Tropical Medicine and International Health doi:10.1111/j.1365-3156.2009.02291.x

VOLUME 14 NO 7 PP 713–721 JULY 2009

Very early mortality in patients starting antiretroviral treatment at primary health centres in rural Malawi

Rony Zachariah[1], Katie Harries[1], Massaquoi Moses[2], Marcel Manzi[1], Arnould Line[3], Beatrice Mwagomba[4] and Anthony D. Harries[5,6]

1 *Medecins sans Frontieres, Medical department (Operational Research), Brussels, Belgium*
2 *Medecins sans Frontieres, Thyolo District, Malawi*
3 *Medecins sans Frontieres, Medical department (Aids advisor), Brussels, Belgium*
4 *Ministry of Health and Population, Thyolo, Malawi*
5 *International Union against Tuberculosis and Lung Disease, Paris, France*
6 *London School of Hygiene and Tropical Medicine, London, UK*

Summary

OBJECTVES To report on the cumulative proportion of deaths occurring within 3 months of starting antiretroviral treatment (ART) and to identify factors associated with such deaths, among adults at primary health centres in a rural district of Malawi.

METHODS Retrospective cohort study: from June 2006 to April 2008, deaths occurring over a 3-month period were determined and risk factors examined.

RESULTS A total of 2316 adults (706 men and 1610 women; median age 35 years) were included in the analysis and followed up for a total of 1588 person-years (PY); 277 (12%) people died, of whom 206 (74%) people died within 3 months of initiating ART (cumulative incidence: 13.0; 95% confidence interval: 11.3–14.8 per 100 PY of follow-up). Significant risk factors associated with early deaths included male sex, WHO stage 4 disease, oesophageal or persistent oral candidiasis and unexplained presumed or measured weight loss >10%. One in every 3 patients who either died or was lost to follow up had unexplained weight loss >10%, and survival in this group was significantly different from patients without this condition.

CONCLUSIONS Seven of 10 patients who die after initiating ART at primary health centres die early. Specific groups of patients are at higher risk of such mortality and should receive priority attention, care and support.

keywords Malawi, HIV/AIDS, antiretroviral treatment, early mortality, health centres

Introduction

Antiretroviral treatment (ART) dramatically improves the survival of patients living with HIV/AIDS (Egger *et al.* 2002; Mocroft *et al.* 1998). In Malawi, a resource-limited country in Southern Africa, ambitious plans to scale-up ART country-wide began in early 2004. By the end of December 2007, 141 449 patients had been placed on treatment from 163 public health facilities (NAC 2007; Lowrance *et al.* 2008).

Reports from second and third line hospital facilities in Malawi and other developing countries show that despite providing ART, between 8% and 26% of patients die within the first year of initiating ART (Coetzee *et al.* 2004; Braitstein *et al.* 2006; Zachariah *et al.* 2006a; Lawn *et al.* 2008) with most deaths occurring during the first few months.

In order to improve geographical equity and ART access for the rural poor, the current focus in Malawi (as in many other sub-Saharan African countries) is to decentralise ART delivery to the level of peripheral health centres (the primary care level) (Zachariah *et al.* 2006b; Deribe *et al.* 2008). Very early mortality, namely deaths occurring within 3 months of starting ART, at the health centre level in such resource-limited settings with potential limitations in human resource capacity and clinical acumen (WHO 2006a; Philips *et al.* 2008) has not yet been described.

We conducted a retrospective analysis among adults initiated on ART at primary health centres in a rural district of Malawi, in order to report on the cumulative proportion of deaths occurring within 3 months of starting ART, and to identify risk factors associated with such deaths.

Methods

Study setting and population

This study was conducted in Thyolo, the largest rural district in Malawi with about 600 000 inhabitants. The inhabitants of Thyolo are principally subsistence farmers, earning less than 4 USD per week. Eighty percent of all income comes through daily labour in tea and coffee plantations.

The district has one main public hospital and nine primary health centres, seven of which progressively started to deliver ART services from June 2006. All ART naïve adults starting ART at health centres between 1st June 2006 and 29th April 2008 were included in this analysis.

All staff involved with ART delivery undertake a standardised national training course, and ART delivery sites require formal accreditation from the Ministry of Health. At health centre level, ART delivery is managed by a medical assistant, one nurse, a clerk and a receptionist. Initial on-the-job training was conducted, in which a supervising doctor or a senior clinician was actively involved with ART initiations at each health centre. A mobile district team with an experienced clinician (a clinical officer) provides ongoing monthly support and monitoring of health centres. A community network of home-based care volunteers and community nurses supported by Médecins Sans Frontiérés facilitate care and referrals (Zachariah *et al.* 2007).

ART eligibility and treatment outcomes

According to the National guidelines, all HIV-positive patients presenting in WHO Clinical stage 3 or 4, or with a CD4 count of <250 cells/mm^3 (irrespective of WHO staging) are eligible for ART (MOHP/NAC 2006). CD4 counts were not routinely available at health centres; however, when a patient presented with a CD4 count performed either at the hospital or elsewhere, this was taken into consideration.

At the time of presentation, all patients undergo a complete medical examination; they are assessed for WHO Clinical Stages, and treated for opportunistic disease. Patients assessed as being eligible for ART undergo group and individual counselling sessions and are educated on HIV infection and the implications of therapy. Once started on treatment, patients are reviewed back at the health centre after 2 weeks and from then at monthly intervals.

The first-line ART regimen in Malawi (MOHP/NAC 2006) is a fixed dose combination of Stavudine (d4T), Lamivudine (3TC) and Nevirapine (NVP) (Triomune®). In case of d4T- and NVP-related side effects, the respective alternatives are Zidovudine (AZT) and Efavirenz (EFV). ART is offered free of charge and monitored using standardised ART treatment master cards and an ART register (Harries *et al.* 2004; Libamba *et al.* 2005). Standardised treatment outcomes are monitored every month in the patient master cards, and updated each month in the ART register. Treatment outcomes are defined as: alive and on ART, a patient who is alive and on ART at the facility where he/she is registered; died, patient who has died for any reason while on ART; loss to follow-up (defaulted), patient placed on ART and not seen at the ART facility for 3 months; stopped, patient who is known to have stopped treatment for any reason during treatment; transferred out, patient who is transferred-out permanently to another treatment facility. A district supervisory team systematically checks the validity of outcome data monthly and reports to a national supervisory team that cross-checks these data independently every quarter.

During the latter part of the study period (from mid 2007 onwards), all patients with moderate malnutrition (body mass index, BMI: 16–17) received a monthly nutritional ration (Likuni Phala–corn-soya blend, CSB) of approximately 1350 kcal/day; those with severe malnutrition (BMI <16) received a ration of 2684 kcal/day (CSB and plumpy nut). HIV positive individuals in Thyolo did not receive isoniazid preventive therapy as this is as yet not part of national guidelines in Malawi.

Statistical analysis

Treatment outcomes for all patients starting ART from 1st June 2006 were censored on 30th April 2008. The cumulative proportion of deaths that occurred at 3 months (early mortality) was designated as the dependent variable for identifying potential risk associations. Since Thyolo has a well-developed network of community volunteers and nurses who follow up HIV-positive individuals at home, reliable ascertainment of deaths was possible (Zachariah *et al.* 2007). Baseline case registration details and the main WHO defining opportunistic disease that was recorded at the time of starting ART were used to compare those who died and those remaining alive and on ART within 3 months. The 10% cut-off for unexplained severe weight loss (presumed or measured) was in line with WHO criteria for weight loss in clinical stage 3 and clinical stage 4 disease (WHO 2006b). The term 'unexplained' means that the reasons for the weight loss have no explanation within the routine healthcare system, and that the aetiology of the weight loss is unclear. As baseline weight was unavailable for all patients, diagnosis of this condition was based purely on self reporting by the patient who on specific questioning

by the clinician stated that he or she had lost >10% of his body weight. This is therefore a subjective (presumed) interpretation, and the case definition is purely clinical. The measures of risk were determined by crude odds ratios (ORs) and adjusted odds ratios (adjusted ORs). The ORs were adjusted using multivariate logistic regression and all related *P*-values are based on the Walds test. Variables with scarce data were excluded from the initial multivariate model and a stepwise backward elimination method. As we were unsure of the reliability of baseline weight that was recorded during the entire study period, we preferred not to include this variable in the regression model.

Differences between groups were compared using the χ^2 test for categorical variables and the Wilcoxon rank-sum test. The χ^2 test for trend was used to test for linear trends. Survival estimates 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 (CIs) were used throughout. Data analysis was performed using the STATA 8.2 software (Stata corporation, Texas 77845, USA).

Ethical approval

General measures are provided in the Thyolo district ART facilities to ensure patient confidentiality, consent for HIV testing, and counselling and support for those who receive a positive HIV test result. The data in this study did not include patient identifiers. The Malawi National Health Science Research Committee provides general oversight and approval for the collection and use of routine programmatic data for monitoring and evaluation, and does not require a formal submission for ethical approval for the type of study conducted in this paper.

Results

Characteristics of the study population and treatment outcomes

Of a total of 4088 individuals receiving ART at the health centre level, 1772 patients were excluded from the analysis; 1688 had initiated ART at the hospital level and were transferred into the health centre and 84 were children aged less than 15 years. The remaining 2316 adults (aged 15 years or more) who had initiated ART at health centres were included in the study. These comprised 706 (30%) men and 1610 women (median age: 35 years, interquartile range (IQR): 29–42 years). The majority of patients were subsistence farmers (76%).

At ART initiation, 18 were in WHO stage 2 with a CD4 count of under 250 cells/mm^3, 2003 (87%) were in WHO stage 3 and 295 (13%) were in WHO stage 4. All patients were placed on a first-line ART regimen; 2312 (99.8%) were started on a regimen of D4T/3TC/NVP while four patients received an alternative first-line regimen (AZT/3TC/NVP).

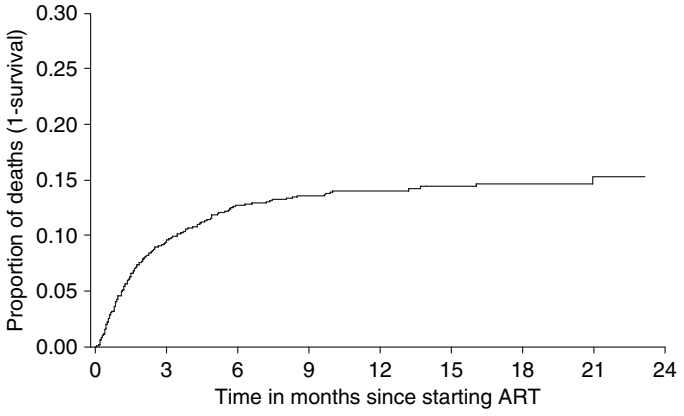
Treatment outcomes censured on 30th April 2008 were: 1868 (81%) alive and on ART, 277 (12%) deaths, 109 (5%) lost to follow up, 57 (2%) transferred out and 5 stopped ART (0.2%). Data on exact cause(s) of death were not available.

Incidence, risk factors for early deaths and differences in survival between groups

Patients were followed up for a total period of 1588 person-years (PY) (mean: 8.2 months, IQR: 2.6–12.2 months) during which time there were 277 ascertained deaths (cumulative incidence per 100 PY of follow up: 17.5, 95% CI: 15.5–19.6 PY). Of the 277 deaths, 206 (74%) occurred during the first 3 months of initiating ART (cumulative incidence: 13.0, 95% CI: 11.3–14.8 PY). Figure 1 shows the cumulative incidence of death while on ART at health centres. Table 1 compares basic case registration details and the main baseline opportunistic disease diagnosed pre-ART among those who died within 3 months of initiating ART when compared with those who remained alive and on ART during the same period. Significantly higher proportions of males, patients in WHO stage 4, patients with oesophageal candidiasis and patients with unexplained presumed or measured weight loss of >10% died (Table 1). Over half of all early deaths were associated with unexplained presumed or measured weight loss >10% and persistent oral candida (Table 1). In the multivariate model, significant risk factors associated with early deaths included male sex, WHO stage 4 disease, oesophageal or persistent oral candidiasis and unexplained presumed or measured weight loss >10% (Table 2). A linear trend for death was observed in relation to WHO stage (χ^2 for trend = 12.35; $P < 0.001$).

Figure 2 shows the significant difference in Kaplan–Meier survival probability in patients with and without unexplained weight loss >10%. Survival probability was also significantly different with regard to WHO stage (log-rank test $\chi^2 = 17.9$; $P < 0.001$) and sex (log-rank test $\chi^2 = 19.4$: $P < 0.001$) (Figures not shown).

During the first 3 months, 10 (0.4%) patients were declared lost to follow-up and this may include concealed deaths. Patients lost to follow-up were five males and five females, eight patients in WHO stage 3 and two in WHO stage 4. Their baseline opportunistic diseases comprised three with unexplained weight loss, one with oral candida, four with severe bacterial infections and two with active



Time in months	0	3	6	9	12	15	18	21	24
Number at risk	2316	1685	1310	956	598	375	245	132	13
Deaths	–	206	52	11	5	2	1	0	0

Figure 1 Cumulative incidence of death since starting antiretroviral treatment at health centre, Thyolo, Malawi.

tuberculosis (TB). The numbers are too small to allow robust statistical comparisons with those who died or remained alive. Since these numbers are few, they are also unlikely to significantly change the reported incidence rate of early mortality.

Discussion

This is one of the first studies reporting on early deaths among a relatively large cohort of patients initiated on ART at health centre level in a sub-Saharan African country where >7 of every 10 declared deaths occurred within the first 3 months of starting treatment. Significant risk factors associated with such very early mortality included male sex, WHO stage 4 disease, presumed or measured weight loss >10% and oesophageal or persistent oral candida. With many sub-Saharan African countries like Malawi embarking on decentralisation of ART to peripheral health facilities (WHO 2006c) the findings of this analysis raise a number of issues.

First, there was a higher proportion of deaths in males than females, which may be due to men seeking medical care at a more advanced stage of immunodeficiency and being less compliant with therapy (ART-LINC 2006). This issue needs to be more actively addressed through targeted information and education sessions as well as targeted counselling.

Second, although the overall death rate of 12% reported in this study is comparable with other hospital-based data from sub-Saharan Africa (Lawn *et al.* 2005) and Thyolo (Zachariah *et al.* 2006a) and might be deemed acceptable, reducing overall mortality and particularly early mortality is still vital to improve overall programme outcomes and to raise the credibility of the ART programme from the perspective of the beneficiaries, health workers and community at large. There are several possible reasons for early mortality in patients starting ART, including delayed presentation of patients and thus advanced HIV/AIDS disease, delayed diagnosis, undiagnosed opportunistic infections and life-threatening HIV-related complications such as anaemia, bacteraemia and TB preceding or during ART, and delays in ART initiation at the health facility. Unrecognised drug-related side effects, drug interactions and immune reconstitution inflammatory syndrome (IRIS) may also contribute to this problem. High early mortality rates among patients on ART mirror mortality rates in the period preceding ART and are likely to reflect patient status at programme enrolment and the quality of preceding healthcare (Lucas *et al.* 1994; Lawn *et al.* 2006, 2008). Possible approaches to address these challenges have been discussed before (Lawn *et al.* 2006, 2008; Zachariah *et al.* 2006a).

Third, patients with unexplained presumed or measured weight loss of over 10%, and those with recurrent oral or oesophageal candidiasis constituted 6 of 10 deaths at health centres, and these patients had a significantly higher risk of dying in the first 3 months of starting ART. Unexplained weight loss may be a proxy for malnutrition, which by further compromising host immunity and predisposing to life-threatening nutritional deficiencies and

Table 1 Characteristics of patients who died and remained alive in the first three months of starting antiretroviral treatment (ART), at health centres, Thyolo, Malawi

Variable	Died n (%)	Alive n (%)	*P*-value*
Total	206 (9.0)	2083 (91.0)	–
Sex			
Females	122 (59)	1472 (71)	
Males	84 (41)	611 (29)	0.001
Age (years)			
≤35 years	85 (41)	918 (44)	0.45
>35 years	121 (59)	1166 (56)	
Age, years, median (IQR)	34 (28–41)	35 (29–42)	0.43
WHO clinical stage			
Stage I or II with CD4 <250 cells/μl	0	18 (1)	0.18
Stage III	164 (80)	1816 (87)	0.002
Stage IV	42 (20)	249 (12)	0.001
Main opportunistic infection at ART start			
Oesophageal candidiasis	9 (4)	44 (2)	0.04
Kaposi sarcoma	12 (6)	69 (3)	0.06
Cryptococcal meningitis	2 (1)	5 (0.2)	0.07
Persistent oral candida	43 (21)	380 (18)	0.35
Unexplained chronic diarrhoea >1 month	22 (11)	238 (11)	0.75
Unexplained persistent fever >1 month	0 (0)	11 (0.5)	0.5
Unexplained presumed weight loss >10%	72 (35)	543 (26)	0.001
Pneumocystics jeroveci pneumonia	1 (0.5)	3 (0.1)	0.3
Recurrent severe bacterial pneumonia	15 (7)	250 (12)	0.03
Active tuberculosis	15 (7)	181 (9)	0.5
Severe bacterial infection†	12 (6)	187 (9)	0.13
Others: Anaemia, skin conditions, herpes simplex, toxoplasmosis	2 (1)	56 (3)	0.12
Low CD4 count‡/no active opportunistic infection on ART start	1 (0.5)	116 (6)	0.001
Duration on ART (months) [Median (IQR)]	1 (0.5–1.6)	253 (8.3–12.6)	–

WHO, World Health Organization; ART, antiretroviral treatment; TB, tuberculosis; IQR, interquartile range.
*χ^2 test for categorical variables and Wilcoxon rank-sum rank-sum test for continuous variables.
†Pneumonia, empyema, pyomyosities, meningitis, suspected bacteremia/septicaemia, bone or joint infection.
‡A CD4 cell count of <250 cells/mm^3 irrespective of WHO clinical stage.

superadded infection, may add to the risk of death. Intensive nutritional rehabilitation and use of micronutrients to improve cell mediated and humoral immunity might be beneficial. Health centre have begun to provide a Ready to Use Therapeutic Food (RUTF) such as the 'plumpy nut' (Wikipedia 2008); which is easy to store, requires no preparation or special supervision, and may be an easily deployable strategy. There may also be a relation between weight loss and undiagnosed TB which could present in an atypical or occult manner. In a study from northern Malawi, 77% of patients who developed TB after starting ART had unexplained weight loss >10% before starting ART, an observation that concurs with this hypothesis (Yu *et al.* 2008). Patients with weight loss should therefore undergo intensified screening for TB which includes at the very least systematic questioning about cough for more than 2 weeks and a sputum examination for anyone with cough for over 2 weeks. Although sputum cultures, chest X-rays (WHO 2006c) and an abdominal ultrasound for glands are desirable, the necessary equipment is not available at peripheral health centre level. Facilitating patient referral to the district hospital such as organising transport on a scheduled basis or paying transport fees may improve the uptake of such investigations. There is evidence from sub-Saharan Africa that often, the only indication of TB might be a positive blood culture. Operational research to determine the prevalence of undiagnosed TB in such patients would thus

Table 2 Risk factors associated with very early deaths (during first three months) in health centres, Thyolo, Malawi (n-2145)

Variables	Very early deaths (%)	OR*	Adjusted OR†	*P*
Gender				
Female	122/1594 (7.7)	1		
Male	84/695 (12.1)	1.6 (1.2–2.2)	1.6 (1.2–2.1)	0.003
Age (years)				
≤35 years	85/1002 (8.5)	1	–	
>35 years	122/1287 (9.4)	1.1 (0.8–1.5)		
WHO Stage‡				
Stage II	0/18 (0)	–		
Stage III	164/1980 (8.3)	1		
Stage IV	42/291 (14.4)	1.9 (1.3–2.7)	1.7 (1.2–2.4)	0.006
Unexplained weight loss				
>10%	134/1674 (8.0)	1		
Absent	72/615 (11.7)	1.5 (1.1–2.1)	1.7 (1.2–2.4)	0.001
Present				
Oesophageal/persistent oral candida				
Absent	154/1813 (8.5)	1		
Present	52/476 (10.9)	1.3 (0.9–1.8)	1.7 (1.1–2.4)	0.007
Kaposi sarcoma				
Absent	194/2208 (8.8)	1		
Present	12/81 (14.8)	1.8 (1.0–3.4)		
Unexplained chronic diarrhoea				
Absent	184/2029 (9.1)	1		
Present	22/260 (8.5)	1.1 (0.7–1.7)		
Active tuberculosis				
Absent	191/2093 (9.1)	1		
Present	15/196 (7.7)	0.8 (0.5–1.4)		
Severe bacterial infections§				
Absent	194/2090 (9.3)	1	–	
Present	12/199 (6.0)	0.6 (0.3–1.1)		
Recurrent bacterial pneumonia				
Absent	191/2024 (9.4)	1		
Present	15/265 (5.7)	0.6 (0.3–1.0)		

WHO, World Health Organization.
*OR, odds ratio; 95% confidence intervals in parenthesis.
†Adjusted using multivariate logistic regression. Adjusted odds ratios of variables that showed statistical significance are presented; 95% confidence intervals in parenthesis.
‡χ^2 for trend = 12.35 $P \leq 0.001$.
§Pneumonia, empyema, pyomyosities, meningitis, suspected bacteremia/septicaemia, bone or joint infection.

be very useful (McDonald *et al.* 1999; Gordon *et al.* 2001; Lewis *et al.* 2002; Peters *et al.* 2004). This issue also highlights the need for access to simpler and more efficient point of care TB diagnostic tools for resource-limited settings. Patients with unexplained weight loss >10% may also have occult lethal bacteraemias, e.g. from *Streptococcus pneumoniae* and non-typhoidal *Salmonella* (Gilks *et al.* 1990; McCarthy 1992) and blood culture studies would also be useful to determine the relative contribution of these pathogens.

This is the first report of an association between recurrent oral or oesophageal candidiasis and death at health centres. We believe that a considerable proportion of individuals diagnosed with oral recurrent candida might also have oesophageal candida. Under-diagnosis of the oesophageal candida is likely at primary health centres with busy health workers not systematically asking about symptoms originating in the oesophagus, such as from epigastric pain, heart burn and particularly difficulty in swallowing. Definitive diagnosis of oesophageal candidiasis requires endoscopy, which is inaccessible for patients at the health centre level; patients with oral candidiasis who remain untreated before starting on ART or who face delays in being initiated on ART undergo immune deterioration with subsequent colonisation and spread of candida into the oesophagus. For these reasons

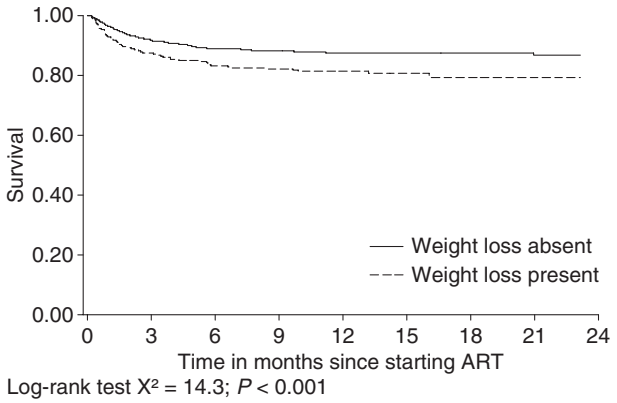


Figure 2 Survival probability among patients with and without unexplained weight loss >10%, on starting antiretroviral treatment. Log-rank test $\chi^2 = 14.3$; $P < 0.001$.

(Dodd 1991; Wilcox *et al.* 1995), patients with a primary diagnosis of recurrent oral candida may have had a much more severe condition than assessed clinically and are thus at high risk of death (Connolly 1989; Morgan 2000).

We thus considered it rational from an operational perspective to combine persistent oral candidiasis and oesophageal candidiasis as a single variable in the regression model. The real reasons underlying death in such patients are unclear but there are a number of possibilities. First, difficulty or the inability to swallow has a profound effect on quality of life, often resulting in reduced nutritional intake, malnutrition and weight loss. This is especially so if treatment-seeking is delayed, as is often the case with poor people. Thus, even if oral and oesophageal conditions alone may not be life threatening initially, these sequelae would tend to weaken patients and make it more difficult to survive other AIDS-related complications. Second, patients may be treated for oral recurrent candidiasis with nystatin or gentian violet paint, treatments with very low cure rates for oesophageal candidiasis (Ravera *et al.* 1999). Third, herpes simplex virus (HSV), cytomegalovirus (CMV) and idiopathic HIV-related oesophagitis may co-exist with oesophageal candidiasis and be missed or left untreated (Ayisi *et al.* 1997). Azole resistance can also be a problem in our setting, where repeated courses of azole treatment are used for relapsing fungal infections, especially oral recurrent candida (Wilcox *et al.* 1996; Dromer *et al.* 1997). There might also have been drug stock interruptions at the health centre. Finally, appropriate palliative and supportive care to relieve symptoms and related complications (e.g. inability to swallow) is virtually non-existent at health centres. But without this, patients may be unable to take their cotrimoxazole prophylaxis, prophylaxis for other opportunistic infections and ART, leading to a worsening of prognosis. All these issues merit further evaluation.

In the meantime, systematically assessing all patients for symptoms of oesophageal candida is justified with the use of sequential empiric therapy as an initial approach if symptoms are present. This would first involve a 14-day trial of fluconazole (USDHH 2003) and if response is unsatisfactory, a subsequent empiric course of acyclovir for HSV which is readily available and well-tolerated. The next in sequence would be an empiric course of IV ganciclovir for suspected CMV. However, this treatment is expensive, has significant side effects, is not readily available in many settings and many clinical teams have little experience administering it. Finally, if aphthous ulcers are present in the mouth, a trial course of corticosteroids for idiopathic oesophagitis would be appropriate (accompanied with an antifungal as steroids can worsen fungal infections).

Patients must also be given priority for initiating ART in order to hasten immune restitution, and those who cannot swallow must be offered supportive care and particularly pain relief (Chen *et al.* 2008). Alternative formulations for buccal, rectal and sublingual administration would make drug administration easier and enhance compliance in patients who cannot swallow.

The strengths of this study were that a large number of patients were included, outcomes were reliably ascertained using master cards and registers that are robust and regularly checked by supervision teams and as the data come from a program setting the findings probably reflect the operational reality on the ground. Deaths were also reliably ascertained and only 10 patients were declared lost to follow-up during the first 3 months. Although some of these patients may have died, with reports on this outcome not getting back to clinic staff, this is unlikely to have affected the overall results.

The limitations of the study are that (i) CD4 counts were not performed at health centres and we were thus unable to compare the degree of immunodeficiency between the groups; (ii) height was not systematically recorded and thus we are unable to report on BMI, (iii) weight loss was presumed weight loss (by the patient) and thus subjective; (iv) laboratory tests, in particular liver enzymes (ALAT), were not available and thus we do not know the contribution of conditions such as fatal liver toxicities; (v) as oesophageal candidiasis is associated with lower CD4 cell counts, and low CD4 counts have been consistently associated with ART-related mortality, the omission of baseline CD4 counts in the model could have resulted in residual confounding.

This study shows that specific groups of patients initiated on ART at health centres are at higher risk of early

mortality and should receive priority attention for care and support. The findings from this study highlight the urgent need to address the issue of high early case fatality in patients at primary level through relevant interventions and operational research while waiting for the results of randomised controlled trials. Some of these are being planned while others are already under way, and the results may better define the precise reasons for early mortality and better inform on disease-specific prevention and treatment interventions to reduce such mortality.

Acknowledgements

The authors are grateful to the Thyolo district hospital management and the Ministry of Health of Malawi for the collaboration and encouragement in trying to implement HIV/AIDS-related activities. The authors are particularly grateful to the Thyolo data base team for their meticulous work with data collection and support. The authors thank Ariane Bauerfiend for her useful comments on this paper. The Thyolo district HIV/AIDS programme is supported by Children Investment Fund Foundation (CIFF), EuropeAID, DGCD, ELMA, Danish Telethon and Medecins sans Frontieres. The authors extend their thanks to the Ministry of Health of Malawi for the excellent collaboration and to the Department for International Development (DFID), KNCV Tuberculosis Foundation, Family Health International, the Norwegian Agency for Technical Cooperation (NORAD), the Global Fund, USAID and WHO for their continuing support for HIV/AIDS activities in Malawi.

References

Braitstein P, Birnkhogf MW, Dabis F *et al.* ART-LINC (2006) The antiretroviral therapy in lower income countries. Collaboration and ART cohort collaboration (ART-CC) groups. Mortality of HIV-1 infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. *Lancet* **367**, 817–824.

Ayisi NK, Wiredu EK, Sata T *et al.* (1997) T-Lymphoctopenia, opportunistic infections and pathological findings in Ghanaian AIDS patients and their sexual partners. *East African Medical Journal* **74**, 784–791.

Braitstein P, Brinkhof MW, Dabis F *et al.* (2006) Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. *Lancet* **367**, 817–824.

Chen SC, Yu JK, Harries AD *et al.* (2008) Increased mortality of male adults with AIDS related to poor compliance to antiretroviral therapy in Malawi. *Tropical Medicine and International Health* **19**, 513–519.

Coetzee D, Hildebrand K, Boulle A *et al.* (2004) Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. *AIDS* **18**, 887–895.

Connolly GM (1989) Oesophageal symptoms, their causes, treatment and prognosis in patients with the acquired immunodeficiency syndrome. *Gut* **30**, 1033–1039.

Deribe K, Hailekiros F, Biadgilign S, Amberbir A & Beyene BK (2008) Defaulters from antiretroviral treatment in Jimma University Specialized Hospital, Southwest Ethiopia. *Tropical Medicine and International Health* **13**, 328–333.

Dodd CI (1991) Oral candidiasis in HIV infection: pseudomembranous and erythematous candidiasis show similar rates of progression to AIDS. *AIDS* **5**, 1339–1343.

Dromer F, Improvisi L, Dupont B *et al.* (1997) Oral transmission of candida albicans between partners in HIV infected couples could contribute to dissemination of fluconazole-resistant isolates. *AIDS* **11**, 1095–1101.

Egger M, May M & Chene G (2002) Prognosis of HIV-1 infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet* **360**, 119–129.

Gilks CF, Brindle RJ, Otieno LS *et al.* (1990) Life threatening bacteremia in HIV-1 seropositive adults admitted to hospital in Nairobi, Kenya. *Lancet* **336**, 545–549.

Gordon MA, Walsh AL, Chaponda M *et al.* (2001) Bacteremia and mortality among adult medical admissions in Malawi. Predominance of non-typhi salmonellae and Streptococcus pneumoniae. *Journal of Infection* **42**, 44–49.

Harries AD, Gomani P, Teck R *et al.* (2004) Monitoring the response to antiretroviral treatment in resource-poor settings: the Malawi model. *Transactions of the Royal Society Tropical Medicine and Hygiene* **98**, 695–701.

Lawn SD, Myer L, Orrel C, Bekker LG & Wood R (2005) Early mortality among adults accessing a community-based antiretroviral service in South Africa: implications for programme design. *AIDS* **19**, 2141–2148.

Lawn SD, Myer L, Orrell C, Bekker LG & Wood R (2006) Determinants of mortality and non-death losses from an antiretroviral treatment service in South Africa: implications for program evaluation. *Clinical Infectious Disease* **43**, 770–776.

Lawn DS, Harries AD, Anglaret X, Myer L & Wood R (2008) Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. *AIDS* **22**, 1897–1908.

Lewis DK, Peters RPH, Schijffelen MJ *et al.* (2002) Clinical indicators of mycobacteraemia in adults admitted to hospital in Blantyre, Malawi. *International Journal of Tuberculosis and Lung Disease* **6**, 1067–1074.

Libamba E, Makombe S, Harries AD *et al.* (2005) Scaling up antiretroviral therapy in Africa : learning from tuberculosis control programmes – the case of Malawi. *International Journal of Tuberculosis and Lung Disease* **9**, 1062–1071.

Lowrance DW, Makombe S, Harries AD *et al.* (2008) A public health approach to rapid scale-up of antiretroviral treatment in Malaŵi during 2004–2006. *Journal of Acquired Immunodeficiency Syndrome* **49**, 287–293.

Lucas SB, De Cock KM, Hounnou A *et al.* (1994) Contribution of tuberculosis to slim disease in Africa. *British Medical Journal* **308**, 1531–1533.

McCarthy GM (1992) Host factors associated with HIV-related oral candidiasis: a review. *Oral surgery, Oral medicine, Oral pathology, Oral radiology, and endodontics* **73**, 181–186.

McDonald LC, Archibald LK, Rheanpumikankit A *et al.* (1999) Unrecognized *Mycobacterium tuberculosis* bacteraemia among inpatients in less-developed countries. *Lancet* **354**, 1159–1163.

Mocroft A, Vella S, Benfield TL *et al.* (1998) Changing patterns of mortality across Europe in patients infected with HIV-1. *Lancet* **352**, 1725–1730.

MOHP/NAC (2006) *Ministry of Health and Population and National AIDS Commission. Guidelines for the use of anti-retroviral therapy in Malawi*, 2nd Edn. Lilongwe, Malawi.

Morgan D (2000) Survival by AIDS defining condition in rural Uganda. *Sexually Transmitted Infections* **76**, 193–197.

NAC (2007) *HIV and Syphilis Sero-Survey and National HIV Prevalence and AIDS Estimates Report*. National AIDS commission, Lilongwe.

Peters RPH, Zijlstra EE, Schijffelen MJ *et al.* (2004) A prospective study of bloodstream infections as a cause of fever in Malawi: clinical predictors and implications for management. *Tropical Medicine and International Health* **9**, 928–934.

Philips M, Zachariah R & Venis S (2008) Task shifting for antiretroviral treatment in sub-Saharan Africa: not a panacea. *Lancet* **371**, 682–684.

Ravera M, Reggiori A, Agliata AM & Rocco RP (1999) Evaluating diagnosis and treatment of oral and oesophageal candidiasis in Ugandan AIDS patients. *Emerging Infectious Disease* **5**, 274–277.

USDHH (2003) *A clinical guide to supportive and palliative care*. United States Department for Health and Human Services. http://hab.hrsa.gov/tools/palliative (accessed 24 October 2008).

WHO (2006a) *Taking stock: health worker shortages and the response to AIDS*. WHO, Geneva. http://www.who.int/hiv/pub/advocacy/ttr/en/index.html (accessed 24 September 2008).

WHO (2006b) Antiretroviral therapy for HIV infection in adults and adolescents in resource limited settings: towards universal access. Recommendations for a public health approach. 2006 revision. http://www.who.int/hiv/pub/guidelines/art/en/index.html (accessed 13 March 2009).

WHO (2006c) *Progress on global access to HIV antiretroviral therapy: a report on '3 by 5' and beyond*. WHO, Geneva, Switzerland. http://www.who.int/hiv/fullreport_en_highres.pdf (accessed 18 July 2008).

Wikipedia (2008) Plumpy'nut. http://en.wikipedia.org/wiki/Plumpy'nut (accessed 4 November 2008).

Wilcox CM, Straub RF & Clark WS (1995) Prospective evaluation of oropharyngeal findings in human immunodeficiency virus-infected patients with oesophageal ulceration. *American Journal of gastroenterology* **90**, 1938–1941.

Wilcox CM, Alexander LN, Clark WS & Thompson SE III (1996) Fluconazole compared with endoscopy for human immunodeficiency virus-infected patients with oesophageal symptoms. *Gastroenterology* **110**, 1803–1809.

Yu JK, Bong CN, Chen SC *et al.* (2008) Outcomes in HIV-infected patients who develop tuberculosis after starting antiretroviral treatment in Malawi. *International Journal of Tuberculosis and Lung Disease* **12**, 692–694.

Zachariah R, Fitzgerald M, Massaquoi M *et al.* (2006a) Risk factors for high mortality in patients on antiretroviral treatment in a rural district of Malawi. *AIDS* **20**, 2355–2360.

Zachariah R, Harries AD, Manzi M *et al.* (2006b) Acceptance of anti-retroviral Therapy among patients infected with HIV and Tuberculosis in rural Malawi is low and associated with cost of transport. *PLoS ONE* **27**, 1–6.

Zachariah R, Teck R, Buhendwa L *et al.* (2007) Community support is associated with better antiretroviral treatment outcomes in a resource-limited rural district in Malawi. *Transactions of the Royal Society Tropical Medicine and Hygiene* **101**, 79–84.

Corresponding Author R. Zachariah, Medicins sans Frontieres Brussels operational center, Medical department (Operational research), 68 Rue de Gasperich, 1617 Luxembourg. Tel.: +352 332515; Fax: +352 335133; E-mail: zachariah@internet.lu