

## CAUSES OF DEATH IN HOSPITALIZED HIV PATIENTS IN THE EARLY ANTI-RETROVIRAL THERAPY ERA

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### SUMMARY

**Objective:** To establish the cause(s) of death among persons with HIV and AIDS admitted to the Fevers Unit of the Korle-Bu Teaching Hospital (KBTH) in 2007 and to determine whether they were AIDS-related in the era of availability of HAART

**Method:** Retrospective chart review of all deaths that occurred in the year 2007 among inpatients with HIV infection. Cause of Death (COD) was established with post mortem diagnosis, where not available ICD-10 was reviewed independently by two physicians experienced in HIV medicine and a consensus reached as to the most likely COD.

**Results:** In the year under review, 215 (97%) of the 221 adult deaths studied were caused by AIDS and HIV-associated illnesses. Of these, 123 (55.7%) were due to an AIDS-defining illness as described in CDC Category 3 or WHO stage 4. Infections accounted for most of the deaths 158 (71.5%), many of them opportunistic 82 (51.8%). Tuberculosis was the commonest COD. Clinical diagnosis of TB was accurate in 54% of deaths, but was not validated by autopsy in 36% of deaths. There were few deaths (14.5%) in patients on HAART.

**Conclusion:** In a developing country like Ghana where HAART was still not fully accessible, AIDS-related events remained the major causes of death in persons living with HIV. Total scale-up of the ART programme with continuous availability of antiretrovirals is therefore imperative to reduce deaths from AIDS and HIV associated illnesses. There is need for interventions for early diagnosis as well as reduction in late presentation and also better diagnostic tools for tuberculosis.

**Keywords** Cause of death, HIV, AIDS, HAART, Ghana, Tuberculosis

### INTRODUCTION

HIV/AIDS is among the leading cause of death worldwide, with a yearly toll of 3.1 million. Most deaths (2.4 million) occur in sub-Saharan Africa.<sup>1</sup> However, there has been a reduction in AIDS-related deaths and a corresponding increase in non-AIDS-related deaths in the era of highly active antiretroviral therapy (HAART), especially in developed nations.<sup>2-6</sup> This phenomenon has been attributed to the increased longevity and better quality of life afforded by HAART.

As more countries scale up antiretrovirals, the phenomenon is also being noted across the world in middle and lower income countries.<sup>3,7,8</sup> AIDS defining illnesses like cryptococcal meningitis, herpes simplex encephalitis, cerebral toxoplasmosis and extrapulmonary tuberculosis are giving way to sepsis, cardiovascular diseases, injuries and non AIDS defining cancers.

In developing countries where the majority of HIV-infected people live, access to HAART has improved, however there still remains a substantial unmet need for antiretroviral therapy. In the treatment 2015 initiative, the UNAIDS recognizes that access to ante-retroviral therapy (ART) be scaled up so that 15 million persons without ART have access by 2015. Ninety percent of those without access who are eligible are found in 30 countries most of which are low and middle income countries.<sup>9</sup>

Initially the high cost and complexity of administration of ART in low income countries was considered a barrier but evaluation of one of the earliest programmes showed similar virological, immunological and adverse effect outcome as in developed countries.<sup>10</sup>

Ghana started its ART programme in 2003 and Korle Bu Teaching Hospital (KBTH) was one of the initial sites to offer ART on a large scale.

The study sought to determine the spectrum of causes of death (COD) among HIV-infected inpatients four years after provision of ART at the KBTH.

## BACKGROUND

The Fevers Unit of Korle-Bu Teaching Hospital serves as the national referral centre for HIV-infected patients. Since the first case of HIV was diagnosed in Ghana in 1986, the Unit has provided care and support to persons living with HIV/AIDS.

In December 2003, the Unit became the third public site to provide HAART in the scale-up of access to treatment by the National AIDS Control Programme (NACP) and its partners. At the time of the study there were about 7000 patients enrolled, and 3192 of these were receiving HAART. There were 716 admissions to the ward in the year under study.

We explore here in detail the causes of death among HIV-infected patients admitted at the Korle-Bu Teaching Hospital in the year 2007, 4 years after the national HAART programme was launched at the Fevers Unit.

## METHODS

### *Study Design*

This was a retrospective study in which the medical and mortality records of all HIV-infected patients who died at the Fevers Unit during the study period (January 2007 to December 2007) were reviewed. Data from multiple sources were used and triangulated. The multiple sources included one or more of the following: death certificates, medical charts, and autopsy reports, where available. The multiple sources also included electronic data capture from the database as well as manual records from the patient folders which included more details of outpatient as well as all details of inpatient admission. Some of the inpatient records were doctors' notes, nurse's notes and results of laboratory tests. Causes of death (COD) were collated from the death certificates and matched with autopsy results.

Where autopsy results were not available, two physicians experienced in HIV medicine using the medical records of admission and concordance established did independent determination of the most likely cause of death. In cases of discordance, a third experienced physician reviewed the records and consensus was reached as to the most likely primary and secondary CODs, taking into account the morbidity at the time of death. Cause of death

was coded according to the International Classification of Diseases, 10th Revision (ICD-10). Variables studied included age, gender, duration of admission at the time of death, HAART use, and morbidity. "Morbidity" represented the number of concurrent illnesses present at the time of death.

Primary causes of death were classified as "AIDS-related death" (ARD), "HIV-associated death" (HIA), or "Other". A death was considered "AIDS-related" when the primary COD was an AIDS-defining event as described in Category 3 of the CDC definition of AIDS<sup>11</sup>, or WHO stage 4. "HIV-associated deaths" included those conditions that were HIV related but not CDC category 3 or WHO stage 4. A cause of death not directly attributable to either of the foregoing was characterized as "Other", i.e. non-HIV-associated. This category included conditions such as hepatic disease or cardiovascular disease from hypertension.

Causes of death were also sub-categorized by organ systems and stratified into "Opportunistic infection", "Opportunistic malignancy", or "Other". Examples of conditions falling into this last category were malignancies such as hepatocellular carcinoma and metastatic choriocarcinoma.

### *Data management*

Data was entered into an excel workbook and cleaned. Missing data were filled in where available and duplications removed. The data was then exported into STATA version 8.2 and variables coded for analysis.

### *Statistical Analysis*

Statistical comparisons were made using the chi-squared test of hypothesis or Fisher's exact test, where appropriate. *P* values were two-tailed, and values of <0.05 were considered statistically significant. All analyses were done using a standard statistical package, STATA, version 8.2 (Stata Corp., College Station, Texas).

### *Ethics*

The study protocol was reviewed and approved by the Ethical and Protocol Review Committee of the University of Ghana Medical School.

## RESULTS

### *Demographic Characteristics*

Between January and December 2007, a total of 716 HIV and AIDS patients were admitted to the Fevers Unit of which 221 of these patients died on admission giving a crude mortality rate of 31.5%. Autopsy records were available for 135 (61%) of the deaths. The mean age was 39.7 (SD 9.01) and the age range was 18-80 years. Patients in the reproductive age group (15-49) made up 187(84.6%) whilst females made up 115 (52%) of the population.

The majority of patients 116 (53%) spent between one and six days on admission before death. Only 32 (14.5%) of the patients were on HAART at the time of death (Table 1).

### Causes of Death

Out of the total deaths, 215 (97.3%) were caused by conditions associated with HIV and AIDS and 6(2.7%) were caused by non-HIV related conditions. Of the HIV and AIDS related deaths, 123 (57.21%) were due to an AIDS-defining illness as described in Category 3 of the CDC definition of AIDS and therefore were categorized as AIDS-related deaths (ARD) (Table 2) whereas 92 deaths (42.79%) were non AIDS related and classified as HIV-associated deaths (HIA).

**Table 1** Comparison of patients dying from AIDS Related deaths (ADR) and HIV Associated deaths (HIA)

Factor(at time of death)	AIDS related deaths No (%) (N=123)	HIV associated deaths No(%) (N=92)	p- value
<b>Age (yrs)</b>			
15-49	103 (83.7)	79 (85.9)	0.81
>49	20 (16.3)	13 (14.1)	
<b>Sex</b>			
Males	61 (49.6)	42 (44.7)	0.71
Females	63 (50.4)	50 (54.3)	
<b>Duration of Admission at time of death</b>			
<24 hrs	2 (2)	6 (6)	0.85
1-6 days	65 (55.5)	50 (49.5)	
7 days or more	50 (42.5)	45 (44.5)	
<b>HAART use</b>			
Yes	16 (13.6)	16 (15.8)	0.80
No	101 (86.4)	85 (84.2)	
<b>Morbidity</b>			
0 concurrent illnesses	48 (41.1)	27 (26.7)	<0.01*
1 concurrent illness	45 (38)	42 (41.6)	
2 concurrent illnesses	23 (20)	20 (19.8)	
3 or more concurrent illnesses	1 (0.9)	12 (11.9)	

\*statistically significant at  $p < 0.05$

Tuberculosis was the commonest cause of death accounting for 69 (57.7%) of all deaths. This was followed closely by cerebral toxoplasmosis and Kaposi's sarcoma.

HIV associated deaths consisted mainly of infections (47.8%), anaemia (27.2%), malignancy (4.3%) and a large miscellaneous group (20.7%) consisting of venous thromboembolism, pulmonary oedema and others (see Table 3).

Infections were again the commonest cause of HIV associated deaths majority of which were lobar or bronchopneumonia. This was followed closely by anaemia.

### Accuracy of Pre-mortem Diagnosis

Autopsy findings were fully in agreement with pre-mortem diagnoses in 24.44% (33) of cases, partial agreement in 51.85% (70) and not in agreement with 23.70% (32) of cases.

**Table 2** AIDS Related Deaths

Infections N=110	N (%)
Disseminated TB	45(36.5)
TB meningitis	7 (6.2)
Pulmonary TB	17 (15)
Cerebral Toxoplasmosis	26 (23)
Cryptococcal meningitis	4 (3.5)
Bacterial meningitis	3 (2.6)
Chronic diarrhea	8 (7)
<b>Malignancies N-13</b>	
Kaposi's sarcoma	10 (8.6)
Lymphoma	3 (2.6)

**Table 3** HIV Associated Deaths

HIV Associated deaths N-92	N (%)
Infections	44 (47.8)
Anaemia	25 (27.2)
Miscellaneous	19 (20.7)
Malignancy	4 (4.3)

### Accuracy of TB Diagnoses

The ante mortem diagnosis of 69 cases of TB was validated using post mortem diagnosis. Clinical diagnosis of TB was accurate in 37(54%) of TB deaths, but was not validated by autopsy in 25 (36%) of cases, revealing a considerably high index of suspicion for the disease. The diagnosis was missed in 7(10%) of patients.

## DISCUSSION

The causes of death for HIV-infected patients admitted to the Fevers Unit in 2007 were examined. The data showed that AIDS-related events continued to be the major causes of death, in contrast to recent studies conducted in industrialized countries which had noted a shift in the causes of death toward non-HIV-related causes since the introduction of HAART.<sup>2,12-14</sup>

Sackoff<sup>12</sup> noted in his study that from 1999-2004, the percentage of deaths from non-HIV causes had increased by 32%, whereas Palella<sup>14</sup> also found that the proportion of deaths attributable to non AIDS diseases had increased and were predominantly hepatic, cardiovascular, pulmonary and non AIDS defining cancers. In the study by De Ollala et al<sup>4</sup>, cause of death from non HIV related causes was 28% with cancers contributing 20% and liver diseases 18.8%.

In this cohort however, non-AIDS-related causes of death such as non-opportunistic malignancies, cardiovascular, hepatic and renal diseases were uncommon. On the other hand, infections were the leading causes of death in this population, notably opportunistic infections. Tuberculosis was the single most important opportunistic infection causing death.

Disseminated TB was the commonest form, with pulmonary TB running a close second and TB meningitis, third. Likewise in a study conducted in Burkina Faso on determinants and causes of mortality in HIV patients on HAART between 2003 and 2008, a multivariate analysis showed that clinical stage, BMI, CD4 count and treatment regimen were significantly associated with death. Common causes of mortality were wasting syndrome, tuberculosis and anemia.<sup>7</sup>

The pattern of diseases causing death in Ghana and Burkina Faso could be attributed to the low penetration of antiretroviral therapy amongst the population studied and also the fact that these countries still continue to have a high burden of communicable diseases as compared to non-communicable diseases. The pattern also depicts the severe immune suppression that exists in the in-patients.

In a study by Agaba *et al*<sup>15</sup> on predictors of mortality in hospitalized HIV patients in Nigeria, tuberculosis was the common diagnosis accounting for 33.6% of the deaths. Pulmonary disease accounted for 53% and extra-pulmonary 47% of TB cases. In this study, tuberculosis was again the commonest cause of death accounting for 57.7% of all deaths. However in contrast to findings from Agaba, disseminated and extrapulmonary accounted for 75% of cases whilst pulmonary TB was 25%.

In this study, we have shown that a significant proportion of TB deaths (10%) were not diagnosed prior to death. This highlights the need for better diagnostic tools for TB a situation which to date has only marginally improved. In about three-quarters of the cases studied, at least one pre-mortem finding was confirmed by autopsy, attesting to the high clinical acumen of the physicians involved and the specificity of the post mortem diagnosis. This is in contrast to the study on causes of mortality conducted by Sackoff, where he observed that death certificates issued lacked specificity of the cause of death.<sup>12</sup>

With regard to demographic characteristics, patients dying from ADIs differed from those dying from non-ADIs only in morbidity. This finding was rather surprising as we expected the opposite, given our definition of morbidity as number of concurrent illnesses at the time of death. In a study on AIDS and non-AIDS mortality in the era of antiretroviral therapy by Falster *et al*<sup>16</sup>, they found that of 215 deaths, 89 were AIDS related, 97 non-AIDS related and 29 were unknown. They found age greater than 50 years and CD4 counts > 100 increased the risk of non AIDS deaths (HR 4.99) whereas CD4 ≤100 and viral load >10,000 increased the risk of AIDS deaths (HR 4.21). Most of our patients did not have CD4 counts and viral load tests were not available at the time.

Most of the patients in this study were not on HAART at the time of their death, suggesting a low admission rate of patients on HAART. Even though this rendered analyses by HAART use inconclusive, it shows the benefit of HAART in reducing morbidity severe enough to warrant admission and subsequently mortality. Increased use of HAART is likely to reduce mortality as shown in other studies around the world.<sup>2,12-14</sup>

Some of the admissions of patients on HAART were attributed to HAART related anaemia caused by zidovudine, one of the first line drugs. Availability and accessibility of blood and blood products continue to be a challenge for patient care. The relatively short duration of admission for most patients reflects the late presentation of HIV-infected patients at the health facility hence the high mortality rate.

Limitations of this study include the frequent inadequacy of death certificates and medical notes to identify causes of death; these are imperfect methods. The autopsy rate was just over 60% in this study. Another limitation was that immunological and virological parameters were not readily available for analysis due to late presentation, short duration of stay and financial challenges. Virological tests were not available at the time. Also, being a tertiary referral centre, mortality at the Fevers Unit may not be representative of HIV mortality in the community but rather in hospitals. Mortality in the community can only be ascertained using verbal autopsies.

## CONCLUSION

The overall mortality rate for 2007 was 31.5%. AIDS-related causes accounted for 55.7% whereas HIV-associated causes accounted for 41.6% of total deaths. Together AIDS and HIV related deaths formed 97% of the deaths showing that the transition from HIV related deaths to causes of deaths similar to those of the general population had not yet occurred in the Unit. Autopsy findings confirmed at least one pre-mortem diagnosis in 76% of deaths. Tuberculosis was the single most important cause of death in the study population.

Accuracy of TB diagnosis was average and still needed to be supported by better diagnostic tools. In a developing country like Ghana where HAART is yet to be widely accessible to PLHIVs, HIV-related deaths remain the major cause of death.

## RECOMMENDATIONS

We recommend further scale-up of the ART programme, early diagnosis of individuals and consistent supply of drugs and other consumables to reduce HIV related mortality, improve quality of life and increase life expectancy. Better diagnostic tools for TB are needed to assist clinicians and patients.

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