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Patient retention and attrition on antiretroviral treatment at district level in rural Malawi

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Summary We report on rates of patient retention and attrition in the context of scaling-up antiretroviral treatment (ART) within a district hospital and its primary health centres in rural Malawi. 'Retention' was defined as being alive and on ART or transferred out, whereas 'attrition' was defined as died, lost to follow-up or stopped treatment. A total of 4074 patients were followed-up for 1803 person-years: 2904 were at the hospital and 1170 at health centres. Approximately 85% of patients were retained in care, both at hospital and health centres, with a retention rate per 100 person-years of 185 and 211, respectively [adjusted hazard ratio (HR) 1.18, 95% CI 1.10—1.28, $P = 0.001$). Attrition rates per 100 person-years were similar: 33 and 36, respectively (adjusted HR 1.17, 95% CI 0.97—1.4, $P = 0.1$). At health centres the incidence of loss to follow-up was significantly lower than at the hospital (adjusted HR 0.24, $P < 0.001$, risk reduction 77%), but the rate of reported deaths was higher at health centres (adjusted HR 2.2, 95% CI 1.76—2.72, $P < 0.001$). As Malawi continues to extend the coverage (and equity) of ART, including in rural areas, attention is needed to reduce losses to follow-up at hospital level and reduce mortality at primary care level.

1. Introduction

''The hospital is too far away''; ''I missed my appointment because I could not find enough money for transport''. For anyone who works in rural districts in Africa, this sort of statement from a patient brings no surprises. Many health-related interventions are often

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centralised in hospitals that are located far from rural communities.

Malawi is a small resource-limited country in southern Africa with about 12 million inhabitants and is facing a severe HIV/AIDS epidemic, with an estimated 900 000 individuals living with HIV/AIDS and 60 000 AIDS-related deaths each year.[1] An estimated 275 000 people were thought to be in need of antiretroviral therapy (ART) by the year 2007, and by December 2007 141 449 patients had been placed on treatment from 163 public health facilities (HIV Unit, Ministry of Health, Malawi). Although this has been a commendable achievement, these efforts have focused mainly on second-level (hospital) facilities located principally in urban areas. There is thus a valid concern of geographical equity in ART access for people living in rural areas, where the cost of transport to hospitals is known to be high and where ART uptake and follow-up may therefore be compromised.[2–4] Progressive congestion of existing hospital-based ART clinics and the need for repeat visits, leading to long waiting times, are also likely to add to the complexity of accessing ART at the hospital level.

If geographical access is to be improved for the rural poor, an unavoidable step is to decentralise ART to health centres. In response to this challenge, from June 2006, Thyolo District in rural southern Malawi started to initiate ART both at the district hospital and a number of primary health centres. Such a perspective of a hub (hospital) and spoke (health centre) approach to ART roll-out is becoming common in sub-Saharan Africa. However, concerns have been raised about the human resource capacity and quality of ART delivery that can be offered at health centres, and there is a dearth of published data on ART outcomes that result from such a decentralised approach to ART delivery in sub-Saharan Africa.

From a public health perspective, patient retention and attrition are important parameters that can be used to judge program quality.[5] We measured and compared these parameters among patients initiated on ART at the main district hospital in Thyolo and its primary health centres.

2. Materials and methods

2.1. Study design, setting and population

This study was a retrospective cohort study and was conducted in Thyolo, the largest rural district in Malawi, with about 550 000 inhabitants. The inhabitants of Thyolo are principally subsistence farmers, earning an average of US$4 per week. Of all income in the district, 80% comes from the agricultural sector through daily labour in tea and coffee plantations. The road networks are poor and public transport is scarce and unaffordable to the majority.

The district has one main public hospital (Thyolo District Hospital) and nine primary health centres. As from June 2006, health centres started initiating ART in a phased manner, with seven of the nine starting during the study period. All patients beginning ART for the first time (ART naïve) at the district hospital and health centres between 1 June 2006 and 31 June 2007 were included in this study.

All staff involved with ART delivery undergo a standardized national training course, and ART delivery sites require formal accreditation from the Ministry of Health before ART services can commence. The district hospital ART clinics are run by a team of one clinical officer, two medical assistants, two nurses, three nurse counsellors and clerical support staff. At the health centre level, ART delivery is managed by a medical assistant, one nurse, a clerk and a receptionist, who received appropriate training from either a doctor or a senior clinician involved with ART delivery at the district hospital. A mobile district team with a more senior and experienced clinician (a clinical officer) provides ongoing support and monitoring of hospital and health centres on a monthly basis. A community network of home-based care volunteers and community nurses facilitate care and referrals to existing health facilities, as has been described previously.[6]

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.

2.2. ART eligibility and regimens

All HIV-positive patients assessed as being in WHO Clinical stage 3 or 4, or with a CD4 count <250 cells/mm^3 (irrespective of WHO staging) are considered eligible for ART.[7] CD4 counts were not routinely available at health centres during the study period. Once patients are assessed as eligible for ART, they are required to return with a patient guardian (or next of kin) to prepare for ART initiation. Patients and guardians undergo group and individual counselling sessions and are educated on HIV infection, and the implications of ART therapy. Once started on ART, patients are reviewed back at the HIV/AIDS clinic after 2 weeks. From then on, provided there are no side effects, patients are seen and given drugs at 4 week intervals.

The first-line ART regimen in Malawi[7] 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 in all public facilities in Malawi, including Thyolo.

2.3. Data collection, treatment outcomes and statistical analysis

ART monitoring is done using standardized monitoring tools: standardized treatment outcomes are monitored every month in the patient master cards and updated each month in the ART register, which have been described previously.[8,9] Treatment outcomes are defined as: (1) alive and on ART — a patient who is alive and on ART at the facility where he/she is registered; (2) died — a patient who has died for any reason while on ART; (3) lost to follow-up (defaulted) — a patient placed on ART that has not been seen at the ART facility for a period of 3 months; (4) stopped — a patient who is known to have stopped treatment for any reason during treatment; (5) transferred out — a patient who is transferred out permanently to another treatment facility.

For the purposes of this analysis, 'retention in care' refers to patients who are alive and on ART at the same facil-

ity or those formally transferred out to another ART unit and thus assumed to be on therapy. 'Attrition' is defined as discontinuation of ART for any reason, and includes death, loss to follow-up and stopping ART medications.[5] A district supervisory team systematically checks the validity of outcome data on a monthly basis and reports to a national supervisory team that cross-checks these data independently every quarter. Data were collated for the hospital and the seven health centres and treatment outcomes of all patients starting ART from June 2006 were censored on 30 June 2007.

Differences between groups were compared using the χ^2 test for categorical variables and the Wilcoxon rank-sum test. Hazard ratios (HR) per 100 person-years of follow-up were used to compare ART outcomes between hospital and health centres. The rates of death and loss to follow-up in the two groups were adjusted using a Cox regression model. 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% CI were used throughout. Data analysis was done using STATA 8.2 (Stata Corp., College Station, TX, USA).

3. Results

3.1. Characteristics of the study population and treatment outcomes

There were 4098 patients who were started on ART during the study period. Of these, 24 patients were excluded from the analysis: 7 patients had initiated ART in another district and were transferred out; and date of treatment initiation was not indicated in 17 patients. A total of 4074 patients was included in the study: 2904 started ART at the district hospital; and 1170 started ART at the health centres.

Table 1 shows the basic details of patients starting ART at the two sites. At health centres, there was a higher proportion of women, patients at WHO stage 3 and patients with active tuberculosis (TB) who started ART; whereas at the hospital a higher proportion of patients started on ART as a result of being at WHO stages 1 and 2 with a low CD4 count or at WHO Stage 4. Patients were followed-up for a total period of 1803 person-years. This included a total follow-up time of 1330 person-years in the hospital cohort and 473 person-years in the health centre cohort. Table 2 shows standardized treatment outcomes in person-years for all patients started on ART at hospital and health centres and censored on 30 June 2007.

3.2. Retention in care

Although retention rates at both hospital and health centres were close to 85%, the rate at health centres was significantly higher (adjusted HR 1.18, 95% CI 1.10–1.28, $P = 0.001$). Individuals starting ART at health centres had a 12.3% (95% CI 5.7–18.5) higher attributable risk of being retained in care than those at hospital (Table 2).

3.3. Attrition from care

Overall rates of attrition at hospital and health centres were similar (Table 2). After adjustment for sex, age, WHO stage and TB, the HR remained insignificant (HR 1.17, 95% CI 0.97–1.4, $P = 0.1$).

Figure 1 shows the probability of attrition from care among patients starting ART at the hospital and health centres. The rate of loss to follow-up at health centres was significantly lower than at the hospital (Table 2, adjusted HR 0.24, 95% CI 0.14–0.39, $P < 0.001$). There was a 77% overall absolute risk reduction in loss to follow-up (becoming a defaulter) in patients who started ART at health centres compared with the district hospital (95% CI 63.8–86.2). The median time between ART start and being lost to follow-up

Table 1 Case registration characteristics of patients started on antiretroviral therapy at the district hospital and health centres, Thyolo District, Malawi

Variable	Hospital *n* (%)	Health centre *n* (%)	*P*-value
Total	2904	1170	
Sex			
Male	1123 (38.7)	326 (27.9)	<0.001
Female	1781 (61.3)	844 (72.1)	
Age (years)			
Children <15	352 (12.1)	24 (2.0)	<0.001
Adults ≥15	2552 (87.9)	1146 (98)	
Age (years) [median (IQR)]	31.8 (26–40)	35.9 (29–42)	–
WHO clinical stage			
Stage I or II with CD4 <250 cells/μl	126 (4.3)	2 (0.2)	<0.001
Stage III	2267 (78)	1044 (89)	<0.001
Stage IV	551 (18)	124 (11)	<0.001
Active TB			
No	2824 (97.3)	1066 (91.1)	<0.001
Yes	80 (2.7)	104 (8.9)	

IQR: interquartile range.

Table 2 Treatment outcomes for all patients started on antiretroviral treatment (ART) at hospital and health centres, Thyolo District, Malawi

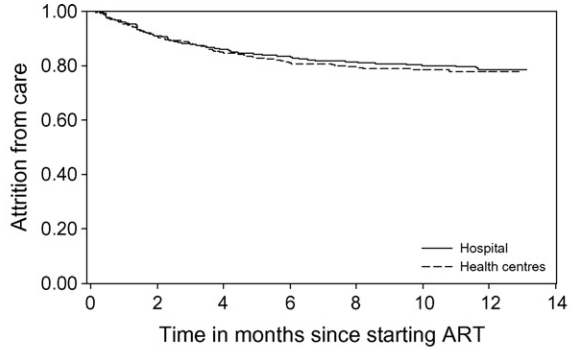
	Hospital *N* (%)	Rate/100py[a]	Health centre *N* (%)	Rate/100 py[a]	Hazard ratio (95% CI)	*P*-value
Started on ART	2904	—	1170	—		
Retained in care[b]	2463 (84.9)	185	999 (85.4)	211	1.14 (1.06—1.23)	<0.001
Alive and on ART	2385 (82.1)	179.3	994 (85.0)	210	1.17 (1.09—1.26)	<0.001
Transferred out	79 (2.7)	5.94	5 (0.4)	1.06	0.17 (0.07—0.44)	<0.001
Attrition[c]	439 (15.1)	33.3	171 (14.6)	36.1	1.07 (0.89—1.27)	0.5
Defaulted	227 (7.8)	17.0	18 (1.5)	3.8	0.22 (0.13—0.35)	<0.001
Dead	202 (7.0)	15.2	150 (12.8)	31.7	2.02 (1.63—2.49)	<0.001
Stopped	11 (0.4)	0.82	3 (0.3)	0.63	0.71 (0.19—2.57)	0.6

[a] Rate/100 py: rate per 100 person-years of follow-up.
[b] Includes patients alive and on ART and formal transfer-outs.
[c] ART discontinuation due to default, death or stopping ART.

was 68 d [interquartile range (IQR) 41—126] at the hospital and 126 d (IQR 106—179) at the health centres.

In contrast to rates of loss to follow-up, the incidence of reported deaths was significantly higher at the health centres compared with the hospital [Table 2; adjusted HR 2.2, 95% CI 1.76—2.72, $P < 0.001$, attributable risk 52% (95% CI 40.8—61.2)]. Of all cumulative deaths that occurred at hospital ($n = 202$) and health centres ($n = 150$), 75% (151 at hospital and 112 at the health centre level) occurred within the first 3 months of starting ART (early mortality). Figure 2 shows the difference in probability of survival among patients who started ART at hospital and health centres.

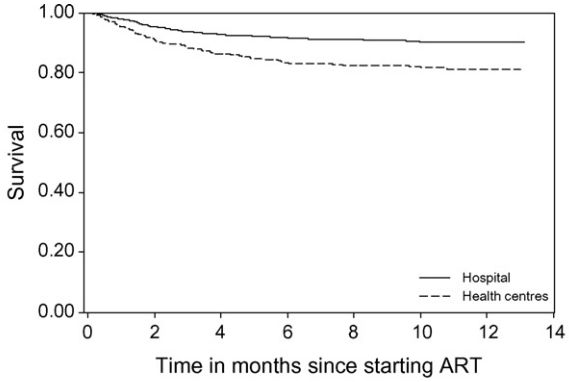
Table 3 shows the baseline characteristics of patients who had 'death' as an outcome at health centres compared with those alive and on ART or transferred out. Patients with unexplained weight loss of over 10% constituted 35% of all deaths and were at a significantly higher risk of dying [odds ratio (OR) 1.72, 95% CI 1.16—2.50, $P = 0.005$), as were male patients (OR 2.1, 95% CI 1.4—3.0, $P < 0.001$). Patients



Log-rank test $\chi^2 = 0.54$, $P = 0.5$.

	Time (months)	0	2	4	6	8	10	12	14
Hospital	At risk	2904	2177	1632	1259	912	572	233	5
	Died, lost to follow-up, stopped ART	—	235	113	46	28	11	6	0
Health centres	At risk	1170	775	561	408	297	230	95	13
	Died, lost to follow-up, stopped ART	—	96	43	21	6	4	1	0

Figure 1 Probability of attrition (deaths, loss to follow-up and stopped) among patients starting antiretroviral treatment (ART) at hospital and health centres, Thyolo District, Malawi.



Log-rank test $\chi^2 = 44.3$, $P \leq 0.001$.

	Time (months)	0	2	4	6	8	10	12	14
Hospital	At risk	2904	2177	1632	1259	912	572	233	5
	Reported deaths	—	117	55	18	7	5	0	0
Health centres	At risk	1170	775	561	408	297	230	95	13
	Reported deaths	—	93	34	16	3	3	1	0

Figure 2 Survival probability in relation to starting antiretroviral treatment (ART) at hospital and health centres, Thyolo District, Malawi.

with severe bacterial infections and oral recurrent candidiasis constituted 11.3 and 23.3% of all deaths, respectively. Along with unexplained weight loss, these three conditions were associated with 69.6% of all deaths that occurred at health centres.

4. Discussion

In a rural district of Malawi, patients who had been started on ART had higher retention and similar attrition rates at the health centre level compared with the district hospital. There has been much debate in Malawi about the appropriate level of care for offering ART, and in particular about the success and safety of offering ART at health centres. Many African countries are now embarking on scaling up ART, and this issue is of wider importance in terms of policy and practice.[10] In this light, the findings of this analysis raise a number of important observations that merit discussion.

First, retention rates both at hospital and health centre level were close to 85%, and this seems acceptable in

Table 3 Characteristics of patients who were known to have died while on antiretroviral treatment at health centres, Thyolo District, Malawi

Variable	Died *n* (%)	Alive/transferred out *n* (%)	*P*-value[a]
Total	150 (12.8)	999 (86.9)	—
Sex			
Male	63 (42)	259 (25.9)	<0.001
Female	87 (58)	740 (74.1)	
Age (years)			
<35	86 (57.3)	542 (54.3)	0.47
≥35	64 (42.7)	457 (45.8)	
WHO clinical stage			
Stage I or II with CD4 <250 cells/μl	0	2 (0.2)	
Stage III	127 (84.7)	900 (90.1)	0.04
Stage IV	23 (15.3)	97 (9.7)	0.04
Main opportunistic infection at ART start			
Oesophageal candidiasis	3 (2)	18 (1.8)	0.87
Kaposi's sarcoma	7 (4.7)	19 (1.9)	0.06
Cryptococcal meningitis	1 (0.7)	2 (0.2)	—
Oral recurrent candida	35 (23.3)	251 (25.1)	0.64
Unexplained chronic diarrhoea >1 month	14 (9.3)	108 (10.8)	0.58
Unexplained persistent fever >1 month	0	6 (0.6)	—
Unexplained presumed weight loss >10%	52 (34.7)	237 (23.7)	0.003
Pneumocystis jiroveci pneumonia	3 (2)	84 (8.4)	0.005
Recurrent severe bacterial pneumonia	4 (2.7)	10 (1.0)	0.17
Active TB	13 (8.7)	90 (9.0)	0.89
Severe bacterial infection (pneumonia, empyema, pyomyosities, meningitis, suspected bacteraemia/septicaemia, bone or joint infection)	17 (11.3)	136 (13.6)	0.44
Others (anaemia, skin conditions, herpes simplex, anaemia, toxoplasmosis)	1 (3.3)	38 (3.8)	0.81
Duration on ART (months) [median (IQR)]	48 (24—92)	129 (51—263)	—

IQR: interquartile range.
[a] χ^2 test.

the resource-limited setting.[5] In the context of this analysis a total of 3461 individuals was retained in care, and this has associated benefits not only for patients but also for their households and the wider community. We feel justified in including transfer-outs as patients who are retained on therapy. An operational research study in Northern Malawi showed that over 90% of patients who transfer out have in fact 'transferred in' to another site and show good survival outcomes.[11]

Second, districts such as Thyolo have been struggling to get more HIV-positive TB patients on ART.[12] The fact that more patients with active TB now access ART at health centres than at hospital is likely to facilitate the linkage of ART and TB services at the primary level. This integration means a more TB-HIV accessible service and the possible perception at patient level of 'two diseases, one patient'.[13]

Third, the loss to follow-up rate was significantly higher at the hospital level (9.9%) than at the health centre level (1.5%). A loss to follow-up rate as low as 1.5% at health centres is rarely reported in Africa.[5] This important finding might be related to better geographical access and other factors known to be important for ART uptake and continued follow-up.[2,4] This finding might also relate to better personal knowledge by the provider of the patient (and vice versa).

Fourth, reported deaths constituted an important component of attrition and were significantly higher at health centre level. This may reflect weaker ascertainment (ascertainment bias) of deaths among patients lost to follow-up at the hospital level. A recent study from Malawi which reported on the 'true outcomes' of patients lost to follow-up showed that 65% of such patients were ascertained to be dead or had stopped ART, 27% could not be traced and barely 8% were still on ART and had actually shifted to another clinic.[4] This finding coupled with the fact that median survival (without ART) in patients with AIDS in Africa is less than 1 year[14] tend to support the argument that the rate of loss to follow-up needs to be taken into consideration when assessing death rates. This aside, the reported mortality of 12.8% at the health centre is still far from desired, as high death rates challenge the credibility of ART programmes in the eyes of patients, health staff and the community. The great majority of deaths (75%) occurred early, within the first 3 months of starting treatment.

There are several possible reasons for early mortality in patients starting on ART, and these include: delayed presentation of patients, possibly influenced by a higher level of stigma of HIV/AIDS in rural areas; delayed ART initiation at the health facility and thus advanced HIV/AIDS disease; delayed diagnosis; undiagnosed opportunistic infections; and life-threatening HIV-related complications such as bacteraemia and TB.[15] Unrecognized drug-related side effects and drug interactions might also contribute to this problem. Possible ways forward in addressing this high early mortality have been discussed previously.[16] In this study, patients with unexplained weight loss of over 10%, recurrent oral candidiasis and severe bacterial infections constituted seven out of ten deaths at health centres. Is unexplained weight loss a proxy for bacteraemia or undiagnosed TB, both of which could present in an atypical or covert manner?[17] A recent study from northern Malawi showed that 77% of patients who developed TB after starting ART had unexplained weight loss and/or fever before starting ART, and these observations concur with this hypothesis.[18] In any case, this is a group of patients in whom intensified case-finding for TB and other opportunistic infections might be worthwhile. Both recurrent oral candida and bacterial infections are conditions that can be diagnosed and treated at health centre level. This raises the question about the quality of clinical assessment at this level and whether there are stock interruptions of drugs known to be effective. Patients with severe bacterial infections need a wider range of antibiotics than are currently available at the primary care level as well as a higher level of clinical supervision to diagnose and manage complications. Countries embarking on public health scale-up of ART should therefore include a strong training programme for non-physician clinicians on the early recognition and prompt referral of opportunistic infections.

Fifth, there was a higher proportion of deaths in males compared with females, and this observation may be due to men seeking medical care at a more advanced stage of immunodeficiency and showing poorer compliance with therapy.[19] This issue also needs to be more actively addressed in the scaling-up process through targeted information and education sessions as well as targeted counselling.

Finally, Thyolo District benefits from assistance from the Department of International Development (DFID), Family Health International (FHI), Norwegian Agency for Development Cooperation (NORAD) and other agencies, as well as additional technical and financial assistance from Médecins Sans Frontières. In many settings in sub-Saharan Africa such resources, particularly at first contact level, are extremely scarce and do not allow allocation of a mobile team, a medical assistant, a nurse, a clerk and a receptionist exclusively to ART delivery, for example. Our findings might thus not apply to rural settings, which are relatively less well resourced than Thyolo. Malawi, like other countries in sub-Saharan Africa, is facing a serious shortage of health staff, particularly doctors and specialists,[20,21] and decentralisation of ART delivery to health centres will require alternative strategies, including task shifting,[21–23] as well as increased resources for staffing, training, supervision and support for referrals.

The strengths of this study were: that a large number of patients were included in the study; that outcomes were reliably ascertained using master cards and registers, which are robust and regularly checked by supervision teams; and as the data come from a programme setting the findings probably reflect the operational reality on the ground. The limitations of the study were: that there were no data on variables such as HIV- or drug-related morbidity; that the causes of death or reasons for default were not ascertained but merit specific investigation; that CD4 count measurements were not performed at health centre level, and we were thus unable to compare the degree of immunodeficiency between hospital-based and health-centre-based patients; and finally, there were fewer children initiated on ART at health centres as children were by preference referred to the district hospital. There is also the consideration that retention and attrition patterns might change as the cohort matures.

In conclusion, as Malawi continues to extend the coverage (and equity) of ART, including in rural areas, attention is needed to reduce losses to follow-up at hospital level and reduce mortality at primary care level.

Authors' contributions: RZ, MMas, MMan, OP, DM, BM, AB and ADH were involved with the conception and design of the study; MMas, MMan, OP, DM and MB were involved with implementation, data entry and overall supervision; RZ, MMas, MMan and DM conducted the analysis and contributed to the intellectual content of the article; RZ wrote the first draft paper and handled the repeated revisions; ADH considerably improved the study design and analytical methods, and contributed significantly to improving the intellectual content and text of the manuscript. All authors were involved with the manuscript and read and approved the final version. RZ is guarantor of the paper.

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Conflicts of interest: None declared.

Ethical approval: 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.

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