Early initiation of antiretroviral therapy and associated reduction in mortality, morbidity and defaulting in a nurse-managed, community cohort in Lesotho.

Early initiation of antiretroviral therapy and associated reduction in mortality, morbidity and defaulting in a nurse-managed, community cohort in Lesotho

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Introduction: The latest WHO guidelines recommend initiating antiretroviral therapy (ART) at CD4 cell counts less than 350 cells/μl. However, donors and national governments are reluctant to support implementation owing to uncertainty regarding feasibility and relative benefit. Lesotho has supported earlier initiation since 2008. We assessed outcomes comparing early (CD4 cell counts >200 cells/μl) and late (CD4 cell counts ≤200 cells/μl) initiation.

Methods: We describe survival probability among patients initiating ART at CD4 cell counts 200 or less and more than 200 cells/μl and assess associations between baseline CD4 cell counts and mortality, morbidity, loss to follow-up and hospitalization using Cox regression adjusting for confounders identified a priori.

Results: Our analysis included 1177 patients; median age was 38 years and the majority (67%) were women. Median time on ART for the overall cohort was 506 days (interquartile range 396–608). Five hundred and thirty eight patients initiated ART at a CD4 cell count 200 cells/μl or less (interquartile range 54–160) and 639 patients initiated at CD4 cell count more than 200 cells/μl (interquartile range 238–321). In multivariate analysis, we found that patients initiating at CD4 cell count more than 200 cells/μl were 68% less likely to die (adjusted hazard ratio 0.32, 95% confidence interval 0.20–0.50), and 39% less likely to be lost to follow-up (adjusted hazard ratio 0.61, 95% confidence interval 0.43–0.87). Initiating ART at CD4 cell count more than 200 cells/μl was also associated with a 27% reduction in the rate of incident morbidity (adjusted hazard ratio 0.73, 95% confidence interval 0.65–0.82) and a 63% decreased rate of hospitalization (adjusted hazard ratio 0.37, 95% confidence interval 0.19–0.73).

Conclusion: Earlier initiation is feasible in a low resource, high HIV prevalence setting, and provides important benefits in terms of reduced mortality, morbidity, retention and hospitalization. Donors should fully support the implementation of the latest WHO recommendations.

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Introduction

In November 2009, the WHO revised its guidelines for antiretroviral therapy (ART) to recommend that ART should be started earlier: although previous WHO guidelines recommended that adolescent and adult patients should begin therapy when their CD4 cell count drops to or below 200 cells/μl [1], the latest recommendations, released in November 2009, recommend that patients should start ART at a CD4 cell count 350 cells/μl or less regardless of the presence or absence of clinical symptoms [2]. This recommendation is in line with guidelines for Western settings [3–5] and recent evidence from randomized trials [6] and cohort studies [7]. However, uncertainty remains around the feasibility and relative benefit of earlier initiation in resource-limited settings, and international donors are equivocal in their willingness to provide funding to support developing countries to provide treatment in line with the latest WHO recommendations [8]. As a consequence, implementation of the new WHO recommendations is varied. Malawi has announced a move towards initiation at less than 350 cells/μl but has yet to implement these recommendations; South Africa and Botswana's latest guidelines limit early initiation to specific patient groups [patients with tuberculosis (TB) or pregnant women]; Mozambique has implemented an intermediate threshold of 250 cells/μl; others, such as Ethiopia, have yet to revise their guidelines beyond 200 cells/μl [9].

Lesotho is a poorly resourced country in southern Africa with the third highest HIV prevalence in the world, with adult prevalence estimated at 23%. The country adopted a policy of earlier initiation of ART for adult patients with less than 350 cells/μl or WHO stage III/IV irrespective of CD4 cell count in late 2007 [10]. This provides an opportunity to assess the impact of the latest WHO recommendations in a routine programme setting. We assess outcomes comparing early (CD4 cell count >200 cells/μl) and late (CD4 cell count ≤200 cells/μl) initiation.

Methods

Study setting

In 2006, Médecins Sans Frontières (MSF) and the Ministry of Health and Social Welfare established a decentralized HIV/AIDS care and treatment programme at the primary healthcare level in the Scott catchment area, serving a population of approximately 200 000 people. ART services were provided from March 2006, and by the beginning of 2010 the programme had cumulatively enrolled a total of 6081 patients on ART. Treatment is provided across 14 primary care health centres and one district hospital, each staffed by nurses who initiate and manage ART with the support of a mobile clinical supervision team; complicated cases are referred to the 102-bed district hospital, with all transfers recorded in the health centre files [11]. After initiation, patients present at the health centres on a monthly basis for check up and ART refills.

Outcome ascertainment

Mortality out-of-facility was reported to clinic staff by relatives, village leaders, community health workers, and facility TB/HIV lay counselors who were responsible for defaulter tracing. Defaulter tracing was done within a few days of a patient missing an appointment such that early mortality among those lost to follow-up was documented within a month of a missed appointment. Incident morbidities were recorded in the clinic files and verified by clinicians and crosschecked against corresponding prescriptions. All hospitalizations documented from the clinic were crosschecked against hospital admission notes.

Data management and analysis

Data were recorded at each clinic by nurses in paper-based registers based on the WHO registers. Variables were extracted by a team of three clinicians and entered into an Access database, then exported into STATA (version 11) (StataCorp LP, Texas, USA) for analysis. All patients aged at least 5 years initiating ART from 1 January 2008 to 31 December 2008 were included in the analysis and followed until 31 December 2009. Patients were categorized according to their baseline CD4 cell count (defined as a CD4 cell count measure within 30 days of ART initiation) according to two groups: early initiation (>200 cells/μl) and late initiation (≤200 cells/μl). Baseline characteristics were described using medians and interquartile ranges (IQRs) for continuous variables and counts and percentages for categorical variables. We used Kaplan–Meier estimates to describe the cumulative probability of progression to death, morbidity, loss to follow-up (defined as missing an appointment for more than 90 days) and hospitalization according to CD4 cell count at initiation. Multivariate Cox proportional hazards models were used to estimate hazard ratios adjusting for potential confounders defined a priori using the following variables: sex (male or female), age (≤40 or >40 years), pregnant at initiation, TB at initiation and migrant worker (yes/no). Hazard proportionality was assessed by analysis of scaled Schoenfeld residuals. The potential effect of misclassification of mortality among patients lost to follow-up was assessed in a sensitivity analysis using a competing risks framework [12], and an analysis that considered all patients lost to follow-up as dead. All reported P values are exact and two-tailed, and for each analysis P less than 0.05 was considered significant.

The analysis was approved by MSF's independent Ethics Review Board.

Results

Our sample included 1228 patients. Median age was 38 years and the majority of patients (67%) were women. Median time on ART for the overall cohort was 506 days (IQR 396–608). Five hundred and thirty eight patients initiated ART late, at a CD4 cell count 200 cells/μl or less (IQR 54–160) and 639 patients initiated early, at CD4 cell count more than 200 cells/μl (IQR 238–321). Fifty-one patients had no baseline CD4 cell count recorded and were excluded from all further analyses. Patient characteristics are summarized in Table 1.

Rates of mortality, morbidity, hospitalization and loss to follow-up according to early or late ART initiation are described in Fig. 1a-d. In multivariate analysis of the risk of death according to CD4 cell count group at initiation, we found that patients initiating ART early were 68% less likely to die [aHR (adjusted hazard ratio) 0.32, 95% confidence interval (CI) 0.20–50] and 39% less likely to be lost to follow-up (aHR 0.61, 95%CI 0.43–0.87) compared with those initiating late (Table 2). The competing risk regression did not alter our mortality estimate in either magnitude or significance (subhazard ratio 0.33, 95%CI 0.21–0.52). In a second sensitivity analysis that treated all loss to follow-up as deaths, the overall mortality estimate was only marginally reduced (aHR 0.47, 95%CI 0.36–0.62). We also assessed the possibility that differences between groups were driven by high mortality among patients with a very low CD4 cell count in a sensitivity analysis that omitted patients who had a CD4 cell count 100 cells/μl or less; this analysis did not importantly affect the magnitude or direction of the observed difference in mortality (aHR 0.45; 95%CI 0.26–0.77).

In our multivariate analysis of risk of morbidity, we assumed that any disease event would represent an additional burden to the health service. Disease events included TB, cryptococcal meningitis, HIV malignancy, herpes simplex virus, toxoplasmosis, oesophageal thrush, oral thrush, *Pneumocystis carinii* pneumonia, diarrhoea, rash and respiratory tract infections. We found that initiating ART early was associated with a 27% reduction in the risk of incident morbidity (aHR 0.73; 95%CI 0.65–0.82).

Finally, in our multivariate analysis assessing risk of hospitalization, we found that earlier initiation was associated with a 63% decreased risk of hospitalization (aHR 0.37; 95%CI 0.19–0.73) (Table 2). TB was the main reason for hospitalization among those initiating late (accounting for 37% of hospital admissions vs. 21.4% for those initiating early).

Table 1. Baseline characteristics of patients initiating antiretroviral therapy.

	Total patients ($n=1228$)	Patients with CD4 $\leq$200 ($n=538$)	Patients with CD4 >200 ($n=639$)	Patients with missing baseline CD4 ($n=51$)
CD4, median (IQR)	212 (120–285)	111 (54–160)	280 (238–321)	–
Sex				
Female	801 (66.7%)	324 (60.2%)	470 (73.6%)	27 (52.9%)
Male	400 (33.3%)	214 (39.8%)	169 (26.5%)	24 (47.1%)
Age, median (IQR)	38.4 (30.3–48.5)	39.1 (30.8–47.3)	37.7 (29.4–49.7)	40.1 (29.1–53.1)
Pregnant at initiation*				
Yes	84 (10.2%)	26 (8.0%)	56 (11.9%)	2 (7.4%)
No	737 (89.8%)	298 (92.0%)	414 (88.1%)	25 (92.6%)
Migrant				
No	1079 (87.9%)	469 (87.2%)	565 (88.4%)	45 (88.2%)
Yes	149 (12.1%)	69 (12.8%)	74 (11.6%)	6 (11.8%)
Median duration of follow up (days), median (IQR)	506 (396–608)	487 (365–587)	522 (424–614)	640 (330–673)
Regimen				
Tenofovir	608 (49.6%)	272 (50.6%)	316 (49.5%)	20 (39.2%)
Zidovudine	275 (22.4%)	97 (18.0%)	169 (26.5%)	9 (17.7%)
Stavudine	345 (28.1%)	169 (31.4%)	154 (24.1%)	22 (43.1%)
TB at initiation				
No	1019 (83.0%)	409 (76.0%)	573 (89.7%)	37 (72.6%)
Yes	209 (17.0%)	129 (24.0%)	66 (10.3%)	14 (27.5%)

IQR, interquartile range; TB, tuberculosis.
*Denominator includes only women.

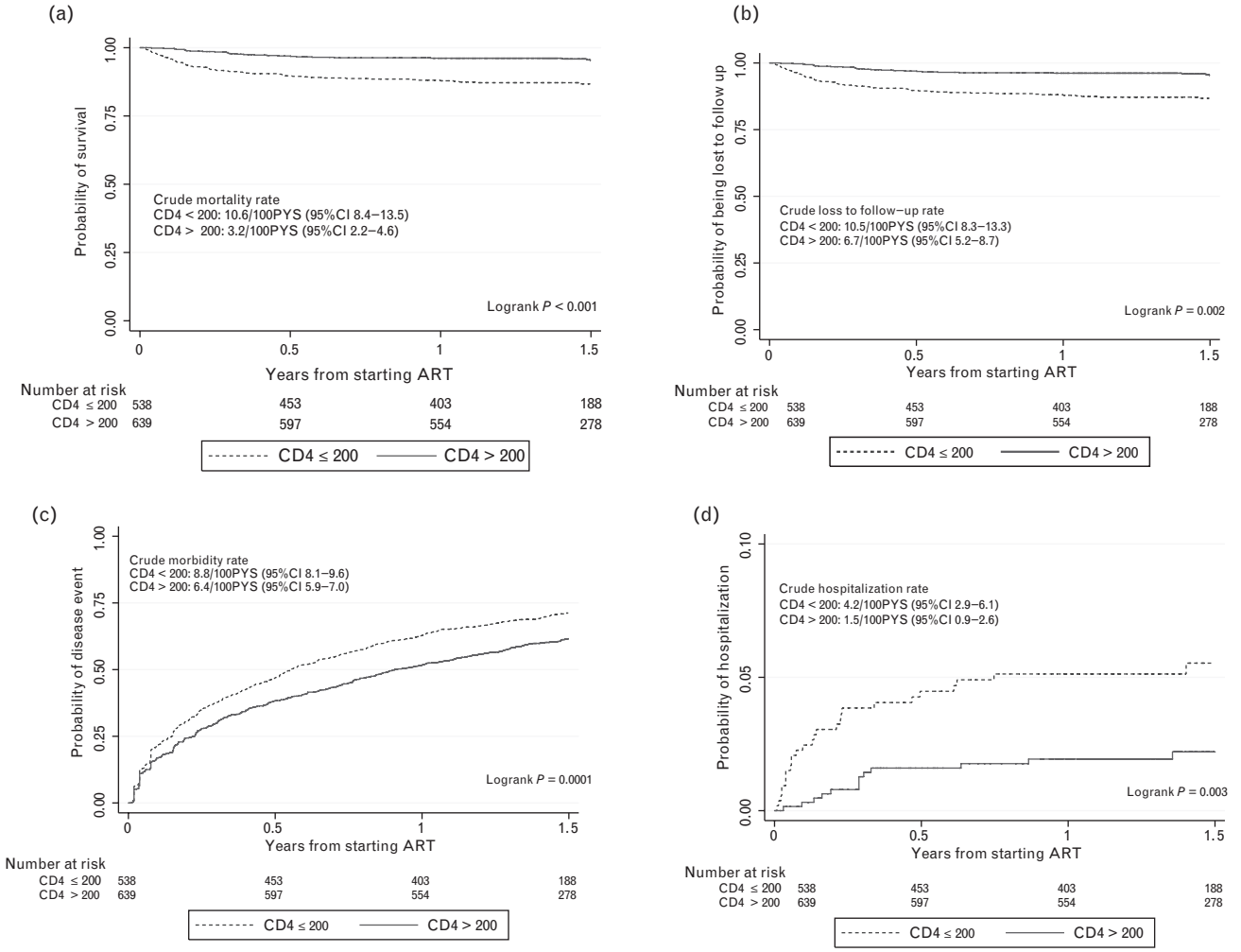

Fig. 1. (a-d) Kaplan–Meier plots showing the probability and rates of adverse events according to CD4 cell count group at ART initiation. ART, antiretroviral therapy; CI, confidence interval; PYS, person years.

Table 2. Multivariate analysis of risk of adverse outcomes comparing early and late antiretroviral initiation.

	Mortality		Loss to follow-up		Incident morbidity		Hospitalization	
	Adjusted hazards ratio (95%CI)	*P*	Adjusted hazards ratio (95%CI)	*P*	Adjusted hazards ratio (95%CI)	*P*	Adjusted hazards ratio (95%CI)	*P*
CD4 cell count group								
≤200 cells/μl	1		1		1		1	
>200 cells/μl	0.32 (0.20–0.50)	<0.001	0.61 (0.43–0.87)	0.006	0.73 (0.65–0.82)	<0.001	0.37 (0.19–0.73	0.004
Sex								
Female	1		1		1		1	
Male	0.90 (0.34–2.38)	0.83	0.37 (0.20–0.68)	0.001	0.74 (0.64–0.85)	<0.001	1.07 (0.56–2.06)	0.83
Age								
<40	1		1		1		1	
>40	1.68 (1.10–2.59)	0.017	0.52 (0.34–0.80)	0.002	1.04 (0.93–1.17)	0.16	1.44 (0.77–2.68)	0.25
Pregnant at initiation								
Yes	1		1		–	–	–	–
No	0.76 (0.30–1.97)	0.57	0.52 (0.34–0.80)	0.012				
Migrant								
No	–	–	1		–	–	–	–
Yes			2.77 (1.83–4.19)	<0.001				
TB at initiation								
Yes	–	–	–	–	1		1	
No					1.00 (0.85–1.18)	0.99	0.87 (0.38–2.00)	0.74
Schoenfelds p		0.54		0.50		0.18		0.50

– variable was not adjusted for in the model. CI, confidence interval; TB, tuberculosis.

Conclusion

Our study, using routinely collected clinic data from a nurse-led, community-based ART programme, provides further evidence of the benefits of early initiation at CD4 cell count less than 350 cells/μl for both the patients and health services.

The significant reduction in mortality and morbidity observed in our cohort is in line with data from other studies. A recent randomized trial conducted in Haiti found a four-fold difference in mortality and a two-fold difference in incident TB among patients who initiated ART early compared with those whose treatment was deferred [6], and an analysis of data from 18 treatment cohorts in Europe and North America found a substantial reduction in opportunistic infections and serious non-AIDS clinical events associated with early initiation (CD4 cell counts <250 vs. CD4 cell counts >350 cellsμl) [13]. The substantial mortality reduction we observed likely reflects the high prevalence of severe opportunistic infections in developing country cohorts, in particular TB [14], and the poorer availability of secondary care services common to many developing country settings. That TB was a major cause of hospitalization among those patients initiating ART late is of concern for both medical and public health reasons, and serves to highlight the importance of providing integrated TB and HIV services in settings like Lesotho where rates of coinfection are high [15].

We found that early initiation was associated with a substantial decrease in the risk of defaulting. This finding is consistent with findings from a recent systematic review [16], although some studies have found higher defaulting among patients initiating ART at higher CD4 cell counts [17,18] with the explanation put forward that patients value their medication less if they have not experienced illness prior to ART. We would suggest that this concern depends to a considerable extent on how patients are counseled at initiation and their understanding of the benefits of early initiation. Implementation of the new WHO guidelines should thus be accompanied by adapted adherence counseling for patients, as was the case in the Lesotho programme.

Recent modeling has suggested that earlier initiation of ART at CD4 cell count less than 350 cells/μl, while initially increasing the need for ART and thus costing more, will be cost effective over time owing to a reduction in illness. The benefits of early initiation found in our cohort were as good as or greater than the estimates used in this costing model, suggesting that early initiation may even be more cost effective than forecast [19]. A related advantage noted by programme staff was that the associated reduction in clinical complications was supportive of the nurse-led approach to ART delivery that is practiced in Lesotho and promoted by the WHO as a way to overcome the lack of doctors working at primary care level in resource-limited settings [20].

Our study is subject to several biases, in particular lead-time bias, which recognizes that a number of unseen AIDS-related mortality and morbidity will have occurred among patients not started at CD4 cell counts between 200 and 350 cells/μl. Statistical methods exist to allow for partial adjustment for lead-time bias by modeling the estimate of mortality among those unseen patients who would have died before reaching the threshold for late initiation [21]. We do not have reliable estimates for these events in our population so have not attempted such an adjustment. However, published estimates of mortality among untreated individuals with higher CD4 from elsewhere in southern Africa [22,23] suggest that such bias would likely lead to an underestimation of the true difference. Studies from Western settings that either adjusted for lead-time bias [24] or avoided it in the study design [25] report higher mortality compared with previous studies in similar populations. A second source of potential bias is related to misclassification of mortality owing to defaulting. In reports of vital status ascertainment among patients lost to follow-up it has been found that a substantial proportion are in fact dead [26]. We assessed this in sensitivity analyses and did not find an important difference to our mortality effect estimate, but recognize that such misclassification will exist. Given that loss to follow-up is higher in the group who initiated late, we can expect that this bias would also lead to an underestimation of effect. For both these reasons, the mortality reduction resulting from early initiation reported in this cohort can be considered as a conservative underestimation of the true difference. Another limitation, common to any observational study, is that even after adjustment for potential confounders, residual confounding may exist. Finally, it is important to note that data on hospitalization are context-specific. In our setting patients may live over half a day's travel from the hospital, and some are unable to afford the associated transport costs. Although we do not expect that such barriers are differential and so unlikely to affect the difference between CD4 cell count groups, hospitalization rates will likely be different in other settings where access to hospital care is less problematic.

In conclusion, far from overwhelming health services and increasing inequities as some have suggested [27], early initiation in Lesotho has been supportive of a simplified approach to delivering ART at the primary care level. The reduced risk of illness and death afforded by early initiation has translated into programme-level gains by resulting in a cohort of patients who require less intensive clinical support. This is of considerable benefit in resource-limited settings like Lesotho where human resources for health are inadequate and the majority of patient care is delivered by nurses. In this way, earlier initiation is not only important from a clinical perspective, but also supports broader

programme objectives in terms of service efficiencies and equitable access to treatment [28].

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K.H. and G.J. contributed to establish the cohort monitoring system. H.B. supervised the data collection. N.F. and K.K. did all analyses. N.F. wrote the first draft of the paper. All authors contributed to subsequent drafts and approved the final version.

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