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Increased mortality of male adults with AIDS related to poor compliance to antiretroviral therapy in Malawi

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Summary

OBJECTIVE To investigate the effect of gender on mortality of HIV-infected adults receiving antiretroviral therapy (ART) and its possible reasons.

METHODS A retrospective study to review the records for outcomes of adult cases receiving ART at Mzuzu Central Hospital, Malawi, between July 2004 and December 2006.

RESULTS Over the study period, 2838 adult AIDS patients received ART. Of these, 2029 (71.5%) were alive and still on ART, 376 (13.2%) were dead and 433 (15.3%) were lost to follow-up. Survival analysis with Kaplan–Meier estimator showed significantly higher survival rates among females than males in WHO stage 1, 2 and 3 (both $P < 0.0001$) and borderline in stage 4 ($P = 0.076$). The Cox model revealed a death hazard ratio (males *vs*. females) of 1.70 (95% confidence interval 1.35–2.15) after controlling for WHO clinical stages, body mass index and age. More men than women were lost to follow-up in all occupations except health workers.

CONCLUSIONS The most important reasons for a higher mortality in male patients starting ART may relate to their seeking medical care at a more advanced stage of immunodeficiency and poorer compliance with therapy. The issue needs to be addressed in scaling up ART programmes in Africa.

keywords gender, age, WHO stage, body mass index, occupation, lost to follow-up

Introduction

Introduction of highly active antiretroviral therapy (ART) has greatly improved the survival outcomes of patients with AIDS, in both rich (Detels *et al.* 1998; CASCADE Collaboration 2000; Porter *et al.* 2003) and poor countries (Weidle *et al.* 2002; Coetzee *et al.* 2004; Wester *et al.* 2005; Ferradini *et al.* 2006; Lawn *et al.* 2006; Stringer *et al.* 2006; Wools-Kaloustian *et al.* 2006; Zachariah *et al.* 2006). Since the World Health Organization (WHO) launched the 'three by five' initiative of placing 3 million people in developing countries on ART by the end of 2005, great strides have been made, particularly in sub-Saharan Africa where 1.3 million patients had started ART by December 2006 (WHO *et al.* 2007).

As expected, the baseline degree of immunodeficiency, measured either by plasma viral load, CD4-lymphocyte count or WHO clinical stage, is one of the most important risk factors for a high mortality (Hogg *et al.* 2001; Weidle *et al.* 2002; Wester *et al.* 2005; Calmy *et al.* 2006; Stringer *et al.* 2006). Other risk factors include low body mass index (BMI) and anaemia (Calmy *et al.* 2006; Stringer *et al.* 2006). Before the introduction of ART, some cohort studies found no evidence of appreciable gender differences in disease progression either from seroconversion to AIDS or from AIDS to death (Suligoi 1997). Since the widespread scale-up of ART began, some studies have identified gender as an important factor in survival outcomes, although this finding is inconsistent (Melnick *et al.* 1994; Farzadegan *et al.* 1998; Prins *et al.* 1999; Hogg *et al.* 2001; Moore

et al. 2002; Napravnik *et al.* 2002; Garcia de la Hera *et al.* 2004; Nicastri *et al.* 2005; Calmy *et al.* 2006; Ferradini *et al.* 2006). We therefore decided to investigate the effect of gender on mortality in adult AIDS cases started on ART at Mzuzu Central Hospital (MCH), North Malawi, and look for possible reasons.

Materials and methods

Study setting and management of antiretroviral therapy

Mzuzu Central Hospital is the main referral hospital in the northern region of Malawi, and through the Rainbow clinic, it has been providing free ART to eligible HIV-infected cases since July 2004 in accordance with the national guidelines (Libamba *et al.* 2005; MoH Malawi 2006).

When a patient is found to be HIV-positive, he/she is referred to the ART clinic for clinical staging. If the patient is found to be eligible for ART (assessed in WHO clinical stage 3 or 4 or with a CD4-lymphocyte count <200/mm^3, if laboratory is available), he/she is asked to come with a guardian for a group counselling session about ART conducted by one of the staff of Rainbow clinic. All eligible HIV-positive cases undergo a thorough clinical assessment before starting therapy. Provided there are no contraindications, all cases are treated with a generic, fixed-dose combination of stavudine 30 (T30) or 40 mg (T40)/lamivudine 150 mg/nevirapine 200 mg (procured from Cipla, Mumbai, India, under the trade name of 'Triomune') in line with the Malawi national recommendations. Adults are concurrently given cotrimoxazole preventive therapy (CPT) according to the national guidelines.

Once started on ART and CPT, cases are followed up, first at 2 weeks and thereafter at 4-week intervals, with assessments and drugs distributed from the ART clinic. Characteristics and standardized treatment outcomes are recorded in ART treatment master cards and the ART registry monthly (Libamba *et al.* 2005). Treatment outcomes of HIV-infected cases receiving ART are classified into: (a) alive and on ART at MCH, (b) death, (c) lost to follow-up for more than 3 months (abbreviated as 'default'), (d) stopped treatment and (e) transferred permanently to another ART clinic. In the Rainbow clinic, an electronic information system using fingerprints is maintained to identify every case at the start of therapy and during follow-up, which has been useful in ensuring the identity of cases attending follow-up at the clinic (Yu *et al.* 2005).

Data collection and statistical analysis

Data were collected from the ART registry on all persons started on ART at MCH, comprising age, sex, date and reason for starting ART. The outcomes for cases alive and on ART were censored on 31 December 2006. Adverse outcomes (death, treatment stop, lost to follow-up for more than 3 months and transferred out) were recorded with their dates up until the censor date of 31 December 2006. Data were entered and cleaned in EXCEL and analysed with SAS statistical software (Version 8.2, SAS Institute Inc., Cary, NC, USA).

Survival analyses were conducted with Kaplan–Meier estimates and the log-rank test to compare the difference between survival functions. We also constructed a Cox proportional hazard model to estimate the hazard ratios (HR) of mortality for the prognostic factors age (every 10 years interval starting from 15 years); gender (male, female); WHO clinical staging (stages 1 and 2 with a CD4 count <200 cells/mm^3, stage 3 and stage 4) and body mass index (BMI) (<17, 17–18.5 and >18.5). Results were presented as HR with 95% confidence intervals (CI).

Ethical approval

The Malawi National Health Science Research Committee does not require studies that use routine programmatic data collection to be formally submitted for ethical or scientific approval. As such, no formal submission for this study was made to the Research Committee. General measures were provided in the Rainbow clinic to ensure patient confidentiality, consent for HIV testing and support for children and guardians upon receiving a positive HIV test result.

Results

Cases and survival rates

A total of 4001 individuals started ART at MCH between July 2004 and December 2006. Children (defined as a person <15 years of age, n = 473) and cases who were transferred out (n = 690) were excluded from further analysis. Of 2838 cases who started ART up to 31 December 2006, 2029 (71.5%) were alive and still on ART at MCH, 376 (13.2%) were dead and 433 (15.3%) were either lost to follow-up or had stopped therapy (Table 1). The survival rates of AIDS cases fell as WHO stage advanced (85.0% in stages 1 and 2, 72.1% in stage 3 and 60.1% in stage 4). Patients with a higher BMI have better survival rates (Table 1).

Gender difference

Among these 2838 AIDS cases, females had a significantly higher survival rate than males (76.0% *vs.* 64.6%;

Table 1 Demographic, clinical characteristics and outcomes of 2838 adult patients infected with HIV who attended and received antiretroviral treatment at Rainbow clinic of Mzuzu Central Hospital, Malawi

Variables	All subjects	Male	Female	*P*-value
Number (%)	2838	1122 (39.5)	1716 (60.5)	
Age (years) at diagnosis	38.6 ± 9.8	41.2 ± 10.0	36.9 ± 9.3	<0.0001
Outcomes at end of period of observation, *n* (%)				
Alive on ART	2029 (71.5)	725 (64.6)	1304 (76.0)	<0.0001
Died	376 (13.2)	188 (16.8)	188 (11.0)	<0.0001
Default	433 (15.3)	209 (18.6)	224 (13.0)	<0.0001
WHO stage at start of ART, *n* (%)				
1 and 2 with CD4 < 200/mm^3	420 (14.8)	155 (13.8)	265 (15.4)	0.232
3	1832 (64.6)	704 (62.8)	1128 (65.7)	0.104
4	586 (20.6)	263 (23.4)	323 (18.8)	0.003
WHO stage: number (% of alive and on ART)				
1 and 2 with CD4 < 200/mm^3	420 (85.0)	155 (75.5)	265 (90.6)	<0.0001
3	1832 (72.1)	704 (65.3)	1128 (76.2)	<0.0001
4	586 (60.1)	263 (56.3)	323 (63.2)	0.091
Body mass index: number (% of alive and on ART)				
<17	194 (78.2)	81 (72.3)	113 (83.1)	0.041
17–18.4	277 (85.2)	113 (83.7)	164 (86.3)	0.513
18.5+	1537 (88.6)	524 (84.5)	1013 (90.9)	<0.0001
Occupation: number (% of alive and on ART)				
Business	592 (80.4)	220 (74.1)	372 (84.1)	0.003
Farmer	293 (82.3)	148 (77.7)	145 (86.9)	0.039
Teacher	135 (87.4)	47 (83.0)	88 (89.8)	0.257
Student	75 (72.0)	36 (69.4)	39 (74.4)	0.797*
Soldier/police	26 (80.8)	18 (77.8)	8 (87.5)	1.000*
Health worker	46 (91.3)	12 (91.7)	34 (91.2)	1.000*
Housewife	635 (76.9)	0 (0.0)	635 (76.9)	–
Other	1036 (56.9)	641 (55.9)	395 (58.5)	0.406

Comparisons performed by chi-square tests; *P* value was to test the difference of survival rates between males and females. A total of 830 cases have no data of body mass index.
*Means comparisons performed by Fisher's exact test.

$P < 0.001$ in Table 1). This finding persists after stratification by WHO clinical stage, BMI and occupation (Table 1). Figure 1 shows the survival analysis by Kaplan–Meier method after stratification by gender and WHO clinical stage. The log-rank test shows that female survival rates are significantly higher ($P < 0.0001$ for stages 1 and 2 and stage 3), but are only of borderline significance for patients in stage 4 ($P = 0.076$). According to the quarter when ART was started, females always showed significantly higher survival rates than males, except in July to September 2006 and October to December 2006 (data not shown).

Multivariate analysis using Cox proportional hazard model

After adjustment using Cox proportional hazard models, male gender, younger age, lower BMI and advanced WHO clinical stages were significantly associated with increased mortality (Table 2). Of these, patients in WHO stage 3 and stage 4 had the highest risk of death with HR of 2.52 (95% CI 1.56–4.39) and 5.25 (95% CI 3.18–9.27), respectively. There was a decreasing trend of HR from the younger to older age group (Table 2).

Discussion

The WHO clinical stage and malnutrition are well-known important prognostic factors for AIDS mortality (Calmy *et al.* 2006; Stringer *et al.* 2006), which corroborate the validity of this study (Table 2). Although the effect of gender on mortality of adult AIDS patients is not a new issue, previous studies have not shown consensus or consistent results (Melnick *et al.* 1994; Suligoi 1997; Farzadegan *et al.* 1998; Prins *et al.* 1999; Hogg *et al.* 2001; Moore *et al.* 2002; Napravnik *et al.*

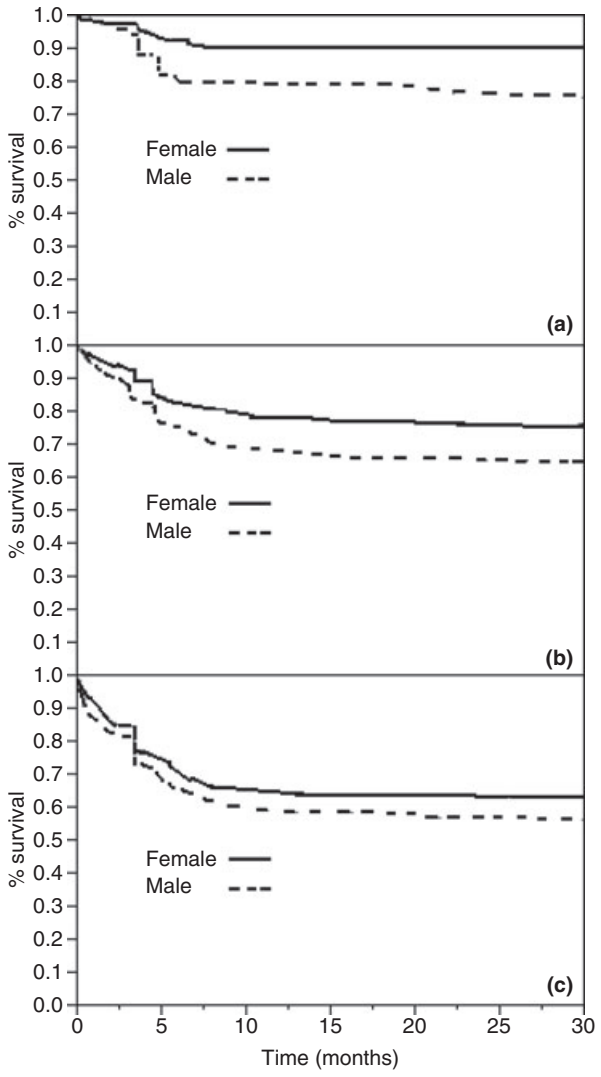

Figure 1 Kaplan–Meier estimates of the survival rate between males and females stratified by WHO stage 1 and 2 (a), 3 (b) and 4 (c) according to duration of follow-up in 2838 AIDS patients. The log-rank tests revealed statistically significant differences between males and females in WHO stage 1 and 2 (a), and 3 (b) (both *P* values < 0.0001), but no statistically significant difference between males and females in WHO stage 4 (c) ($P = 0.076$).

Table 2 Hazard ratios (HR) with 95% confidence interval (CI) of mortality based on the Cox proportional hazard model of 2838 AIDS patients receiving ART at Rainbow clinic of Mzuzu Central Hospital, Malawi

Variables	HR (95% CI)	*P*-value
Gender		
Male (reference group: female)	1.70 (1.35–2.15)	<0.001
Age (years)		
15–24 (reference group: >55)	2.64 (1.27–5.87)	0.009
25–34 (reference group: >55)	2.26 (1.23–4.64)	0.007
35–44 (reference group: >55)	2.26 (1.25–4.60)	0.005
45–54 (reference group: >55)	1.39 (0.73–2.94)	0.328
BMI		
<17 (reference group: ≥18.5)	1.52 (1.10–2.07)	0.011
17–18.5 (reference group: ≥18.5)	1.09 (0.79–1.49)	0.596
WHO stage		
3 (reference group: 1 and 2)	2.52 (1.56–4.39)	<0.001
4 (reference group: 1 and 2)	5.25 (3.18–9.27)	<0.001

2002; Garcia de la Hera *et al.* 2004; Nicastri *et al.* 2005; Calmy *et al.* 2006; Ferradini *et al.* 2006). Many of these studies have documented increased mortality in male AIDS patients (Prins *et al.* 1999; Hogg *et al.* 2001; Moore *et al.* 2002; Weidle *et al.* 2002; Garcia de la Hera *et al.* 2004; Nicastri *et al.* 2005; Calmy *et al.* 2006), but some studies failed to show statistically significant results, probably due to a small sample size, a short duration of follow-up (Ferradini *et al.* 2006) or lack of control of confounding factors such as the WHO clinical staging, nutritional condition and age. In this study from Malawi, a poor country in sub-Saharan Africa, we tried to clarify the effect of gender on mortality in patients started on ART by undertaking a more comprehensive analysis of the long-term follow-up of a cohort up to 30 months. The results confirm the relationship between male gender and mortality after controlling for confounding by other risk factors and deserve further exploration for HIV/AIDS control.

At the Rainbow clinic of MCH, more women (60.5%) than men (39.5%) receive ART. Some reasons may be explanatory of the gender difference of case numbers starting ART in Malawi. First, this reflects the gender distribution in HIV testing in the country, with more women coming for HIV testing than men (MoH Malawi 2005). As the main caretaker for children in the Malawian family, women are usually more motivated to undergo voluntary counselling and testing (VCT) and to take ART regularly. In contrast, men may be more reluctant to undergo VCT and then seek treatment, because infection with HIV still attracts stigma in Malawi. Second, the percentage is a period prevalence during 30 months. The men come for ART usually at a more advanced clinical stage and suffer from a higher mortality. So, they generally have a shorter average duration of the disease or life expectancy than women. Third, in Malawi and other developing countries in Africa, women are more likely to be underprivileged and more vulnerable to sexual exploitation. As the transmission pattern in Malawi is largely through heterosex-

ual intercourse, there may be more women-infected HIV than men. Some orphaned girls are forced to have the commercial sex which also adds to the number of female HIV-positive clients.

After stratification by WHO clinical staging, males showed increased mortality. If further stratified by different occupations, the trend of a consistent lower survival among males persisted, except for health workers (Table 1). Females had significantly higher survival rates than males both in the occupations with a higher socioeconomic status, such as businessmen and in occupations with a lower socioeconomic status, such as farmers. Teachers, students, soldiers and police officers had the same trend, though not significant probably due to their small sample sizes. Only health workers had similar outcome rates for both males and females, probably because both are equally aware of the health impact of HIV/AIDS, the benefits of ART and would have easier access to ART than the general population. Fewer patients with an occupation default than those without. Since occupation is a good indicator for socioeconomic status, different occupations may imply different lifestyles and behaviours. The general better survival of women across different occupations indicates that the gender difference is a common factor in all societal groups.

At the Rainbow clinic, fewer women were lost to follow-up than men (13.0% *vs.* 18.6%, Table 1), which may be considered as an indicator of better compliance to therapy among women. In our previous study of finding the true outcomes of 126 patients lost to follow-up (defaulter) initially treated for AIDS at Rainbow clinic, there were 18 (14%) alive, 58 (46%) dead and 50 (40%) lost to follow-up. The major reasons of lost to follow-up were incorrect address (84%) and moving out (16%) (Yu *et al.* 2007). Among these movers, four men had moved but family remained, one man and three women had moved with their whole families. Men are more likely to migrate to other places and thus default.

This study showed a statistically significant trend of males starting on ART with more advanced clinical immunosuppression than women (Table 1), a finding reported in previous studies (Iliyasu *et al.* 2006; Weiser *et al.* 2006). This would make them more vulnerable to adverse outcomes such as death while on ART. According to our anecdotal observation and qualitative study, one of the major reasons for males to seek for medical care at a later stage and poorer compliance to ART may be related to their dignity in the Malawian culture. This result corroborates our hypothesis that males generally start ART later than females and had a worse compliance with therapy, which may lead to higher mortality (Garcia de Olalla *et al.* 2002; Ferradini *et al.* 2006; Wood *et al.* 2006; Wools-Kaloustian *et al.* 2006). Attention should be paid to unemployed men and women, who both showed relatively poor compliance.

One of the limitations of this study was the lack of data on CD4 lymphocyte count or viral load during the course of ART, which would be more suitable to serve as immunological or virological markers for adherence to therapy. However, given the life-threatening nature of AIDS, we believe that the biggest motivation of these patients for compliance is for ART, and any potential bias, if ever existed, would be minimal.

Conclusions

Gender difference was a significant factor influencing survival and mortality in adult patients on ART in both univariate and multivariate analyses in this study. Males generally sought medical care at a later clinical stage. The rates of survival and lost to follow-up of males are also worse than females across different occupations. Thus, the significantly higher mortality in male patients may be associated with their poor compliance to the ART, which may be related to the culture of masculinity. To improve the survival outcome, it is crucial to increase patients' access for earlier treatment and to improve the compliance of patients, especially among male adults and people without definite employment, in ART scaling up programmes.

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