ORIGINAL ARTICLE

Mortality and causes of death in HIV-positive patients receiving antiretroviral therapy at Tshepang Clinic in Doctor George Mukhari Hospital

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KEY WORDS

antiretroviral therapy, causes of HIV-infections, mortality, sub-Saharan Africa, trends

ABSTRACT

INTRODUCTION Since the initiation of regular antiretroviral therapy and highly active antiretroviral therapy (HAART) in South Africa in 2004, data on effects of HAART on mortality are not available in our hospital.

OBJECTIVES We sought to describe mortality trends and causes of deaths among HIV-infected patients in the HAART era.

PATIENTS AND METHODS Consecutive HIV-infected adults who were prescribed HAART in our hospital were prospectively followed-up from July 2004 to December 2006 or until death, loss to follow-up, discontinuation of HAART or referral to another center.

RESULTS Out of 2605 HIV-infected patients analyzed at the end of 2006, 7.8% (n = 205) died. The causes of these 205 deaths were dominated by AIDS related disorders such as opportunistic infection (47.6%) and advanced AIDS status (37.3%). Non-AIDS infectious diseases, liver diseases, cardiovascular diseases, and cancers were rare. Mortality rate was higher in males (28%, p <0.0001) than females (8%) as well as in subgroup with CD4 cell counts <200/μl (8%, p <0.0001) than in subgroup with CD4 cell counts >200/μl (4.9%). There was a negative significant dose – response relationship (p for linear trend <0.0001) between mortality and baseline CD4 cell counts among patients with CD4 cell counts <200/μl, 13% in the CD4 <50/μl group, 6% in the CD4 51–100/μl group, 5.5% in the CD4 101–150/μl group, and 3% in the CD4 >151/μl group. Mortality was not associated with age and HAART regimens.

CONCLUSIONS Prevention of AIDS-defining conditions and expansion of earlier access to HAART could substantially reduce mortality in resource-poor settings.

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INTRODUCTION The HIV/AIDS-related mortality rate has decreased since the routine use of antiretroviral therapy (ART) and highly active antiretroviral therapy (HAART).[1-3]

As the HIV infection course has been changed from rapidly fatal to chronic manageable disease in developed countries[1,4,5], seemingly the HAART has the ability to produce sustained suppression of viral replication.[6] Accordingly researchers in those industrialized western countries have elaborated guidelines with goals, criteria for patient selection and patient decision, contraception, ART regimen, opportunistic infections and mental health management.[3]

However, in developing countries such as sub-Saharan African (SSA) countries, the picture is different. The burden of HIV/AIDS in SSA countries is extensive with almost 30 million of the 40 million individuals infected by HIV in the world.[7-9] Patients report late in the HIV/AIDS disease, when

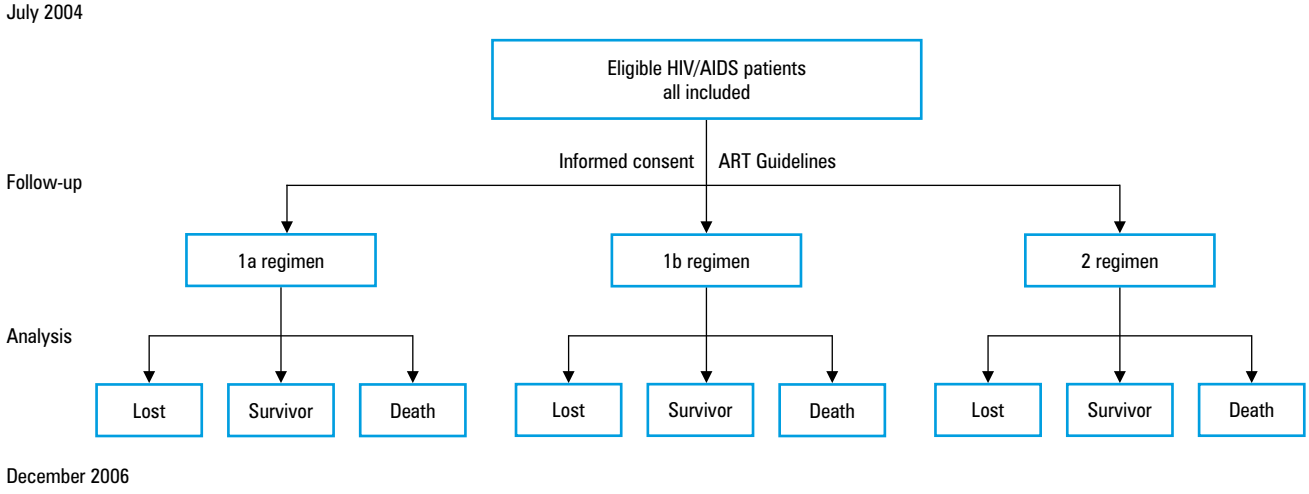

FIGURE 1 Diagram of the study design Abbreviations: ART – antiretroviral therapy

they are already sick, to medical care due to stigma. The lack of resources lead to long waiting lists, which is for months and therefore the CD4-count drop down to very low levels before the treatment is started. The patients in our South African population are admitted in the general wards with severe opportunistic infections, HIV related diseases, and from other unrelated causes.[8] The Department of Health in South Africa started supplying ART to HIV-infected persons later than many countries in the world, precisely since 2004. Despite this ART introduction, it is still very difficult to put such patients on ART as the compliance cannot be assessed because of the condition of the patient and lack of knowledge of their background. Furthermore, data show significant higher morbidity and mortality reported after ART introduction in some resource poor countries[10], these are lacking in South Africa. To avoid such early mortality in HIV/AIDS patients, we need to identify its predictors and mobilize to prevent and eliminate them. This requires availability of more information like that obtained by this study. We evaluated mortality rates according to etiology, demographic parameters, CD4-counts, and ART regimen among South African HIV/AIDS patients.

PATIENTS AND METHODS

Design and setting

This was a prospective observational ongoing study which is part of monitoring of all the patients treated with antiretroviral drugs among adult HIV/AIDS patients admitted to Tshepang clinic at Doctor George Mukhari Hospital (DGMH), Pretoria, South Africa. DGMH is a 1700-bed tertiary health institution in Gauteng. It receives referrals from part of Gauteng Province, North West, Limpopo, and part of Mpumalanga Province. Tshepang clinic is the site accredited to supply ART in this hospital. This clinic receives HIV/AIDS patients referred from primary health care centers, general practitioners, and regional hospitals from the provinces mentioned above. Some of the patients are self referrals.

Study population

Patients considered were all patients who were enrolled on ART conforming to the South African guidelines for inclusion in this program as depicted in FIGURE 1. They were proven HIV-positive on ELISA antibody tests with CD4-counts 200 cells/μl or less irrespective of World Health Organization (WHO) stage, or stage 4 irrespective of the level of CD4-count.

Patients referred to this clinic came with the CD4 count as baseline.

Procedures and follow-up

Investigators (medical doctors, nurses, psychologists, social workers) had experience treating HIV-infected persons. Data were abstracted from the database and patient's charts from July 2004 to December 2006 (30 months) at each monthly visit and entered electronically by trained medical doctors and then compiled centrally and reviewed and edited before being analyzed.

Data collected included age, sex, baseline CD4-counts, date of starting ART, date of death, treatment regimen give, the date of last visit or lost of review, the date of transfer out, and the cause of death. We analyzed all deaths, including those not directly due to AIDS or indirectly from conditions exacerbated by HIV-infection (such as hepatic, renal, or cardiac disease).

Screening

The HIV Combi Immunoassay for the *in vitro* determination of HIV-p24 antigen and antibodies to HIV-1, including group O, and HIV-2 in human serum and plasma was used for screening with Elecsys 2010 modular analytics E170 machine (Roche Products, Basel, Switzerland and Hitachi High-Technologies Coporation, Tokyo Japan). The sensitivity of the Elecsys HIV Combi assay is 100%. The 95% lower confidence limit is 99.80%. The specificity of the Elecsys HIV Combi is 99.63%, and the 95% lower confidence limit was found to be 99.42%. Samples that tested positive with the Elecsys HIV Combi were confirmed using AxSYM® HIV Ag/Ab Combo using Abbot Axsym Automated Immunoassay Analyzer (Abbot Laboratories, Donegal/Chicago, USA). AxSYM HIV Ag/Ab Combo is a microparticle enzyme immunoassay for simultaneous qualitative detection of antibodies to human

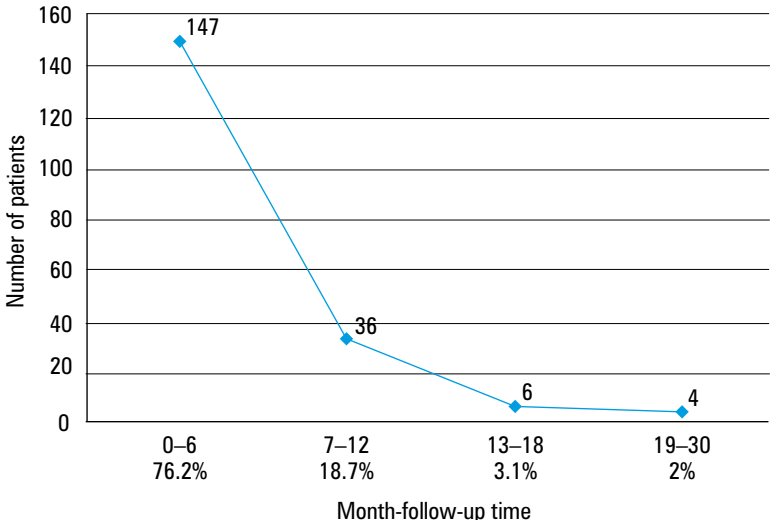

FIGURE 2 Incidence rates of mortality in 2605 HIV/AIDS patients during the month-follow-up time after the initiation of antiretroviral therapy

immunodeficiency virus type 1 and(or) type 2 (HIV-1/HIV-2) and HIV p24 antigen in human serum or plasma. AxSYM HIV Ag/Ab Combo is used as an aid in the diagnosis of HIV infection. Specificity based on 0 prevalence of antibodies to HIV-1/HIV-2, and(or) HIV p24 antigen in random blood donors (7900 tested) is estimated to be 99.87% (7890/7900) for the AxSYM HIV Ag/Ab Combo assay. Specificity based on low prevalence of antibodies to HIV-1/HIV-2, and(or) HIV p24 antigen in a hospitalized population (1938 tested) is established to be 99.90% (1929/1931) for the AxSYM HIV Ag/Ab Combo assay.

Sensitivity of HIV-1 antibody detection rate in a population of 615 HIV-1 antibody confirmed seropositive individuals is 100% (615/615). This rate includes 453 clinically diagnosed patients from different disease stages of HIV-1 infection and 55 HIV-1 subtyped sample. HIV-2 antibody detection rate in a population of 108 HIV-2 antibody confirmed seropositive individuals is 100% (108/108). HIV p24 antigen detection rate in a defined (≥25 pg/μl) population of 50 HIV p24 antigen confirmed positive individuals is 100% (50/50). HIV-1 group 0 antibody detection rate in a population of 19 HIV-1 group 0 antibody confirmed positive specimens tested is 100% (19/19).

CD4 cell counts have been measured using Flow Cytometry Epics XL-MCL (Beckman Coulter, Miami, Florida, USA).

Operational definitions Advanced HIV/AIDS disease was defined by the WHO stage III/IV disease. HAART was defined as at least triple therapy including 2 nucleoside reverse transcriptase inhibitors (NRTI: 1a regimen) plus at least 1 protease inhibitor or 1 non-nucleoside reverse transcriptase inhibitor (1b regimen) or a 3rd NRTI (2 regimen). Criteria for initiation or maintenance of HAART were based on the updated recommendations existing at the time of this study. Antiretroviral therapy could be modified at the discretion of the treating physician. All the patients remained in the study as long as they remained on HAART till the end of the study.

The patients were encouraged to use injectable contraceptives. If unable to guarantee reliable contraception, Nevarapine was substituted for Efavirance. Deaths were identified directly from patient's records and social worker's reports.

Statistical analysis Age was presented as mean standard deviation while categorical variables were presented as percentages (proportions). The Student t-test or χ^2 test procedures were used to assess the univariate associations between age or categorical variables and mortality. All analyses were performed with a p-value set at <0.05 (significant) using SPSS software version 14.0 for Windows (SPSS, Chicago, IL, USA).

RESULTS Out of 3073 patients included, 1002 were males, 2071 were females, 2924 were on regimen 1a, 82 were on regimen 1b, 29 were on regimen 2,434 were lost of view, and 34 were transfers out. Therefore, out of the analyzed population, 2605 patients (response rate: 84.8%), a total of 204 individuals (7.8%) died during the follow-up. There were 3.3 deaths/100 years between 2004 and 2006.

Underlying causes of mortality The causes of these 204 deaths were dominated by opportunistic infections (42.7%, n = 87: 42 cases of tuberculosis, 25 cases of chronic diarrhea, 18 cases of *Cryptococcus meningitis* infection, and 12 cases of bacterial pneumonia/pneumocystis pneumonia) and advanced AIDS (37.3% n = 76), whereas HIV/AIDS – related cancers represented 8.3% of deaths (11 cases of Kaposi Sarcoma, and 6 cases of lymphoma). Other causes of death were hepatitis (n = 6) and stroke (n = 3).

The most frequently reported opportunistic infections among infectious causes of deaths were tuberculosis (48.3%) in comparison with other opportunistic infections.

There was no patient who died of non-AIDS malignancies, but 12 cases with lactic acidosis (ART-related complications).

Deaths and time of ART Although 95% of deaths occurred during the first year of ART, there was a significant decrease (p for linear trend <0.0001) of mortality rates over the period of ART for these HIV-infected patients (FIGURE 2).

Deaths and demographic characteristics There was not a significant association between age groups and mortality rates (results not shown). However, sex was only reported for 2176 patients whose 689 (31.7%) were males and 1487 (68.3%) females. The mortality rate was higher ($p < 0.0001$) in males (28%, n = 193) than females (8%, n = 119).

Deaths and CD4-counts The mortality rate was higher ($p < 0.00001$) in 2380 patients with CD4-counts <200/μl (8.1%, n = 193) than 225 patients with CD4-counts ≥200/μl (4.9%,

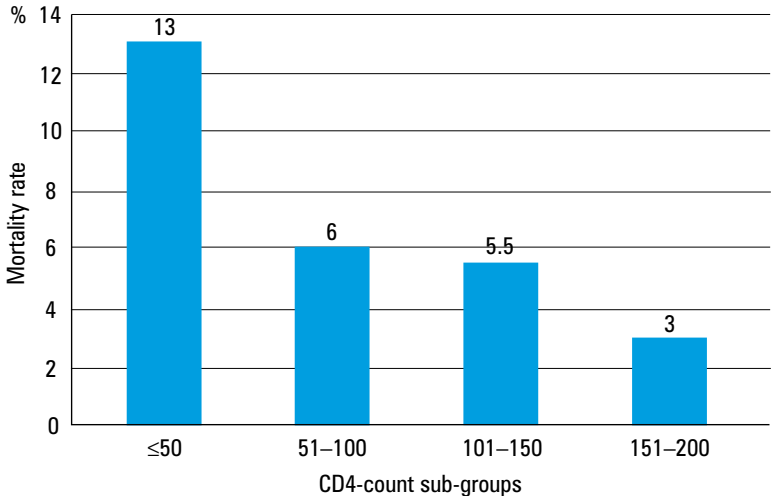

FIGURE 3 Mortality rate according to the CD4-count sub-groups among 2380 HIV/AIDS patients with CD4-count <200/µl

n = 11). Furthermore, there was a negative significant dose – response relationship (p for linear trend <0.0001) between the mortality rates and the CD4-counts subgroups among the 2380 patients with CD4-counts <200/µl (FIGURE 3).

Deaths and ART regimens The mortality rates did not vary (p >0.05) between the 3 ART regimens: 8.8% (n = 184/2083) in 1a regimen, 8.9% (n = 7/78), and 8% (n = 2/26) in regimen 2.

DISCUSSION

Since 2004 the Department of Health started supplying antiretroviral drugs to HIV-infected persons in South Africa, attention of this study was then turned to causes of death and marked and sustained reduction in HIV/AIDS-related morbidity and mortality as consequence of extensive use of ART.

Indeed, SSA including South Africa has one of the highest prevalences of HIV/AIDS as well as the highest AIDS-related mortality in the world.[7-9] We conducted this study because measuring the impact of HIV disease and its treatment on mortality is the key to developing and assessing the impact of programmes to mitigate the effects of the HIV pandemic at global, regional and national levels in our country South Africa in particular). Major findings of the present study are discussed below.

Potent antiretroviral therapy This study showed that total mortality has decreased substantially among these HIV/AIDS patients with access to ART as reported in developed countries[1-6] and another SSA country such as Senegal[10].

Before the era of ART, crude mortality rates were 18.3% in South Africa[8] and 35% in Kenya[9]. Thus HIV/AIDS related mortality has been reduced 2–4 time (7.8%) by ART in this study in comparison with mortality rates from previous African studies.[8,9] The mortality rates in ART-treated HIV-infected at the first experience of initiation of HAART era in developed countries (7 deaths/100 per years in 1996)[11] and Senegal (6.3 deaths/100 person-years in 1998)[10] were higher than 3.3 deaths/100 person-years obtained at the first South African experience of initiation of ART in this study. The changing bio-clinical spectrum of HIV infection in Africans (lower rates of gastro-intestinal complications such as diarrhea and National tuberculosis control program) and that in developed countries (increase of non-AIDS causes: non-AIDS malignancies, cardiovascular and metabolic complications, smoking) may explain the observed difference in mortality rates. However, recognition of these constraints favored continuous decline of mortality in HIV/AIDS patients from developed countries estimated near to 1 death/100 person-years in 2004[11,12] and 2 deaths/100 person-years in 2002 in Senegal[10].

Risk of dying during the first year of ART The absolute risk (probability) of dying during the first year of ART in this study was estimated 95% and 8-fold more elevated than that of 11.7% reported in Senegal.[10] This highest mortality during the 1st year of ART attenuates the benefits of ART on overall mortality and raises the problem of appropriate and specific guidelines of HIV/AIDS management in South Africa. Highest proportions of advanced AIDS disease and Tuberculosis and lowest levels of CD4-counts may explain this highest probability of dying.[10] Efforts towards an earlier initiation of ART in African HIV/AIDS patients and a better approach to avoid late diagnosis of HIV-infection as well to diagnosis and management of tuberculosis, opportunistic infections, and malnutrition will be the next step to limit the still too high mortality during the first year of ART.

This study suggests that more research is needed on the threshold of CD4-counts to initiate ART in Africans. CD4-counts <200/µl, identified with higher probability of dying in this study, should be the cut-off point to start any ART regimen. Indeed, not only mortality did not vary with ART regimens, no side effects related to ART were reported in this study. Furthermore male sex appeared to affect prognosis (28% vs. 8% mortality in females) more markedly than CD4-counts <200/ml and age. This study is the only to report a significant association between mortality and sex in HIV/AIDS patients.

Implications for prevention and research The delay in diagnosis of HIV-infection and initiation of ART calls for increased screening efforts, particularly in marginalized black South Africans. Prevention policies set up in South Africa to decrease the transmission of HIV-infection are deceiving. More research is needed on the considerable variation of the causes of death between countries.[13]

HIV-infection in African countries and Western developed countries It is difficult to compare the present information on HIV-infection/AIDS outcomes and that from other Sub-Saharan African

Countries with data obtained from high-income European and North American countries. Indeed, many factors limit the control of HIV infection and the effectiveness of HAART in African countries: poverty, co-infections (tuberculosis, bacterial diseases), limited access to HAART, malnutrition, and interruption in supply at the program level might compromise adherence, treatment efficacy and prognosis.[14-16] Compared with the developed Western countries, patients starting HAART in African settings have lower CD4 cell counts (<200 cells/μl *vs* median 234 cells/μl), were more likely to be females (51% *vs* 25%), and more likely to start therapy with NNRTI (70% *vs* 23%).[4,17-20]

The non-AIDS causes of mortality in developed countries (cardiovascular disorders, cancers, hepatitis)[11,13,21-25] contrast with AIDS-related causes of mortality in African countries (infectious opportunistic diseases such as tuberculosis or malnutrition)[10,26-29]. So HIV infection, established now as a non-fatal chronic disease in the era of HAART[12], resulting in prolonged life and HAART induces cardio-metabolic complications[30,31], will exacerbate the worldwide burden of non-communicable diseases including cardiovascular diseases, cancer, diabetes mellitus, and mental disorders. In Africa, people will face double burden of disease comprising both communicable (tuberculosis, malaria) and non-communicable diseases.

Limitations This study has several limitations. The diagnosis of HIV infection using ELISA methods was always confirmed in this study with sensitivity and specificity both around 100%. In other more deprived African regions, ELISA test is the alternative strategy recommended by World Health Organization. ELISA anti-HIV tests have sensitivity between 95% and 100%, and a specificity of 96% in the majority of these African laboratories.

The side effects of HAART and the change of weight and the CD4 cell counts are being monitored by our Pharmacovigilance center for further analysis.

We compared the causes of death in a hospital-based cohort study. The comparison of non-HIV related deaths with the HIV infected patients and the general population was not feasible, since the number of cases was small. The general population is not an epidemiologically relevant reference group.

We acknowledge that summarizing the course of events leading to death in one underlying cause, according to ICD-10 rules, is questionable. The lack of an internationally standardized definition of causes of death does not facilitate comparisons with other data from literature. Despite the limitations, this first study in South Africa presented detailed information with potentially valuable insight into trends of mortality in HIV/AIDS patients treated by antiretroviral therapy.

CONCLUSIONS Mortality in HIV/AIDS patients receiving ART has decreased since 2004 with the routine introduction of ART in South Africa. Despite the lethal 1st year of ART administration, mortality decreased over follow-up time. CD4-counts <200/μl and male sex are significantly associated with higher mortality. Tuberculosis and advanced AIDS are the main underlying causes of death.

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