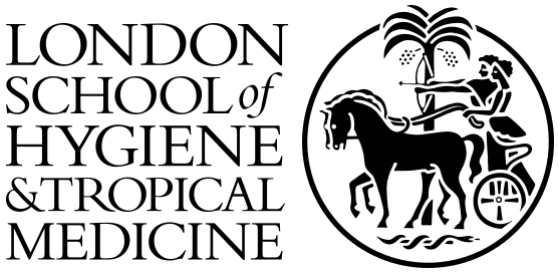

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Home-based versus clinic-based care for patients starting antiretroviral therapy with low CD4$^+$ cell counts: findings from a cluster-randomized trial

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Objectives: African health services have shortages of clinical staff. We showed previously, in a cluster-randomized trial, that a home-based strategy using trained lay-workers is as effective as a clinic-based strategy. It is not known whether home-based care is suitable for patients with advanced HIV disease.

Methods: The trial was conducted in Jinja, Uganda. One thousand, four hundred and fifty-three adults initiating ART between February 2005 and January 2009 were randomized to receive either home-based care or routine clinic-based care, and followed up for about 3 years. Trained lay workers, supervised by clinical staff based in a clinic, delivered the home-based care. In this sub-analysis, we compared survival between the two strategies for those who presented with CD4$^+$ cell count less than 50 cells/μl and those who presented with higher CD4$^+$ cell counts. We used Kaplan–Meier methods and Poisson regression.

Results: Four hundred and forty four of 1453 (31%) participants had baseline CD4$^+$ cell count less than 50 cells/μl. Overall, 110 (25%) deaths occurred among participants with baseline CD4$^+$ cell count less than 50 cells/μl and 87 (9%) in those with higher CD4$^+$ cell count. Among participants with CD4$^+$ cell count less than 50 cells/μl, mortality rates were similar for the home and facility-based arms; adjusted mortality rate ratio 0.80 [95% confidence interval (CI) 0.53–1.18] compared with 1.22 (95% CI 0.78–1.89) for those who presented with higher CD4$^+$ cell count.

Conclusion: HIV home-based care, with lay workers playing a major role in the delivery of care including providing monthly adherence support, leads to similar survival rates as clinic-based care even among patients who present with very low CD4$^+$ cell count. This emphasises the critical role of adherence to antiretroviral therapy.

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Introduction

Over 7.5 million people are on combination antiretroviral therapy (ART) in Africa [1], which is just over half of those in need according to current guidelines. It is the largest and most rapid scale-up of a chronic care programme on the continent. A major challenge for sustaining and increasing the scale-up further is the

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shortage of clinically qualified staff, particularly doctors. In many countries in Africa there are less than 10 doctors per 100 000 people [2]. Delivery of HIV services, which rely less on clinically qualified staff, are needed but the evidence-base on such models of care remains limited.

In a cluster-randomised trial in Jinja, Uganda, we have shown previously that HIV home-based care, with trained lay-workers delivering care and support in the home, was as effective as a standard clinic-based model using qualified clinical staff to manage patients. The lay-workers were monitored and supervised by clinical staff based at the clinic. The home-based care strategy was marginally cheaper for the health service through reduced contact time with doctors and nurses, and was cost saving for patients [3].

Various studies have shown that mortality is high just prior to initiating ART and in the first few weeks and months after initiating therapy; this high death rate is associated strongly with late presentation as indicated by low $CD4^+$ cell count [4–10]. It is not known whether an HIV home-based care model which incorporates use of lay-workers is appropriate for people who present with advanced disease (i.e. with low $CD4^+$ cell count) or whether such patients should be managed by clinical staff in health facilities. Using data from the Jinja trial, we have examined mortality rates between the HIV home-based care and facility-based care trial arms for people who presented with low $CD4^+$ cell counts (<50 cells/μl) and those who presented with higher $CD4^+$ cell counts.

Methods

Study design and participants

A description of the study has been published elsewhere [3]. In brief, the trial was based at The AIDS Support Organisation (TASO) clinic in Jinja district, Uganda. The clinic was by far the largest provider of ART within a 100 km radius. The catchment area was divided into nine strata based on whether the area was urban or rural and the distance to the clinic. Clusters were defined in each stratum with a similar estimated number of HIV-infected patients registered at the clinic, and then randomized to either home-based or facility-based care by drawing cards from a concealed box.

Patients over 18 years old who started on ART between February 2005 and December 2006 were invited to join the trial. Eligibility for ART was based on the Ugandan guidelines at the time: WHO HIV clinical stage IV or late stage III or $CD4^+$ cell count less than 200 cells/μl. Eligible patients were initiated on ART at the TASO clinic and supplied with 30 days of drugs. Subsequent care was provided according to their randomized study arm (details below). Study participants were followed-up until January 2009.

The trial was integrated into routine health services and TASO clinic staff followed national guidelines. No incentives were given to either patients or staff [11]. Standard care involved study patients attending clinic monthly to collect drugs and receive adherence support. They had routine appointments with a clinician scheduled at 2, 3 months and 3-monthly thereafter following initiation of ART. At the other monthly visits, they were seen by a nurse and referred to a clinician if indicated or if they requested. In the intervention arm, participants were visited monthly in their homes by trained lay-workers travelling on motorbikes. The lay-workers used a checklist to assess patients clinically, delivered the antiretrovirals and provided adherence support. They referred participants to the TASO clinic in cases where clinical deterioration or intercurrent illness were suspected, or discouraged self-referral otherwise. In cases of doubt, they were able to phone a clinical team member at the clinic for advice. Participants who were absent at the time of the visit received one follow-up visit within 1–2 days. If they were absent again, a note was left for them to visit the clinic. Visits to the TASO clinic to see a clinician were scheduled at 2 months after ART initiation, then at 6 months and 6-monthly thereafter. Antiretrovirals were not provided at the clinic for participants in this arm at these or other visits – this was always through home visits. Consequently, routine outpatient visits in this arm were much fewer than in the standard care arm in which patients collected all their drugs from the clinic [3].

Deaths were ascertained from TASO records or home follow-up visits, depending on where the patient died. Causes of death were ascertained by verbal autopsy methods as described previously [12]. In brief, relatives of the deceased were interviewed by a study physician about the signs and symptoms leading up to the death and documentation from any recent visit to a clinic or hospital was reviewed. The study physician's notes were reviewed by two research physicians who assigned a probable cause of death. These diagnoses and the records were then reviewed by a senior independent physician from the government referral hospital to confirm the diagnoses or to resolve discrepancies.

Data analysis

Data analysis was performed using STATA version 12.1 (STATA Corp., College Station, Texas, USA). Follow-up time was calculated from enrolment to either the end of the study or the date of death. Those who withdrew or were lost to follow-up were censored on the date that they were last seen. Mortality rate ratios were calculated using a Poisson regression random effects model with gamma distribution to account for clustering. All analyses were adjusted for study strata. Statistical significance was

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assessed using likelihood ratio tests. A Cox proportional hazards model using robust standard errors was fitted as a consistency check and produced similar results. Multivariable analyses were adjusted for WHO stage and $CD4^+$ cell count (using a square root transformation) in addition to study strata [12]. Age, sex, education and marital status (as shown in Table 1) were not associated with mortality. Their inclusion in the multivariable regression model made no difference to the adjusted mortality rate ratio. They were therefore dropped from the model.

We chose to stratify analyses by baseline $CD4^+$ cell count below 50 cells/μl as it is widely used as a marker of advanced HIV disease when the risk of death is known to be very high [5,8]. We also stratified some analyses by follow-up time of 6-months on ART because during this period, mortality risk is highest and a greater proportion of the mortality is likely to be attributable to HIV.

Results

Description of the study population

One thousand, four hundred and fifty-three participants (98% of those eligible) were enrolled into the original trial [3]. Twenty-two clusters (859 people) were randomized to home-based care and 22 clusters (594 people) to facility care. Those receiving home-based care spent a median of 28.2 months in the study [interquartile range (IQR) 18.4–35.0] and facility care participants were followed for a median of 27.6 months (IQR 13.8–34.1). The majority were female (71%), a sex distribution that is common in African ART programmes [13], and the median age was 37 years ((IQR 32–44). Almost a third of patients (31%) had $CD4^+$ cell counts less than 50 cells/μl at the start of the study. Overall, baseline $CD4^+$ cell counts were lower in the home-based care arm (median 99, IQR 34–162) compared with patients receiving facility-care (median

Table 1. Baseline characteristics by trial arm and $CD4^+$ count category.

	$CD4^+$ cell count <50 cells/μl		$CD4^+$ cell count ≥50 cells/μl	
	Home-based care ($n=272$)	Facility-based care ($n=172$)	Home-based care ($n=587$)	Facility-based care ($n=422$)
Female	190 (70%)	111 (65%)	435 (74%)	295 (70%)
Age in years (IQR)	36 (31–41)	38 (33–44)	38 (32–45)	38 (33–44)
Education, number (%)				
No education	47 (17%)	28 (16%)	104 (18%)	55 (13%)
Primary	153 (56%)	96 (56%)	331 (56%)	236 (56%)
Secondary or tertiary	72 (26%)	48 (28%)	152 (26%)	131 (31%)
Marital status, number (%)				
Married/cohabiting	98 (36%)	69 (40%)	202 (34%)	147 (35%)
Widowed	102 (38%)	54 (31%)	249 (42%)	178 (42%)
Divorced/separated	67 (25%)	49 (28%)	127 (22%)	88 (21%)
Single	5 (1%)	0 (0%)	9 (2%)	9 (2%)
Median (IQR) hours to reach clinic	1 (0.5–2)	1.5 (1–2)	1 (0.5–2)	1 (0.75–2)
Main form of transport to clinic, number (%)				
Walking	7 (3%)	5 (3%)	29 (5%)	26 (6%)
Minibus/car taxi	226 (83%)	143 (83%)	490 (83%)	336 (80%)
Motorbike/bike taxi	27 (10%)	18 (10%)	39 (7%)	33 (8%)
Other	12 (4%)	6 (3%)	29 (5%)	27 (6%)
WHO stage				
I/II	89 (33%)	64 (37%)	309 (53%)	200 (47%)
III	152 (56%)	87 (51%)	238 (41%)	196 (46%)
IV	31 (11%)	21 (12%)	40 (7%)	26 (6%)
$CD4^+$ cell count (cells/μl)	17 (5–30)	14 (6–29)	143 (96–182)	151 (113–179)
Plasma viral load (copies/ml), number (%)				
<1000	5 (2%)	2 (1%)	7 (1%)	7 (2%)
1000–9999	3 (1%)	4 (2%)	18 (3%)	15 (4%)
10 000–99 999	54 (20%)	40 (23%)	198 (34%)	162 (38%)
100 000–999 999	189 (69%)	113 (66%)	325 (55%)	325 (49%)
≥1000 000	21 (8%)	13 (8%)	39 (7%)	39 (8%)
Median (IQR)	217 544 (110 408–437 530)	179 514 (88 648–357 292)	147 108 (59 416–341 264)	127 805 (46 844–361 260)
Weight (kg), median (IQR)	52 (46–58)	52 (47–57)	54 (48–60)	55 (50–61)
Antiretroviral therapy at enrolment, number (%)				
Stavudine, lamivudine, nevirapine	124 (46%)	76 (44%)	277 (47%)	193 (46%)
Stavudine, lamivudine, efavirenz	28 (10%)	17 (10%)	47 (8%)	44 (10%)
Zidovudine, lamivudine, nevirapine	79 (29%)	57 (33%)	174 (30%)	131 (31%)
Zidovudine, lamivudine, efavirenz	40 (15%)	21 (12%)	89 (15%)	54 (13%)
Other	1 (<1%)	1 (1%)	0 (0%)	0 (0%)

IQR, interquartile range.

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122, IQR 36–167) but other characteristics were well balanced between the two arms [3].

Baseline characteristics by trial arm and $CD4^+$ cell count are shown in Table 1. The characteristics were similar in the two arms within each $CD4^+$ cell count category. As expected, participants with $CD4^+$ cell count less than 50 cells/μl were more likely to present at more advanced clinical stage and have higher plasma viral load but were otherwise similar to participants in the higher $CD4^+$ cell count category.

Mortality rates

During the study period, the number of participants lost-to-follow-up were eight (1.8%) (six home-based arm, two facility arm) among those who presented with $CD4^+$ cell count less than 50 cells/μl and 26 (2.6%) (14 home-based arm, 12 facility arm) among those who presented with $CD4^+$ cell count at least 50 cells/μl. Withdrawals from the trial were slightly higher and mostly because participants moved out of the area or changed service provider [3]. Thirty (6.8%) (18 home-based, 12 facility-based) withdrew among those who presented with $CD4^+$ cell count less than 50 cells/μl and 89 (8.8%) (42 home-based arm, 47 facility arm) withdrew among those who presented with $CD4^+$ cell count at least 50 cells/μl. The majority of those who withdrew were alive at the end of the trial [3].

One hundred and ninety-seven participants died over a median follow-up time of 28 months (IQR 15–35) giving an overall mortality rate of 6.36 deaths per 100 person-years [95% confidence interval (CI) 5.53–7.32]. Kaplan–Meier survival curves by study arm for participants with a baseline $CD4^+$ cell count less than 50 cells/μl and those who had higher counts are shown in Fig. 1. Overall, 110 (25%) deaths occurred among participants with baseline $CD4^+$ cell count less than 50 cells/μl and 87 (9%) in those who had presented with higher $CD4^+$ cell count. There was no evidence of a difference in the survival curves between study arms within either stratum of $CD4^+$ cell count ($CD4^+$ cell count less than 50 cells/μl $P = 0.32$, $CD4^+$ cell count at least 50 cells/μl $P = 0.39$).

Rate ratios comparing mortality in the home-based versus facility-based care arms are shown in Table 2. There was no evidence of a difference in mortality rates between those who received home-based care compared with those who received facility-based care in either stratum of $CD4^+$ cell count. Table 3 shows the causes of deaths by study arm. Overall 131 of 197 (67%) of deaths occurred at home and the distribution of the places of deaths were similar between the two arms for both $CD4^+$ cell count strata. Among participants who presented with $CD4^+$ cell count less than 50 $CD4^+$ cells/μl, deaths attributed to tuberculosis were more common in the home-based care arm than in the facility arm but this was not statistically significant ($P = 0.09$, Fisher's exact test). Conversely, deaths attributed to poor nutritional intake (poor feeding/starvation) were more common in the facility-based care arm than in home-based care ($P = 0.02$, Fisher's exact test).

Effect of the intervention stratified by time period

During the first 6 months following initiation of ART, the 1453 study participants contributed 681 person-years. 112 deaths occurred giving a mortality rate of 16.5 deaths per 100 person-years (95% CI 13.7–19.8). Among participants with $CD4^+$ cell count less than 50 cells/μl, mortality rates were similar for both study arms (adjusted mortality rate ratio 0.94, 95% CI 0.57–1.55). One thousand, two hundred and ninety-five participants remained in the study after 6 months and contributed a further 2416 person-years. Eighty-five deaths occurred during this time giving a mortality rate of 3.52 (95% CI 2.84–4.35). Mortality rates were similar between the two arms (Table 4).

Discussion

This analysis shows that in a Ugandan trial, HIV-infected people presenting with very low $CD4^+$ cell count, who subsequently started on ART, and whose management included home-based care delivered by trained lay workers, had similar survival outcomes as those who received clinic-based care. The adjusted mortality rates for home-based care were actually 20% lower than in facility care but this was probably due to small numbers. When we restricted the analysis to within 6-months of treatment initiation (i.e. when mortality is high and more likely to be HIV-specific), the results were similar.

It is possible that we did not detect an increased mortality among home-based care patients because stratification of participants by $CD4^+$ cell count and follow-up period reduced the power of the analysis. However, the confidence intervals were reasonably narrow and the study size was sufficient to rule out major differences. We may also have failed to detect a difference because all the patients were relatively healthy, albeit at low $CD4^+$ count. However, we have no reason to think that we systematically excluded sick people. We are likely to have enrolled the vast majority of those eligible for ART who present to health services, since TASO was providing almost all of the ART in the district during the period of the trial (the TASO clinic was based in the grounds of Jinja District Hospital and almost all patients came to TASO for their HIV care).

At the start of the roll-out of ART programme in Uganda and in most African countries, patients presenting with HIV-infection and eligible for treatment were required to

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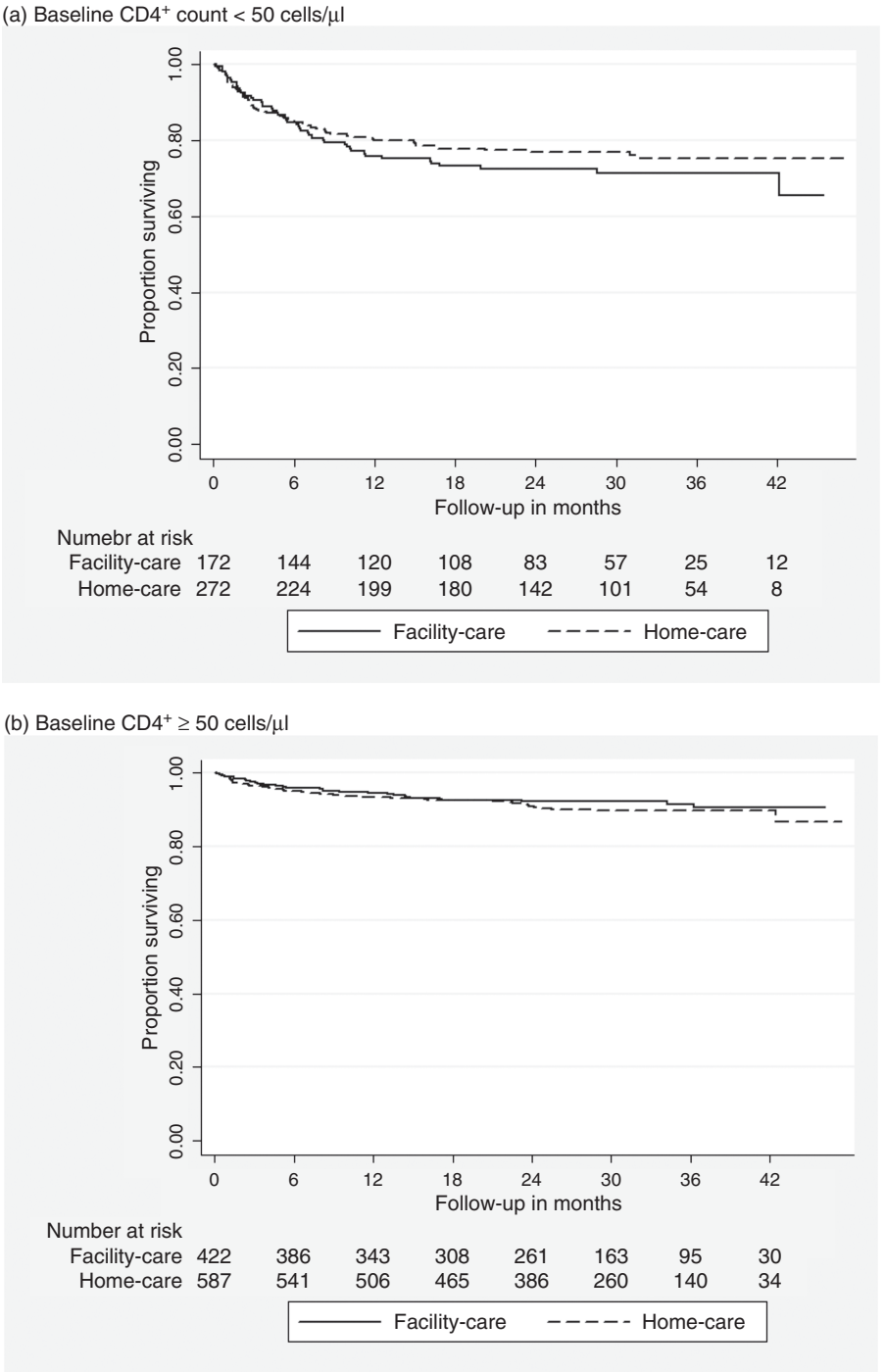

Fig. 1. Kaplan–Meier survival curves showing the proportion surviving in the home and facility-based arms by baseline CD4$^+$ cell count stratum. (a) Baseline CD4$^+$ cell count less than 50 cells/μl. (b) Baseline CD4$^+$ cell count at least 50 cells/μl.

undergo 3–4 adherence counselling sessions over a period of about a month or so. During this time, mortality was high; in our case over 30 deaths per 100 person years [10]. Thus, this process is likely to have screened out before randomization some of the very sick patients who might have benefited more from facility care. However, the policy of initiating ART after patients have been informed about adherence remains in place in most countries in Africa, and our results are intended to generalize to this population. We are currently conducting a trial to evaluate immediate initiation of ART followed by adherence counselling (ISRCTN20410413) to target the very sick patients who present late and die before ART is initiated. Late presentation will continue to occur in Africa. Our analysis confirms that the mortality rate in the first 6-months for patients who

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Table 2. Mortality rate ratios for home-based versus facility-based care, stratified by baseline CD4$^+$ cell count.

CD4$^+$ cell count (cells/μl)	Study arm	No (%) of deaths	Mortality rate per 100 person-years (95% CI)	Crude mortality rate ratio (95% CI)[a]	*P*-value	Adjusted mortality rate ratio[b] (95% CI)	*P*-value
<50	Home-based care	62/272 (23%)	11.76 (9.17–15.08)	0.81 (0.55–1.19)	0.28	0.80 (0.55–1.18)	0.26
	Facility-based care	48/172 (28%)	14.98 (11.29–19.08)	1.00		1.00	
≥50	Home-based care	55/587 (9%)	4.12 (3.16–5.36)	1.19 (0.77–1.85)	0.44	1.20 (0.77–1.87)	0.41
	Facility-based care	32/422 (8%)	3.51 (2.48–4.96)	1.00			

[a]Adjusted for stratum.
[b]Adjusted for stratum, WHO stage in three categories, and CD4$^+$ cell count.

present with low CD4$^+$ cell count is very high, comparable to that seen during the pretreatment period [7,10], and that the major route to reducing HIV-associated mortality must be to reach patients and initiate treatment earlier.

Why the outcomes in the home-based care arm, which comprised lay-workers delivering care and support in the community, supported by clinical staff based in the clinic, were approximately equivalent to those in the standard clinic-based arm needs further investigation. The comparison standard care arm was well functioning with qualified doctors and nurses, a reliable drug supply, laboratory back-up and reasonable equipment. Indeed the mortality rate of 6.36 deaths per 100 person-years observed in this study is similar or lower than the rates reported in most other mortality studies in Africa [5,7,8,14]. One explanation might be that the monthly personalized HIV adherence counselling provided by lay-workers in the home during drug delivery resulted in better adherence in the intervention arm and that the effect of this was as powerful as the better clinical monitoring and care that patients may have received at clinic at 3-montly intervals. This confirms that getting patients to adhere to ART should be a very high priority, irrespective of the stage of their illness, and especially where high quality clinical monitoring is not available. Mortality rates of people on ART remain four to five times higher in Africa than in developed countries [6,15,16] and retention in HIV care is a major concern [17]. It is not known whether combining clinic management by doctors and nurses with enhanced and personalized adherence support might reduce mortality even further.

The distribution of causes of deaths suggested that deaths attributed to tuberculosis were more common in the home-based care arm than in facility care and deaths attributed to poor nutrition (poor feeding and starvation) were more common in the facility-based arm. However,

Table 3. Places of deaths and their causes of death as estimated by postmortem questionnaire stratified by CD4$^+$ cell count category and trial arm.

	CD4$^+$ cell count<50 cells/μl		CD4$^+$ cell count ≥ 50 cells/μl	
	Home-based care	Facility-based care	Home-based care	Facility-based care
Number enrolled in trial arm	272	172	587	422
Cause of death				
Central nervous system infections	9 (3.3)	9 (5.2)	5 (0.9)	2 (0.5)
Diarrheal disease with dehydration	7 (2.6)	8 (4.7)	3 (0.5)	7 (1.7)
Tuberculosis	11 (4.0)	2 (1.2)	6 (1.0)	3 (0.7)
Acute febrile illness	6 (2.2)	4 (2.3)	7 (1.2)	5 (1.2)
Poor feeding/starvation	2 (0.7)	8 (4.7)	4 (0.7)	0
Anaemia	3 (1.1)	1 (0.6)	7 (1.2)	2 (0.5)
Septicaemia	5 (1.8)	3 (6)	4 (0.7)	1 (0.2)
Pneumonia	2 (0.7)	1 (1.7)	3 (0.5)	1 (0.2)
Haemorrhage	1 (0.4)	0	1 (0.2)	3 (0.7)
Cardiovascular disease	2 (0.7)	0	1 (0.2)	1 (0.2)
Kaposi's sarcoma	1 (0.4)	1 (1.7)	2 (0.3)	0
Trauma/accidents	3 (1.1)	0	0	0
Liver failure	2 (0.07)	1 (1.7)	0	0
Suicide	0	0	2 (0.3)	0
Other	1 (0.4)	2 (1.2)	0	1 (0.2)
Unknown	7 (2.6)	8 (4.7)	10 (1.7)	6 (1.4)
Total number of deaths	62 (22.8)	48 (27.9)	55 (8.2)	32 (7.6)
Place of death				
At home	42 (15.4)	38 (22.1)	32 (5.5)	19 (4.5)
At Jinja District Hospital	16 (5.9)	4 (2.3)	15 (2.6)	4 (0.9)
Elsewhere	4 (1.5)	6 (3.5)	8 (1.4)	9 (2.1)

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Table 4. Mortality rate ratios for home versus facility care, stratified by baseline CD4$^+$ cell count and time period.

CD4$^+$ cell count, (cells/μl)	Study arm	Deaths *N* (%)	Mortality rate per 100 person-years (95% CI)	Mortality rate ratio (95% CI)[a]	*P*-value	Adjusted mortality rate ratio (95% CI)[b]	*P*-value
First 6 months on ART							
<50	Home-based care	40/272 (15%)	33.13 (24.30–45.17)	0.96 (0.58–1.58)	0.86	0.94 (0.57–1.55)	0.83
	Facility-based care	26/172 (15%)	33.15 (22.57–48.69)	1.00		1.00	
≥50	Home-based care	29/587 (5%)	10.36 (7.19–14.91)	1.16 (0.63–2.13)	0.63	1.15 (0.63–2.11)	0.65
	Facility-based care	17/422 (4%)	8.44 (5.25–13.57)	1.00		1.00	
After 6 months on ART							
<50	Home-based care	22/224 (10%)	5.41 (3.56–8.22)	0.63 (0.35–1.16)	0.14	0.63 (0.35–1.16)	0.14
	Facility-based care	22/144 (15%)	9.09 (5.98–13.80)	1.00		1.00	
≥50	Home-based care	26/541 (5%)	2.46 (1.68–3.62)	1.22 (0.64–2.33)	0.54	1.25 (0.66–2.38)	0.50
	Facility-based care	15/386 (4%)	2.11 (1.27–3.50)	1.00		1.00	

[a]Adjusted for stratum.
[b]Adjusted for WHO stage in three categories and study stratum and CD4$^+$ cell count.

these findings need to be interpreted with caution as numbers were small and causes of deaths were ascertained by verbal interviews of the relatives of the deceased. However, if these findings are confirmed in other studies, it would suggest that tuberculosis is better detected and managed (and therefore more tuberculosis deaths are averted) in the facility arm than in the home-based arm while lay-workers visiting the homes of patients are better at detecting and averting deaths from poor nutritional intake. There was no difference overall between the two arms in the admissions or outpatients diagnoses [3].

The findings published in the original article from the Jinja trial [3] were used recently to inform the WHO's guidelines on task shifting from doctors to nurses and trained lay-workers and decentralized care from hospitals to primary care centres and the community [18]. The present analysis shows that this public health approach could be considered for all patients, including those presenting with very low CD4$^+$ cell count. We have shown previously, that this approach could be cost-saving for health services from reduced utilisation of clinics and doctor and nurse time and hugely cost saving for patients. Greater cost-effectiveness might be achieved if such models of care are extended to other high burden clinical conditions and to approaches involving integrated care. It is important to remember that the lay-workers in our study had clear referral guidelines and were supervised by clinical staff based in the clinic and modification of the support structures for lay-workers and their nature of responsibilities will need further research. Our study also confirms the importance of adherence support to patients receiving complex lifelong therapy.

As far as we are aware this is the first study to consider the effect of a home-based strategy of ART in patients with low baseline immune function. The achievement of similar survival to clinic-based patients, including during the high-risk period immediately after starting ART, further supports the use of decentralized care in resource-constrained settings.

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Contribution of the authors: S.L.W.: wrote the first draft of article and conducted the first analyses.

H.G.: Designed the original trial and advised on trial procedures.

J.L.: Supervised the analyses.

B.A.: Co-ordinated the trial on the ground.

G.N.: Managed the data, contributed to data analyses.

J.B.: Implemented the trial.

A.C.: Designed the original trial and advised on trial procedures.

S.J.: Co-ordinated the original research programme, conceptualised the current article and supervised the writing and analyses.

All authors: All of the authors above commented on drafts of the article.

Conflicts of interest

The authors declare no conflict of interest.

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