Risk factors for high early mortality in patients on antiretroviral treatment in a rural district of Malawi

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Objectives: Among adults started on antiretroviral treatment (ART) in a rural district hospital (a) to determine the cumulative proportion of deaths that occur within 3 and 6 months of starting ART, and (b) to identify risk factors that may be associated with such mortality.

Design and setting: A cross-sectional analytical study set in Thyolo district, Malawi.

Methods: Over a 2-year period (April 2003 to April 2005) mortality within the first 3 and 6 months of starting ART was determined and risk factors were examined.

Results: A total of 1507 individuals (517 men and 990 women), whose median age was 35 years were included in the study. There were a total of 190 (12.6%) deaths on ART of which 116 (61%) occurred within the first 3 months (very early mortality) and 150 (79%) during the first 6 months of initiating ART. Significant risk factors associated with such mortality included WHO stage IV disease, a baseline CD4 cell count under 50 cells/μl and increasing grades of malnutrition. A linear trend in mortality was observed with increasing grades of malnutrition (χ^2 for trend = 96.1, $P \leq 0.001$) and decreasing CD4 cell counts (χ^2 for trend = 72.4, $P \leq 0.001$). Individuals who were severely malnourished [body mass index (BMI) < 16.0 kg/m^2] had a six times higher risk of dying in the first 3 months than those with a normal nutritional status.

Conclusions: Among individuals starting ART, the BMI and clinical staging could be important screening tools for use to identify and target individuals who, despite ART, are still at a high risk of early death.

AIDS 2006, **20**:2355–2360

Keywords: malawi, HIV/AIDS, antiretroviral therapy, malnutrition, early mortality

Introduction

Malawi is a small, resource-poor country in sub-Saharan Africa with one of the highest HIV/AIDS prevalence rates in the world with 14% of those aged 15–49 infected [1]. In 2003, the National AIDS Commission estimated that there were 900 000 people living with HIV/AIDS with 86 000 adult and childhood deaths attributed to HIV/AIDS annually, and an estimated 170 000 people in need of antiretroviral treatment (ART) [1].

ART is known to dramatically improve survival of patients living with HIV/AIDS [2,3]. Since early 2004, Malawi has embarked on an ambitious plan to scale-up ART country-wide and by the end of December 2005, a total of 37 840 patients had been started on ART [4,5].

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Received: 5 May 2006; revised: 26 July 2006; accepted: 5 September 2006.

ISSN 0269-9370 © 2006 Lippincott Williams & Wilkins

Early outcomes of patients initiated on ART in Malawi and other developing countries show that despite ART, between 10 and 15% of individuals die within a median follow-up period of about 15 months [4,6,7]. A substantial proportion (about 70%) of these deaths occur very early (within the first 3 months) after starting ART. Identifying individuals who are at risk of such early deaths would be useful for targeting potential interventions to prevent such deaths. Factors associated with early mortality in patients placed on ART in resource-limited settings are at present not well characterized.

We conducted a study among adults started on ART in a rural district of Malawi in order to: (a) determine the cumulative proportion of deaths that occur within 3 and 6 months of starting ART; and (b) identify risk factors that may be associated with such deaths.

Methods

Study setting and population

This study was conducted between April 2003 and June 2005 in Thyolo district, a rural district in southern Malawi with approximately 500 000 inhabitants. All adults who were ART naive and starting treatment in the main district hospital (Thyolo hospital) HIV/AIDS clinic over a 2-year period (April 2003 to April 2005) were included in the study.

Counseling and rapid on-site HIV-testing (CT) is available in the hospital and 10 other public health facilities in the district. HIV testing is conducted using rapid whole blood test kits and follows the World Health Organization (WHO) strategy II for HIV antibody testing [8]. All HIV-positive individuals who present at the HIV/AIDS clinic undergo a complete medical assessment for HIV-related diseases and they are subsequently categorized using the WHO clinical staging system [9]. Individuals are managed for their opportunistic diseases and those in WHO stage III and IV are offered cotrimoxazole prophylaxis at the dose of 960 mg daily, provided there are no contraindications. A community network of home-based care volunteers and nurses facilitate referrals of known HIV-positive individuals and others with suspected HIV-related diseases to the hospital HIV/AIDS clinic [10].

Antiretroviral therapy eligibility, regimens and treatment outcomes

All individuals classified in WHO stage II with a CD4 count ≤ 200 cells/μl, in WHO stage III with CD4 cell count ≤ 350 cells/μl or in WHO stage IV irrespective of CD4 cell count are considered eligible for ART. In most facilities in Malawi individuals in WHO stage III are considered eligible for ART on clinical grounds alone as there is no access to CD4-lymphocyte counts. Although not a requirement in the rest of the country, in Thyolo, ART-eligible individuals are required to return with a patient guardian (or next of kin) to prepare for ART initiation, to try to ensure treatment support. Patients and guardians undergo group and individual counseling sessions and are educated on HIV infection, and the implications of ART. The process of preparation for ART initiation takes between 4 and 8 weeks. The first-line ART regimen in Malawi [9,11] is a fixed dose combination of stavudine (d4T), lamivudine (3TC) and nevirapine (NVP) (Triomune; CIPLA, Bombay, India). In cases of d4T and NVP-related side-effects, the respective alternatives are zidovudine (ZDV) and efavirenz (EFV). Second-line regimens are available in cases of first-line failure [11].

Treatment outcomes are monitored every month using the patient master card, and every quarter by cohort analysis, which is carried out retrospectively every 3 months using patient master cards and an ART patient register, as has been described previously [12]. Outcomes are standardized and include; alive and on ART, died, lost to follow-up, stopped and transferred out. ART is offered free of charge in Thyolo and all public health facilities in Malawi.

Data collection and statistical analysis

A structured record form and patient cards were used to gather information on basic demographic data, WHO clinical stage, CD4 cell counts, and opportunistic infections including tuberculosis (TB). CD4 cell counts were systematically performed in all patients, using strict quality control standards [13].

On admission, height and weight measurements were carried out and this was used to determine the body mass index [BMI; weight (kg) divided by height $(m)^2$]. A normal BMI was defined as 18.5–24.9 kg/m^2. Malnutrition was defined as a BMI < 18.5 kg/m^2. Different degrees of malnutrition were defined as follows: mild malnutrition, BMI = 17.0 to 18.4 kg/m^2; moderate malnutrition, BMI = 16.0 to 16.9 kg/m^2; and severe malnutrition, BMI < 16.0 kg/m^2. The personnel conducting weight and height measurements had been trained and were supervised during the entire course of the study.

The cumulative proportion of deaths that occurred within the first 3 months (very early mortality) and 6 months (early mortality) of initiating ART were designated as dependent variables for identifying potential risk associations. Since Thyolo has a well developed network of community volunteers and nurses that follow up HIV-positive individuals at home, reliable ascertainment of deaths is possible [10]. The measures of risk were determined by crude odds ratios (ORs) and adjusted odds ratios (adjusted ORs). The ORs were adjusted using multi-variate logistic regression, and all related *P*-values were based on the Wald test. The χ^2 test for trend was used to test for linear trends. Survival estimates between groups were determined using the

Kaplan–Maier method and compared using the Cox–Mantel (log-rank test). The level of significance was set at $P = 0.05$ or less and 95% confidence intervals (CI) were used throughout. Data was analysed using the STATA 8.2 software (Stata Corporation, College Station, Texas, USA).

Results

Characteristics of the study population

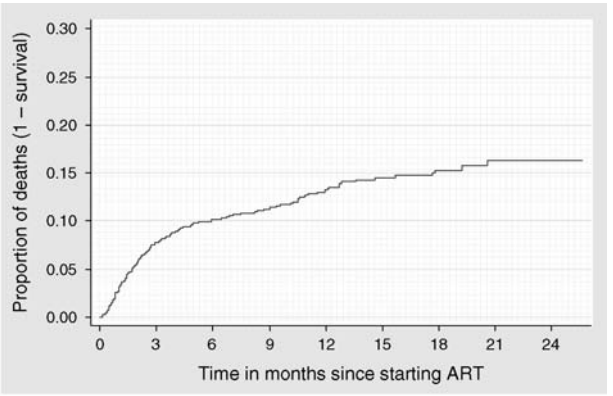
There were 1584 adults who were started on ART during the study period. Of these, BMI was not recorded in 77 patients who were excluded from the study. Among the 1507 individuals in whom data was complete, there were 517 (34%) men and 990 women, whose median age was 35 years [interquartile range (IQR), 30–42 years]. At ART initiation, 1149 (76%) adults were in WHO stage III, 338 (23%) were in WHO stage IV, and 20 (1%) were in WHO stage II but with a CD4 cell count ≤ 200 cells/μl. A total of 225 (15%) had active TB and were also receiving anti-TB treatment. There were 542 (36%) adults starting ART who were malnourished. Of these, 250 (17%) had mild malnutrition, 127 (8%) had moderate malnutrition and 165 (12%) were severely malnourished. The median CD4 cell count for all individuals at ART initiation was 123 cells/μl (IQR, 58–206 cells/μl) and the mean BMI was 19.6 kg/m^2.

Patients were followed up for a total of 1361 person-years. Specific ART regimens included d4T/3TC/NVP in 1412 (93.7%) patients, d4T/3TC/EFV in 66 (4.4%) patients, ZDV/3TC/NVP in 20 (1.3%) patients, and ZDV/3TC/EFV in five (0.3%) patients. Five (0.3%) patients were on a second line regimen of ZDV/didanosine/nelfinavir.

Treatment outcomes at the end of April 2005 included: 1181 (78%) alive and on ART, 38 (2.5%) transferred out, 46 (3%) lost to follow-up and 52 (3.5%) stopped ART. There were 190 (12.6%) deaths after starting ART. All individuals in the study were receiving cotrimoxazole prophylaxis, which had been initiated either before or at the same time as ART. Adverse side effects to ART were reported in 56 (3.7%) patients, including 48 cases of peripheral neuropathy, five cases of skin reactions, and three cases of hepatotoxicity. Two patients, one of whom had peripheral neuropathy and another who had skin reactions decided to stop ART permanently because of side effects.

Early deaths, risk factors associated with such deaths and differences in survival between groups

Out of 190 ascertained deaths, 116 (61%) occurred in the first 3 months and 150 (79%) in the first 6 months. Figure 1 shows the cumulative incidence of deaths in patients started on ART.



Time(months)	0	3	6	9	12	15	18	21	24
At risk	1507	1339	1150	845	576	423	255	150	48
Deaths	–	116	34	13	14	8	3	2	0

Fig. 1. Cumulative incidence of death since starting antiretroviral treatment (ART).

Significant risk factors associated with mortality in the first 3 months included WHO stage IV disease, a CD4 cell count under 50 cells/μl and increasing grades of malnutrition (Table 1). These were similar for mortality

Table 1. Risk factors associated with very early deaths (during first 3 months) of patients started on antiretroviral treatment (ART; *n* = 1507).

Variables	Very early deaths (%)	OR	Adjusted OR[a]	*P*
Gender				
Female	80/990 (8.1)	1	1	
Male	52/517 (10.1)	1.3	1.2 (0.8–1.8)	0.40
Age (years)				
≤35	49/681 (7.2)	1	1	
>35	67/826 (8.1)	1.2	1.0 (0.6–1.4)	0.81
WHO Stage				
Stage II	2/20 (10)	1.8	2.9 (0.6–13.4)	0.17
Stage III	68/1149 (5.9)	1	1	–
Stage IV	46/338 (13.6)	2.5	2.1 (1.4–3.3)	0.001
CD4 cell count (cells/μl)[b]				
200–350	19/406 (4.7)	1	1	
51–200	48/790 (6.1)	1.3	1.2 (0.7–2.1)	0.44
≤50	49/311 (15.8)	3.8	2.2 (1.2–4.0)	0.01
Active tuberculosis[c]				
Present	15/225 (6.7)	1	1	
Absent	101/1282 (7.9)	1.1	1.4 (0.8–2.6)	0.25
BMI on starting ART (kg/m^2)[d]				
≥18.5	37/962 (3.9)	1	1	
17.0–18.4	20/250 (8.0)	2.1	2.1 (1.2–3.8)	0.01
16.0–16.9	15/127 (11.8)	3.3	2.4 (1.7–6.3)	<0.001
≤15.9	44/168 (26.2)	7.6	6.0 (4.6–12.7)	<0.001

BMI, body mass index; OR, odds ratio; WHO, World Health Organization.
[a]Adjusted for gender, age, World Health Organisation clinical stage, CD4 count, presence or absence of active tuberculosis, and body mass index on starting antiretroviral treatment; 95% confidence intervals in parenthesis.
[b]χ^2 for trend = 72.4; $P = < 0.001$.
[c]Pulmonary (smear positive or negative) and extra-pulmonary tuberculosis.
[d]BMI; χ^2 for trend = 96.1; $P = < 0.001$.

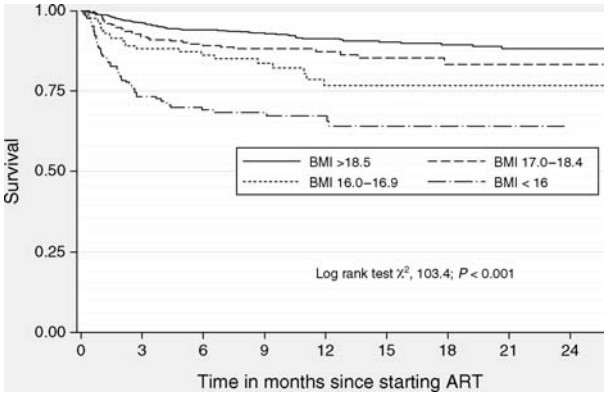


Fig. 2. Survival probability among patients with different grades of malnutrition when starting antiretroviral treatment (ART). BMI, body mass index.

within the first 6 months (Table not shown). The results for mortality within the first 6 months included: WHO stage IV, OR, 2.1 (95% CI, 1.4–3.0; $P < 0.001$); CD4 cell count ≤ 50 cells/μl, OR, 2.2 (95% CI, 1.3–3.7; $P < 0.01$); BMI = 17.0–18.4 kg/m^2, OR, 1.8 (95% CI, 1.1–3.0; $P = 0.02$); BMI = 16.0–16.9 kg/m^2, OR, 2.4 (95% CI, 1.3–4.3; $P < 0.01$); and BMI ≤ 15.9 kg/m^2, OR, 5.8 (95% CI, 3.7–9.1; $P < 0.001$).

Mortality within the first 3 months was 3.9% in patients with normal nutrition, 8.0% in those with mild malnutrition, 11.8% in those with moderate malnutrition, and 26.2% in those with severe malnutrition (χ^2 for trend = 96.1; $P \leq 0.001$, Table 1). Similarly, a linear trend in death rates was observed with decreasing baseline CD4 cell counts on starting ART (χ^2 for trend = 72.4; $P < 0.001$).

For mortality within the first 6 months, this trend was maintained both for increasing grades of malnutrition (χ^2 for trend = 84.03; $P < 0.001$) and decreasing baseline CD4 cell counts (χ^2 for trend = 23.5; $P < 0.001$). Figures 2 and 3 depict significant differences in survival probability

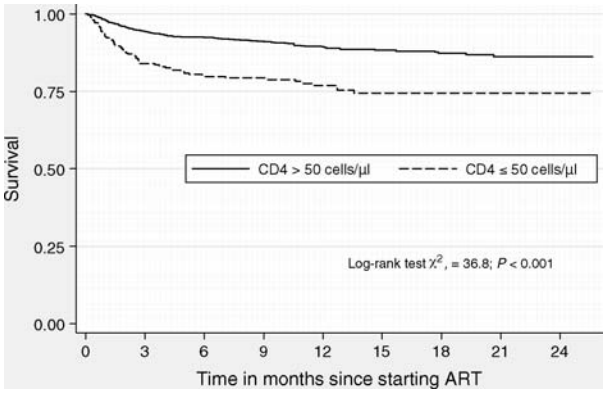


Fig. 3. Survival probability among patients with baseline CD4 cell counts ≤ 50 or > 50 cells/μl on starting antiretroviral treatment (ART).

with differing grades of BMI and baseline CD4 cell counts on starting ART.

In 105 (91%) of 116 individuals who died in the first 3 months, an active WHO defining opportunistic disease was recorded and this was attributed as the main cause of death. Attributed causes of death included: 26 (22%) oral recurrent Candida, 15 (13%) oesophageal candidiasis, 13 (11%) Kaposi's sarcoma, 12 (10%) severe bacterial pneumonia, 10 (9%) active tuberculosis, 10 (9%) chronic diarrhea > 1 month, seven (6%) cryptococcal meningitis, six (5%) chronic wasting, four (3%) chronic fever, and two (2%) *Pneumocystis jeroveci* pneumonia. No specific cause of death was recorded in 11 (10%) individuals. Seventy-nine (68%) of 116 patients who died within the first 3 months of starting ART were malnourished (BMI < 16–18.4 kg/m^2).

Discussion

This study shows in patients started on ART in a rural setting, the great majority of deaths (six out of every ten) occur within 3 months of starting treatment. Significant risk factors associated with such 'very early deaths' included increasing grades of malnutrition, WHO stage IV disease and a CD4 cell count under 50 cells/μl. Although, it may be argued that the overall death rate of 12.6% is acceptable, we feel that addressing early mortality is important in order to improve overall program outcomes and particularly the credibility of the ART program in the eyes of patients, health workers and the community at large.

The strengths of this study are that a large number of patients were studied, deaths were reliably ascertained, the loss to follow-up was low and as the data comes from a program setting, the findings probably reflect operational reality on the ground. One of the limitations of this study was that the exact cause(s) of death could not be determined, as there were no post-mortem facilities nor access to sophisticated laboratory diagnostic facilities, and therefore the attributed cause(s) of death in this study might be erroneous. An additional limitation is the lack of viral loads to assess response to therapy.

There are several possible reasons for very early mortality in patients started on ART. For example; late diagnosis of HIV, delays in the ART initiation process at the health facility, delayed presentation of patients and thus advanced HIV/AIDS disease, and life-threatening HIV-related complications such as severe anemia, or bacteremia [14,15]. Drug-induced adverse reactions or immune reconstitution disease (IRIS) are other possible causes of death. However, the incidence of adverse reactions to first line ART in this setting is low [16] and patients are well educated to immediately stop ART in case of such an

event. Unfortunately, due to the absence of a universal case definition for IRIS that is applicable to our setting, we were unable to assess the relative contribution of IRIS particularly with TB [17].

We have shown that increasing grades of malnutrition are strongly associated with very early mortality. However, we do not know if nutritional impairment on its own predisposes to early death, or whether it is a marker of extensive HIV disease or other covert opportunistic infections. For example, 40% of patients dying with the HIV wasting syndrome in Cote d'Ivoire were found at autopsy to have disseminated TB [18].

Preventing early deaths in patients started on ART will be a major challenge in resource-poor settings such as Malawi that are rapidly trying to scale-up ART. There are several possible 'ways forward'.

Early diagnosis of HIV-status and early access to preventive medication such as cotrimoxazole prophylaxis could have a beneficial effect on the incidence of certain opportunistic infections, the evolution of CD4 cell counts and viral load [19] and HIV related mortality [20]. Patients already on cotrimoxazole prophylaxis (when starting ART) might be in a better physical state and thus at a lower risk of very early mortality.

Minimizing delays in ART initiation and the burden of scheduled visits to the hospital for ART initiation is needed, and this could be achieved by basing ART eligibility on simple clinical criteria (WHO staging) without CD4 cell counting, not insisting on always having a guardian present, and decentralizing group counseling sessions to the community under the aegis of community nurses and ART support groups. This last strategy would serve to enhance community empowerment in ART delivery. Finally, individuals in WHO stage IV disease, should be 'fast-tracked' for ART initiation.

At present, the initiation of ART is 'centralized' to the main district hospital facility. In a rural setting, where inhabitants are mainly subsistence farmers earning less than US$ 4 per week [21], this is likely to be an 'access barrier' contributing to delayed presentation for ART [22]. 'Decentralization' of ART and follow-up to health centres closer to home communities would be an important step to addressing this bottleneck, although limited infrastructure and shortage of human resources make this a considerable challenge [23].

Almost all patients who died within the first 3 months of starting ART had WHO stage IV diseases, affirming their advanced stage of immune suppression. Although Thyolo hospital is fortunate to have access to exceptional resources in terms of clinical staff and drug supplies through the international non-governmental organization (Medecins Sans Frontieres), these patients still died. There might be a number of possible ways forward in addressing this specific problem. First, there is a need to prevent patients presenting 'too late', possibly by increasing community awareness, improving HIV/AIDS health-seeking behavior and addressing access issues. Second, patients who are malnourished should be offered intensive nutritional rehabilitation and nutritional supplements. Third, TB in the late stages of immunodeficiency and bacteremia in patients who are malnourished may present in an atypical or 'covert' manner and the diagnosis may be missed [18]. Until better diagnostic techniques become available, a more systematic search for TB in patients with low BMI including detailed questioning about cough, sputum examination for anyone who coughs (even if less than 3 weeks), a chest X-ray and abdominal ultrasound for glands might be cost-effective approaches, meriting operational research. Diagnosis of bacteremia in most African hospitals is difficult because of the lack of blood culture facilities. Patients at risk of very early mortality might therefore require an empirical course of antibiotics or antibiotic prophylaxis with drugs such as ciprofloxacin to treat, or prevent commonly occurring but potentially lethal infections due to *Streptococcus pneumoniae* and *non-typhoidal Salmonella* [14,15].

The results of this study might help in finding immediate solutions to this problem. Assessing the BMI and examining patients for active WHO defining diseases constitute part of routine clinical procedures in the Thyolo clinic, as in other HIV/AIDS clinics in Malawi and thus do not add any additional workload for clinic staff. This is an important operational consideration for settings which are often overloaded and understaffed [23]. HIV-positive individuals with a BMI under 18.5 have a 'two to six times' higher risk of dying within the first 3 months of starting ART than those with a normal nutritional status. Individuals in WHO stage IV have about twice the risk of dying than those in WHO stage III. Although it is currently unclear whether interventions (nutritional rehabilitation and antibiotic treatment) might reduce early mortality in these sub-groups, they could nevertheless be explored while awaiting the results of randomized controlled trials. In a rural district of Malawi, the BMI and clinical staging could be important screening tools to identify individuals who, despite ART, are still at a high risk of very early death.

Acknowledgements

We are grateful to the Thyolo district hospital management and the National AIDS Commission of Malawi and the Ministry of Health of Malawi for the collaboration and encouragement in trying to implement HIV/AIDS related activities, including ART in Thyolo. We wish to thank Dalitso Misinde for her help in data collection and

entry and Drs Vincent Janssens and Pierre Humblet for their useful comments.

Sponsorship: The Thyolo district HIV/AIDS program is supported by Medecins sans Frontieres. We are very grateful to the Department for International Development (DFID), the Norwegian Agency for Technical Cooperation (NORAD), The Global Fund, USAID, CIFF and WHO for supporting HIV/AIDS control and ART scale-up country-wide in Malawi. A.D.H. is supported by Family Health International, USA.

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