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WHO stage 4 conditions among adults accessing outpatient HIV care: A retrospective cohort study in Kisumu, Kenya

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INTRODUCTION

Opportunistic infections (OIs) are the main cause of morbidity and mortality in patients with HIV-1 infection throughout the world, particularly among patients who have not had access to anti-retroviral therapy (ART) and other HIV care services. [1, 2, 3] Among patients taking ART, OIs can present when the immune system starts to recover aka immune reconstitution inflammatory syndrome (IRIS). [4, 5] Also, some patients do not have a sustained response to ART due to lack of adherence to medications, development of drug resistance, or suboptimal therapeutic regimens. [1] Therefore, OIs continue to cause substantial morbidity and mortality even after initiation of ART.

The World Health Organization (WHO) developed HIV clinical staging criteria based on OIs to standardize disease severity classification in the absence of virologic or immunologic measurements. [6, 7] Diagnosis of WHO stage 4 conditions remains important in the ART era in order to: 1) help determine timing of ART initiation, and 2) treat OIs to reduce morbidity

Conflicts of Interest: None

and mortality. There are no published data from Kenya that quantify the burden of WHO stage 4 conditions that persist in the ART era and continue to negatively impact patient survival. We therefore set out to determine the prevalence and gender distribution of WHO stage 4 conditions among patients enrolled in a large peri-urban HIV clinic in western Kenya.

METHODS

We performed a retrospective review of adult patients who enrolled into care in a comprehensive outpatient HIV clinic between March 2005 and July 2008, and analyzed the frequency of WHO stage 4 conditions.

Setting

The Family AIDS Care and Education Services (FACES) program, a collaboration between the Kenya Medical Research Institute (KEMRI) and University of California San Francisco (UCSF), pioneered a family model of HIV prevention, care, and treatment in Nyanza Province and Nairobi, Kenya.[8] This study was conducted at Lumumba Health Centre (LHC), which is one of FACES' largest outpatient HIV clinics in Kisumu, Nyanza Province. Nyanza Province has an HIV prevalence of 15.3%, which is more than twice the national prevalence of 6.3%. [9] LHC has the capacity for on-site laboratory tests including complete blood count, serum chemistries, CD4+ cell count assays, Rapid Plasma Reagin (RPR), and serum cryptococcal antigen (sCrAg) testing. Tissue biopsies for cytology and chest radiographs are available within Kisumu and are routinely paid for with program funds. Additional tests such as ultrasound, computed tomography (CT) scans and endoscopy are available, but coverage depends on the availability of extra program funds or the patients' ability to pay. ART is available at no cost to patients who qualify based on WHO stage and/or CD4 count, following the Kenya national guidelines.[10] Patients attending LHC for HIV care are staged according to WHO criteria as part of their enrollment assessment and reassessed at every follow-up visit.

Data Sources

The HIV clinic at LHC has an electronic medical record system (EMRS) that captures important patient-level demographic and clinical variables at each clinic visit. At every visit, patient encounters are documented using standardized clinical forms, after which the information is entered into the EMRS. Information collected using patient encounter forms includes demographic characteristics such as age and gender, ART status, and clinical variables such as WHO stage and staging criteria, and laboratory test results. In September 2009, we used the EMRS database to identify all adult patients (age >15 years old) who enrolled into care between March 2005 and July 2008. Out of these newly enrolled patients, we identified those with WHO stage 4 conditions at enrollment or subsequent visits. We obtained data on CD4+ cell count at enrollment, gender, age, and status in care [dead, alive in care, transferred out, or lost to follow-up (LFU)] at the time of data abstraction. The patient files were reviewed to confirm diagnosis and abstract missing variables. For patients who had not attended the clinic for three or more months, a community health worker (CHW) called or attempted a home visit to determine their current status. If the CHW was not able to locate them or receive a reliable report of their status, then they were classified as LFU.

Statistical Methods

Data from the EMRS were exported into an Excel (Microsoft Inc, Redmond, WA) spreadsheet. Data abstracted from manual chart reviews were entered into a standardized data abstraction tool then transferred to the spreadsheet. Bivariate analysis was performed to

examine the association between various WHO stage 4 conditions and age, gender, and CD4+ cell count. Chi- square or Fishers exact tests were used for categorical variables, and the student's t-test was used to compare continuous variables. Data were analyzed using STATA version 11.0 (StataCorp, College Station, TX). A value of $p < 0.05$ was considered significant.

Ethical Considerations

The FACES program obtained ethical approval from the KEMRI Ethical Review Committee and the UCSF Committee on Human Research to utilize routinely gathered retrospective medical information for evaluation and dissemination purposes, including the data abstracted for this study. To protect patient privacy, all data were de-identified and de-linked with patient identifiers.

RESULTS

Of the 5,784 adult patients enrolled during the study period, 437 (7.6%) had a WHO stage 4 diagnosis during the study period at enrollment and follow up of which 260 (59.5%) were females. Among all females enrolled into care, 6.7% had a WHO stage 4 diagnosis compared to 9.3% among all enrolled men ($p<0.001$). The mean age of females was 34.7 years (SD: 9.0) compared to 37.2 years (SD: 8.4) for men. The median CD4+ cell count at enrollment was 84 cells/μL (IQR: 31, 191) and 325/423 (76.8%) patients had a baseline CD4+ cell count below 200 cells/uL. Of the 437 patients with WHO stage 4 diagnoses, 427 (97.7%) patient files were found and reviewed. These 427 patients contributed 483 WHO stage 4 conditions to the analysis as 56 patients had two conditions.

Out of the 427 patients, 367 (85.9%) were initiated on ART during the study period; 346 of the 367 who had been initiated on ART had dates recorded for ART initiation and the WHO stage 4 diagnosis. Of the 346 patients, 127 (36.7%) had started on ART before the WHO stage 4 diagnosis, 34 (9.8%) started ART on the day of their WHO stage 4 diagnosis and 185 (53.5%) started ART after the WHO stage 4 diagnosis. Of the 127 patients diagnosed with a WHO stage 4 diagnoses after ART initiation, 78 (61.4%) had the diagnosis within six months of ART initiation.

At the end of the study period, 253 (59.2%) were active in care, 60 (14.0%) were confirmed dead, 28 (6.6%) had transferred out to other HIV clinics, and 86 (20.1%) were LFU.

The most common conditions in order of frequency were esophageal candidiasis, extra pulmonary tuberculosis, HIV wasting syndrome, Kaposi's sarcoma (KS), and cryptococcal meningitis (Table 1). Esophageal candidiasis was significantly more frequent among women with WHO stage 4 conditions than men ($p=0.029$), and KS was more frequent among men ($p<0.001$). When analyzing frequency of WHO stage 4 conditions based on a CD4+ cut-off of 100 cell/μL, only esophageal candidiasis was significantly associated with CD4+ count ≤ 100 cell/μL ($p=0.003$) (data not shown).

Among the 56 patients with more than one WHO stage 4 condition, the most frequent combination was esophageal candidiasis and HIV wasting syndrome (15 (26.8%)). Pleural effusion was the most frequent type of extra pulmonary tuberculosis (58.8%), while cutaneous KS involving the lower limbs was the most frequent presentation of KS (64.4%) (data not shown).

Those initially diagnosed with esophageal candidiasis, HIV wasting syndrome, KS, and extra-pulmonary tuberculosis contributed most to the number of deaths (data not shown).

DISCUSSION

Our study found that 7.6% of our patients had a WHO stage 4 diagnoses. We also found a higher proportion of WHO stage 4 conditions among men compared to women enrolled in care, a finding consistent with two other studies in East Africa which found that at enrolment, men were more immunocompromised compared to women. [11, 12] This could be attributed to the poor health seeking behavior of men delaying or avoiding enrollment in care even after they know their HIV status.[13,14,15]

We found that esophageal candidiasis was more common among women. This gender distribution is consistent with other HIV-positive cohorts.[16,17] KS was more common among men, which is consistent with studies among non-HIV positive cohorts, [18,19] and among HIV-positive patients.[16]

The major limitation of our study was reliance on clinical diagnosis for many of the WHO stage 4 conditions of interest. Although this may contribute to an underestimation or overestimation of the disease prevalence for certain conditions, it is representative of how patients are diagnosed and treated in similar resource-limited settings.

This study identified the most common WHO stage 4 conditions in a peri-urban HIV clinic in western Kenya. These findings can provide guidance to HIV programs for prioritizing resources to ensure adequate diagnosis and management of these conditions.

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Table 1

Frequency of WHO stage 4 conditions by sex in a cohort of adults enrolled in outpatient HIV care in Kisumu, Kenya

WHO Stage 4 Conditions	Total	Female (n=286 WHO stage 4 conditions among 253 women)	Male (n=197 WHO stage 4 conditions among 174 men)	p-Value
Esophageal candidiasis	184	120 (47.7%)	64 (36.8%)	0.029
Extra pulmonary tuberculosis	94	52 (20.6%)	42 (24.1%)	0.378
HIV wasting syndrome	67	45 (17.8%)	22 (12.6%)	0.151
Kaposi's sarcoma	49	14 (5.5%)	35 (20.1%)	<0.001
Cryptococcal meningitis	25	14 (5.5%)	11 (6.3%)	0.733
Pneumocystis jirovecii pneumonia	23	15 (5.9%)	8 (4.6%)	0.549
Cervical cancer*	6	6 (2.4%)	N/A	N/A
Others OIs†	35	20 (7.9%)	15 (8.6%)	0.791

*For cervical cancer the n only applies for the number of women in the study

†Other OIs include: Central nervous system toxoplasmosis: 14 (2.9%); genital herpes simplex virus infection: 8 (1.7%); HIV encephalopathy: 8 (1.7%); cytomegalovirus (CMV) infection: 1 (0.2%); mycobacterium avium complex (MAC): 1 (0.2%); progressive multifocal leukoencephalopathy (PML): 1 (0.2%); and lymphoma: 1 (0.2%)