Given the potential for excess mortality in this cohort we found it necessary to identity risk factors for death after initiating ART in order to target patients who might benefit from interventions designed to enhance survival. As such we undertook a retrospective case-control study of deceased patients within our HIV-care system in Western Kenya in order to identify factors associated with death. The resulting model could also be used to adjust analyses or stratify patients by mortality risk.

MATERIALS AND METHODS

Study design: The Moi University Institutional Research and Ethics Committee (IREC) and Indiana University Purdue University at Indianapolis/Clarion Institutional Review Board (IRS) approved this study. This was a retrospective, case-control study employing de-identified data from the prospectively compiled electronic medical records of HIV-infected patients on ART at the MOH-USAID-AMPATH Partnership (AMPATH). All deceased adult patients on ART within the AMPATH system were identified as cases while controls were selected from living patients on ART who were enrolled within a month of the case. This method of selection was undertaken in order to control for the impacts of changes in our care programme over time.

Study site: In November 2001 Moi University School of Medicine (MUSoM) and Moi Teaching and Referral Hospital (MTRH) in Kenya and Indiana University School of Medicine founded the Academic Model for the Prevention and Treatment of HIV programme (AMPATH, now known as Academic Model Providing Access To Healthcare) in response to the HIV pandemic(11,12). AMPATH has enrolled >110,000 HIV-infected patients in 46 Ministry of Health clinics spread throughout western Kenya (national HIV prevalence rate 71 % (11). Core to the activities of AMPATH is the AMPATH Medical Record System (AMRS) a fully electronic medical database which stores and manages demographic and clinical data for all enrolled patients and visits (14-16). The AMPATH Training Institute is responsible for the initial training and continuing medical education of all AMPATH staff (17).

AMPATH Clinical care: Patient care is standardised within the programme by use of locally developed clinical algorithms consistent with the Ministry of Health, Government of Kenya and WHO guidelines for care of the HIV-infected patient (18,19). Patient medical history including socio-demographic data, review of symptoms and WHO staging are conducted at enrollment. During the follow-up visits data is collected on inter-current symptoms and adherence assessment is carried out. A complete physical examination is done at enrollment and symptom-directed exams at each follow-up visit. Laboratory testing (complete blood counts, liver enzymes, renal tests and CD4 cell count) is done at baseline and repeated every six months. Plasma viral load testing was not available during the first three years of the programme but is currently being used in a subset of patients in which ARV failure is suspected. A chest radiograph is obtained in all non-pregnant patients at enrollment. All clinical and laboratory data are recorded on a standard case report form and later transcribed into the electronic database (16).

A consulting physician attends in the urban clinic on a daily basis and once a week in the rural clinics. The programme recommends that very ill patients be reviewed by the consultant physicians initially and followed jointly by the physician and clinical officer (mid-level clinician; equivalent to a physician assistant). All patients with CD4 cell counts <200/mm^3 are given co-trimoxazole to reduce the risk of pneumocystis pneumonia. Patients with documented allergy to sulfa drugs are given Dapsone. All patients without signs and symptoms of tuberculosis who have a normal chest radiograph are given nine months of isoniazid preventative therapy.

AMPATH's standard 1st line ART regimen consists of zidovudine (or stavudine), lamivudine, and nevirapine. Efavirenz is substituted for nevirapine in patients receiving induction therapy for tuberculosis in order to decrease risk of hepatotoxicity. No patient has ever experienced treatment interruptions due to stock shortages. In response to ART toxicity single drug substitutions are made; however, in the face of ART failure a full regimen change is required as per local protocol. Patients are seen two weeks after ART initiation and then monthly thereafter, at which time they receive a months worth of medication. An outreach and lost to follow-up programme locates patients who fail to return for their scheduled appointments. Deaths are reported to the clinic from the outreach team and / or the patients' relatives and friends. In addition, a research assistant collects data on all patients admitted to the wards at MTRH and relays information on patient deaths directly to the AMPATH data management centre.

Study subjects: Data from patients were eligible for analysis by this study if the patient was enrolled at any of the AMPATH clinics and initiated ART between December 2001 and December 2005. Patients' data were excluded from the analysis if the patients were ARV experienced prior to joining AMPATH or if they started ART for PMTCT only. Random sampling was used to match deceased with living patients in a ratio of 1: 2. Patients were matched using date of ART initiation (control patients had to have started ART within a month of the case patient) in order to account for programmatic changes over time as availability of ART and ancillary services (nutrition, outreach, psycho-social support and adherence) have expanded over time.

Data Collection and Management: As a first step, all the patients who had died or were lost to follow-up (defined as missing their clinic appointments for at least three months after the initiation ART) were identified retrospectively from the AMRS database. Those patients identified as lost to follow-up and whose locator information was available were then actively tracked by the outreach team in order to determine those who had died. Vital status information obtained by the outreach team was added to the AMRS prior to pulling the final dataset for analysis.

Adherence evaluation was based on a self-reported instrument. Patients responded to the following question: "During the last seven days, how many of her / his ARV pills did the patient take?" The available responses were: None, Few, Half, Most. and All. In the present analyses we have dichotomised each patient as exhibiting perfect adherence (every response at every visit is "All") versus imperfect adherence (any response other than "All" reported at even a single visit).

Statistical methods: Descriptive statistics such as mean, standard deviation, median and range were calculated for the continuous variables. The Kruskal-Wallis test was used to compare means. Frequency tables were produced for all categorical variables and these were compared via the Fisher's exact test. Analyses of time until an event were undertaken using the Kaplan-Meier method for the categorical variables. To identify independent risk factors for mortality, univariate and multivariate Cox proportional hazard regression models were performed with time from initiation of ART to death as the outcome Control patients were censored as of the date of their last AMPATH clinic visit. The regression co-efficient is interpreted as the increase of the log-hazard ratio resulting in an increase of one unit in the covariate. Mortality rates were estimated using Kaplan Meier survival analysis. We considered as candidat predictors socio-demographic characteristics (age, gender, weight, marital status, school attendance and employment status); care site (urban versus rural) and clinical data identified a *priori* as being likely related to mortality. These clinical data included laboratory test results (CD4 cell count, alanine aminotransferase and haemoglobin): overall adherence to ARVs, WHO Stage at initiation of ART or the closest assessment measurement prior to starting ART. Because the exact date of death was missing for some of the deceased patients, three different assumptions were made for the date of death: (1) the patient died on the day of his or her last appointment, (2) the patient died midway between the last appointment and the next scheduled visit and (3) the patient died on the date of the next scheduled visit (maximum of one month from last visit). Models were fitted based on these three assumptions and since all the models led to the same conclusions, the results of the model where we assume the next months clinic visit as the date of death are used. All analyses were carried out using STATA version 8.0 (Stata Corporation, College Station, TX).

RESULTS

During the study period, a total of 16,134 HIV-infected adult patients (69% females) were enrolled in AMPATH of who 8,603 (53%) initiated ART. In the same period, 527 out of the 760 patients (69%) documented to have died initiated ART. All 527 deceased patients on ART were successfully matched with two patients on ART who were not known to have died as of the date of this analysis. The analysis cohort thus contained 527 deceased patients and 1054 living controls.

The characteristics for both groups at the time of ART initiation are shown in Table 1.

Table 1
Frequency distribution of various categorical variables by deceased status

Patient characteristic	Deceased patients (N=527)	Living patients (N=) 1054)	p-value
Age at enrolment (years)	n=512	n=1019	
Median (range)	37.6 (16-77)	36.2 (15-73)	0.015[1]
Gender	n=527	n=1054	
Male	241 (46%)	372 (35%)	<0.00 1[2]
Female	286 (54%)	682 (65%)	
Weight (Kg)	n=516	n=1042	
Median (range)	49 (22.5-80)	55 (26.5-94)	<0.001[1]
Time from enrolment to initiation of ART (wks)	n=522	N=1033	0.07[1]
Median (range)	2.0 (1-140)	2.14(1-163)	
Duration of follow-up initiation ART	n=347	n=1054	<0.001[1]
Median (range)	7.7 (0-110)	42 (0-288)	
CD4 cell count/mmJ at initiation of ART	n=427	n=806	
Median (range)	40 (1-94)	95 (0-1230)	<0.001[1]
Haemoglobin (g %)	n=401	n=752	
Median (range)	10.0(4.4-21.5)	13.8(1.4-19.4)	<0.001[1]
Clinic enrolled	n=527	n=1054	
Urban	123 (23%)	445 (42(Ycl)	<0.001[1]
Rural	404 (77%)	609 (58%)	
ART adherence	n=366	n=974	
Adherent	289 (79%)	872 (89.5%)	<0.001[2]
Non adherent	77 (21%)	102 (10.5%)	
Marital status	n=527	n=1054	
Married	287 (55%)	598 (57%)	
Single	240 (45%)	456 (43<10)	0.39[2]
Formal education	n=439	n=897	
Yes	401 (91 %)	836 (93%)	0.22[2]
No	38 (9%)	61 (7%)	
Employment	n=527	n=1054	
Yes	175 (33%)	360 (34%)	0.73[2]
No	352 (67%)	694 (66%)	
WHO stage at start of ART	n=410	n=840	
Stage 1	128 (7%)	214 (25%)	
Stage 2	51 (12%)	161 (19%)	<0.001[1]
Stage 3	226 (55%)	392 (47%)	
Stage 4	105 (26%)	73 (9%)	

[1] Kruskal- Wall is test

[2] Fisher's exact test

* The missing data represents patients who's date of death was missing

Deceased patients were slightly older than controls. The median time from programme enrollment to ART initiation was two weeks for both groups. The median duration of follow up while on ART was (by virtue of patient selection) five times longer for control patients. Deceased patients had significantly lower weight at ART initiation, 49 kg versus 55 kg respectively (p<0.0001). Other characteristics found to be significantly different (p<0.0001) at initiation of ART included: CD4 cell count, haemoglobin concentration, location of clinic attendance and WHO stage. Medication adherence during follow-up was also found to be significantly different between the two groups (p<0.0001).

Kaplan Meier plots by initial CD4 cell count (dichotomized as <1 00/mm3 versus >1 00/mm^3) are shown in Figure 1.

Figure 1

Kaplan-Meier survival estimates for HIV infected adult African,treatment naive patients on anti-retroviral therapy, by baseline CD4 counts (<100 versus. 100 cells/ ml

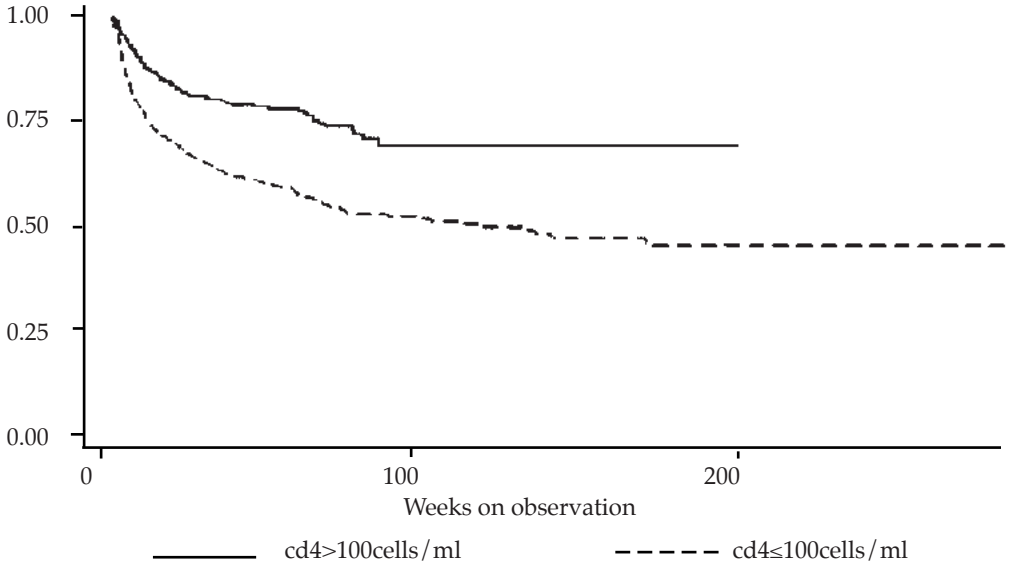


Figure 2

Kaplan-Meier survival estimates for HIV-infected adult African, treatment naive patients on anti-retroviral therapy, by baseline WHO stage.

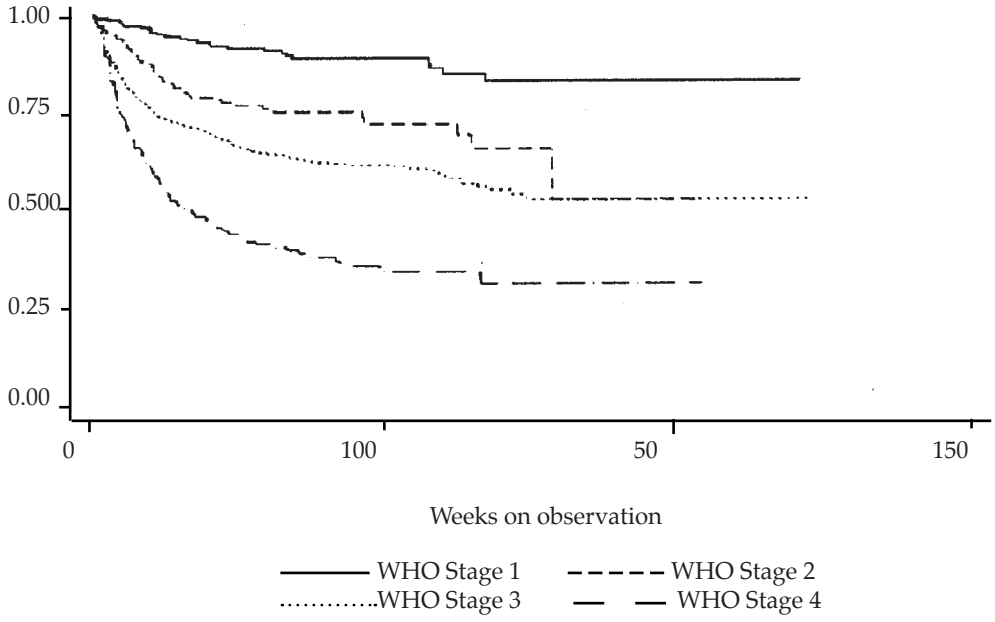
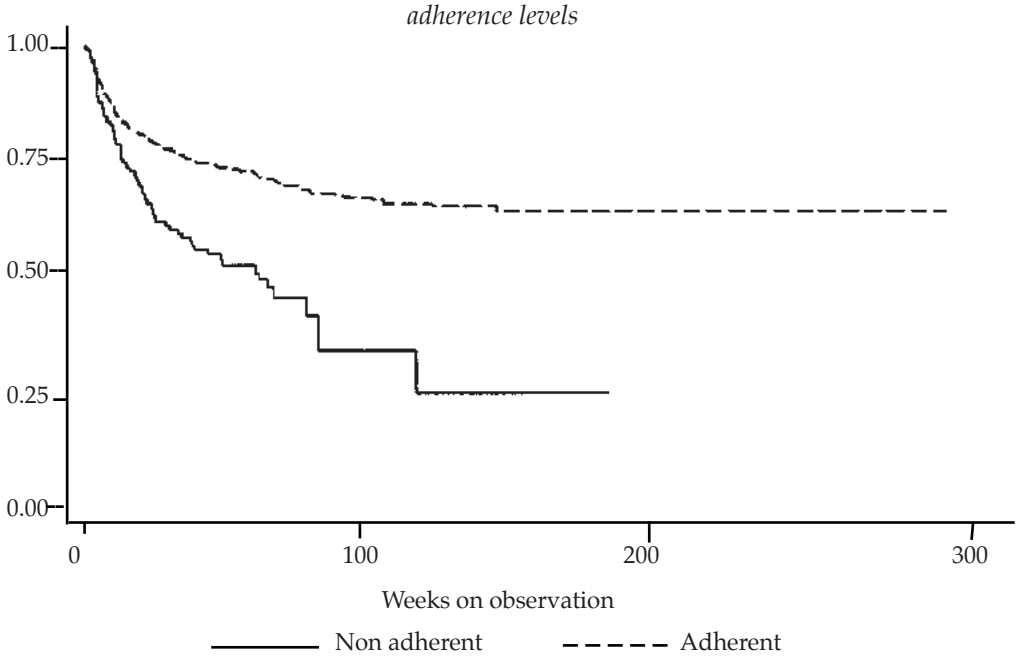


Figure 3

Kaplan-Meier survival estimates for HIV-infected African, treatment naive patients on anti-retroviral therapy, by adherence levels



The hazard of death is higher for patients started on treatment with CD4 cell counts <100/mm^3 as compared to those starting treatment with CD4 cell counts >100/mm^3. In a univariate proportional-hazards regression model it was estimated that patients initiating ART with CD4 cell counts <100/mm^3 had almost twice the risk of dying compared to those starting at higher CD4 cell counts (p<0.0001). As anticipated, the hazard of death was greater for patients with higher WHO stage (Figure 2). In addition, non-adherent patients had a higher hazard of death with less than 50% being alive two years after initiation ART compared to close to 75% of adherent patients (Figure 3). Characteristics not found to be significantly different between cases and controls were marital status, receipt of a formal education and employment at the time of enrollment.

Multi-variable proportional hazards model: A multi-variable proportional hazards model was fitted with the variables that were found to be statistically significant in the univariate model at the 20% level.

Table 2:

Multivariable proportional hazards model: Next scheduled clinic visit date assumed to be the death date for deceased patients without a death date

Variable	Hazard ratio	95% CI		p-value[3]
Age at enrollment	1.012	0.999	1.026	0.07
Adherence (Adherent versus non adherent)	0.661	0.475	0.919	0.01
Urban versus rural clinic	0.356	0.248	0.513	<0.001
Gender (female vs. male)	0.714	0.546	0.933	0.01
CD4 cell count (100 vs. > 100/mm^3)	1.553	1.156	2.087	0.003
Haemoglobin (10 vs. >10g%)	1.448	1.112	1.886	0.006
WHO stage 2 vs. 1	1.922	1.086	3.401	0.03
WHO stage 3 vs. 1	2.503	1.533	4.087	<0.001
WHO stage 4 vs. 1	5.332	3.151	9.022	<0.001

As shown in Table 2, the factors associated with time to death in this analysis were: gender, location of clinic, CD4 cell count, haemoglobin and WHO stage at initiation of ART as well as documented adherence to medication. Holding all other factors constant, male patients were found to be one and one-half times more likely to die than their female counterparts. The hazard for death increases monotonically with increasing WHO stage from one to four. We observed that the hazard for death in patients attending the rural clinic was almost three times that for urban clinic attendees. Similarly, patients initiating ART with haemoglobin less than 10gm% had increased chances of dying compared to those with higher haemoglobin levels. The hazard for death for adherent patient is markedly lower than that for non-adherent patients. In this model patients started on ART with CD4 cell counts <1 00/mm^3 were found to be one and one half times more likely to die compared to those initiating at counts >1 00.mm^3

DISCUSSION

While medical, clinical and socio-behavioural-demographic factors that predict poor outcomes in patients on ART have been documented in different populations from around the world, (20-33) to our knowledge, this study is the first to do so in a cohort of Kenyan adult patients on ART. We found that male gender, low CD4 cell count, higher WHO Stage and low haemoglobin concentration at initiation of ART, poor adherence during treatment and clinic location (urban compared to rural clinic) are significant independent risk factors for mortality. The fact that male gender is a risk factor for mortality is not surprising given our previous study which found that men tended to present with higher WHO stages and lower CD4 cell counts than women (7). We theorise that the traditional male role in Kenyan society which discourages the show of weakness leads to delays in men seeking healthcare thus placing them at higher risk for death. In addition concerns about stigma and blame may also contribute to delays in seeking care. Nevertheless, the fact that gender was found to be an independent risk factor in the multi-variable model, even after adjusting for CD4 count and WHO stage at initiation of ART, means that there are other factors, not measured in this study, that are associated with the male role in Kenya. A possible explanation for the higher mortality rates in men is the increased use of alcohol in this group when compared to their female counterparts, a factor that has previously been associated with worse HIV outcomes (34).

As expected, low CD4 cell count and late WHO stage were significantly associated with the risk of death. In addition, individuals who succumbed to this disease died a median of eight weeks after initiation of therapy. Whether these deaths are related to opportunistic infections acquired prior to immune reconstitution, the immune reconstitution inflammatory syndrome or drug toxicity cannot be determined from our current data. However these data do suggest the need for earlier identification of HIV infected individuals and more timely initiation of ART and 01 prophylaxis and/or treatment.

Accomplishing the goal of early identification will require a multi-pronged approach including de-stigmatisation of HIV within the community; strengthening of voluntary counselling and testing services; and introduction of diagnostic HIV testing in tuberculosis and sexually transmitted infection clinics as well as on the hospital wards. It will also require an increase in the number of healthcare workers trained to identify and treat HIV and its complications as well as the number of healthcare facilities equipped to provide anti-retroviral care.

The association between adherence and HIV progression has been well documented in previous studies (35-38). We found that the use of a single item to assess self-reported patient adherence was predictive of mortality. This is consistent with our previous finding that this item is predictive of CD4 cell response to anti-retroviral therapy (7). More detailed studies to establish how levels of adherence influence clinical response to ART as well as studies aimed at identifying factors that contribute to poor adherence are currently underway within AMPATH. However, it is clear that closer attention must be paid to adherence issues and that interventions targeted at improving adherence are likely to decrease mortality rates in individuals who initiate ART.

Significant differences in mortality rates recorded in urban and rural sites may be associated with the cadre of health workers providing care. In the urban clinic physicians play an active day-to-day role whereas in the rural sites consulting physician only visit once per week. A greater level of laboratory, radiological and other diagnostic support at the MTRH clinic as well as the presence of more extensive in-patient facilities may also contribute to the differential mortality rates. It is also possible that the distance patients have to travel to clinic for care may impact mortality since patients in the rural clinics have to travel longer distances than their urban counterparts, most of who live close to the hospital. Another possible explanation for the mortality differences is differential reporting. Because the rural communities are smaller and have much closer ties to the health centre staff than do urban patients with MTRH staff, it is possible that deaths are more likely to be reported at the rural centres while at the urban clinic these patients may be labeled as lost to follow-up. Further study is necessary in order to determine which explanation for the urban-rural divide is valid. Since difference in staffing for rural health centres impact most sub-Saharan Africa,

confirmation of this as an issue would indicate the need to find a solution. Such a solution might include the training of more physicians, identifying ways to retain physicians in rural areas, improving training for clinical officers, increasing back-up and support of clinical officer through web-based or telephone-based consultation with physicians or the development of clinical decision support systems (39).

The limitations of this study include significant dependence on a passive reporting system for mortality, which does not allow for the capture of all deaths within this system. This study was designed as a case-control study rather than a cohort study in order to counter this issue. The other limitation of this study is the absence of data on cause of death. As such it is not possible to know if deaths were related to opportunistic infections, drug toxicity or immune reconstitution syndrome.

In conclusion we confirm that advanced HIV infection (based on WHO stage and CD4 cell count) at initiation of ART is associated with early mortality in a population of patients in western Kenya. This finding substantiates the need for early identification and treatment of HIV infected individuals in sub-Saharan Africa. Attention needs to be focused on those patients presenting with lowest CD4 cell counts to understand causes of death and develop intervention methods. In addition it demonstrates the need for continued commitment from the international community to provide funds to establish and support HIV treatment services in resource poor settings. We also identify male gender as a risk factor for death due to HIV infection even after the initiation of ART. This indicates a need to improve our understanding of male health care seeking behaviors within our cultural context as well as a need to design healthcare interventions specifically targeted toward men. Last, but not least, the finding that patients attending rural clinics are at greater risk of dying than those attending the referral centre call for more operations-type research on the subject matter. Such research might determine the factors that cause such differentials in mortality, hence provide useful information for mitigating interventions to be put in place.

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