

Effect of point-of-care CD4 cell count tests on retention of patients and rates of antiretroviral therapy initiation in primary health clinics: an observational cohort study

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See Comment page 1532

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Background Loss to follow-up of HIV-positive patients before initiation of antiretroviral therapy can exceed 50% in low-income settings and is a challenge to the scale-up of treatment. We implemented point-of-care counting of CD4 cells in Mozambique and assessed the effect on loss to follow-up before immunological staging and treatment initiation.

Methods In this observational cohort study, data for enrolment into HIV management and initiation of antiretroviral therapy were extracted retrospectively from patients' records at four primary health clinics providing HIV treatment and point-of-care CD4 services. Loss to follow-up and the duration of each preparatory step before treatment initiation were measured and compared with baseline data from before the introduction of point-of-care CD4 testing.

Findings After the introduction of point-of-care CD4 the proportion of patients lost to follow-up before completion of CD4 staging dropped from 57% (278 of 492) to 21% (92 of 437) (adjusted odds ratio [OR] 0·2, 95% CI 0·15–0·27). Total loss to follow-up before initiation of antiretroviral treatment fell from 64% (314 of 492) to 33% (142 of 437) (OR 0·27, 95% CI 0·21–0·36) and the proportion of enrolled patients initiating antiretroviral therapy increased from 12% (57 of 492) to 22% (94 of 437) (OR 2·05, 95% CI 1·42–2·96). The median time from enrolment to antiretroviral therapy initiation reduced from 48 days to 20 days ($p < 0·0001$), primarily because of a reduction in the median time taken to complete CD4 staging, which decreased from 32 days to 3 days ($p < 0·0001$). Loss to follow-up between staging and antiretroviral therapy initiation did not change significantly (OR 0·84, 95% CI 0·49–1·45).

Interpretation Point-of-care CD4 testing enabled clinics to stage patients rapidly on-site after enrolment, which reduced opportunities for pretreatment loss to follow-up. As a result, more patients were identified as eligible for and initiated antiretroviral treatment. Point-of-care testing might therefore be an effective intervention to reduce pretreatment loss to follow-up.

Funding Absolute Return for Kids and UNITAID.

Introduction

Despite advances in the expansion of access to antiretroviral therapy for HIV-positive patients in resource-limited settings, two-thirds of patients in need of treatment currently do not receive it.¹ Although worldwide funding for treatment in these settings has increased and the cost of delivery of antiretroviral therapy has decreased, the financial sustainability of current coverage and the expansion of treatment to new patients are still concerns.^{2–5} Accordingly, efforts to improve the efficiency and sustainability of antiretroviral therapy are increasing.^{6,7}

Low retention of patients undermines efforts to scale up antiretroviral therapy. Up to 45% of patients (median 22%) are lost to follow-up in the first year after initiation of treatment.^{8–13} The rate of loss between diagnosis of HIV infection and initiation of treatment is much higher than the first-year rate—up to 80%; losses are associated with distance travelled to the clinic, weak referral linkages, and high death rates.^{14–21} To find patients who are lost to follow-up can be difficult, costly, and ineffective,²² which highlights the need to prevent losses. Most losses happen between HIV diagnosis and CD4 cell staging,^{15–18} but few interventions have been reported.

We postulate that the use of point-of-care CD4 cell tests for immunological staging in antiretroviral therapy clinics will reduce loss to follow-up before the initiation of treatment. We did a study to assess the effect of point-of-care testing on loss to follow-up and time to antiretroviral therapy initiation in primary health clinics in Mozambique.

Methods

Study setting

This study was done at four public primary health clinics (Matola, Machava, Munhava, and Mafambisse), in the Maputo and Sofala provinces of Mozambique. The sites were selected from a range of settings; rural versus peri-urban, and high versus low numbers of patients. Voluntary and provider-initiated HIV tests, and antiretroviral therapy services were routinely available at all clinics.

All patients found to be HIV-positive at the clinics were referred for registration (enrolment) into HIV care services. After enrolment, patients were referred to the clinic's phlebotomy room for blood sampling. Before the introduction of point-of-care tests, blood samples were collected once a week and sent to nearby laboratories;

	Pre-POC CD4 test	Post-POC CD4 test	p value
All patients enrolled	534	487	..
Machava	137	142	..
Mafambisse	138	54	..
Matola	136	149	..
Munhava	123	142	..
Study participants*	492	437	..
Machava	132	135	..
Mafambisse	109	54	..
Matola	134	143	..
Munhava	117	105	..
Younger than 18 years (%)	20 (4.1%)	24 (5.5%)	0.32
Female (%)	331 (67.3%)	314 (71.9%)	0.13
Median (IQR) age			
Overall	30 (24–38)	29 (24–37)	0.21
Male	33 (27–42)	32 (27–40.5)	0.10
Female	28 (23–36)	28 (23–36)	0.98
Median (IQR) initial CD4 cell count per μL			
Overall	290 (157–458)	309 (133–472)	0.99
Male	259 (94–409)	260 (75–431.5)	0.40
Female	298 (170.5–462)	347.5 (174–532)	0.60
Median (IQR) CD4 cell count per μL at ART initiation			
Overall	165.5 (78–226)	132 (48–206.5)	0.85
Male	127.5 (34.5–220.5)	111.5 (35–212.5)	0.16
Female	168 (96–227)	136 (70–195)	0.53

POC CD4=point-of-care CD4 cell count. ART=antiretroviral therapy. *Excludes enrolled patients who transferred to another health facility during the study and patients younger than 12 months at the start of the study.

Table 1: Study population before and after the introduction of point-of-care CD4 testing at primary health clinics in Mozambique

patients were then asked to return for a staging visit after the test results were available. If eligible by CD4 cell count or clinical signs, patients usually had three counselling visits, and haemoglobin and liver function tests, before initiation of antiretroviral therapy.

Study design

This study was an observational cohort study. Demographic data, CD4 cell counts, and the dates of clinic visits, CD4 tests, and antiretroviral therapy initiation were extracted from clinic records. These data were used to calculate the time that enrolled patients took to proceed through each stage before treatment initiation and the associated loss to follow-up. Between September, 2009, and November, 2009—before the introduction of point-of-care testing—baseline data were collected for about 125 patients enrolled consecutively in 1 month at each clinic (or 2.5 months at Mafambisse because of low numbers of patients). Point-of-care CD4 testing (Alere Pima CD4, Waltham, MA, USA) was introduced at the clinics between March, 2010, and April, 2010. After a 5–6 week period to train staff, about 125 patients enrolling consecutively at each clinic in

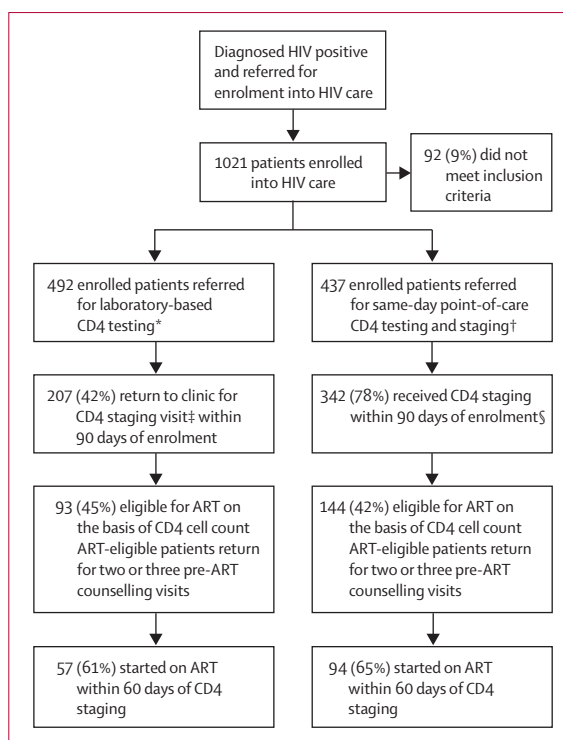


Figure 1: Flow of patients from enrolment to initiation of antiretroviral treatment

ART=antiretroviral therapy. *Steps included in conventional CD4 tests; patient returns for CD4 blood sampling draw, sample transported to the laboratory, test done at the laboratory, result sent to clinic. †Point-of-care CD4 testing occurred on the same day for 38% (130 of 342) of patients tested. ‡25% of patients were staged within 14 days without point-of-care CD4 testing. §90% of patients were staged within 5 days of point-of-care CD4 testing.

1 month were included in the study. The sample size was designed to detect a difference in loss to follow-up of at least 10% between the baseline and point-of-care cohorts, with the assumption of a 10–20% loss because of eligibility violations and incomplete patients' records. For point-of-care testing, enrolled patients were referred to the phlebotomy room where a laboratory assistant tested fingerprick blood samples. Patients with results were referred to consultation rooms to be staged and to have eligibility for antiretroviral therapy assessed, on the same day whenever possible. Subsequent steps to initiation of treatment and information given to patients did not change from baseline.

HIV-positive patients older than 1 year were eligible for inclusion in the analysis. Patients younger than 1 year were excluded throughout, because CD4 cell count was not a criterion for treatment in this age group, according to the Mozambique and WHO paediatric treatment guidelines at the time of the study.²³ Patients whose records suggested that they had transferred to another facility were also excluded. There were no other exclusion criteria. All extracted data were dissociated from personal identifiers and remained anonymous and unlinked throughout the study. To

minimise observer bias, standard procedures were used to extract information about patients and track data gaps. Records with implausible errors, for example impossible dates, were either corrected in consultation with the clinic or excluded from specific analyses. This study was reviewed and approved by the Mozambique National Health Bioethics Committee and a waiver of signed consent from patients was provided on the basis

of the anonymous, unlinked nature of data collection and analysis.

Data analysis

The primary study outcomes were completed CD4 staging and initiation of antiretroviral treatment of enrolled patients. Successful CD4 staging was defined as a staging visit to give the patient their CD4 results and assess

	Not lost	Lost	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p value*
Before staging					
Total	559	370			0.4572 (unadjusted)
Male	176 (62%)	108 (38%)	0.8970 (0.67-1.19)
Female	383 (59%)	262 (41%)	1.0
Age					0.0018
1-14 years	21 (66%)	11 (34%)	1.00 (0.44-2.30)	1.33 (0.55-3.24)	..
15-29 years	229 (53%)	201 (47%)	1.69 (1.10-2.60)	1.82 (1.14-2.90)	..
30-44 years	231 (67%)	116 (33%)	0.97 (0.62-1.51)	1.02 (0.63-1.64)	..
≥45 years	75 (66%)	39 (34%)	1.0	1.0	..
POC CD4 available?					<0.0001
Yes	345 (79%)	92 (21%)	0.21 (0.15-0.27)	0.20 (0.15-0.27)	..
No	214 (44%)	278 (57%)	1.0	1.0	..
Clinic					0.0930†
Matola	188 (68%)	89 (32%)	0.47 (0.314-0.696)	0.64 (0.41-0.98)	..
Machava	166 (62%)	101 (38%)	0.601 (0.405-0.891)	0.83 (0.54-1.27)	..
Munhava	124 (64%)	130 (36%)	0.781 (0.520-1.171)	0.99 (0.64-1.56)	..
Mafambisse	81 (50%)	82 (50%)	1.0	1.0	..
Between staging and ART					
Total	151	86			0.6885 (unadjusted)
Male	54 (62%)	33 (38%)	1.12 (0.65-1.93)
Female	97 (65%)	53 (35%)	1.0
Age					0.1493 (unadjusted)
1-14 years	3 (38%)	5 (63%)	4.69 (0.96-23.0)
15-29 years	53 (64%)	30 (36%)	1.60 (0.70-3.62)
30-44 years	64 (62%)	40 (38%)	1.76 (0.89-3.89)
≥45 years	31 (74%)	11 (26%)	1.0
POC CD4 available?					0.1196
Yes	94 (65%)	50 (35%)	0.84 (0.49-1.45)	2.84 (0.76-10.56)	..
No	57 (61%)	36 (39%)	1.0	1.0	..
Clinic					0.0118
Matola	55 (72%)	21 (28%)	0.33 (0.13-0.82)	0.34 (0.13-0.88)	..
Machava	57 (69%)	26 (31%)	0.39 (0.16-0.96)	0.46 (0.18-1.16)	..
Munhava	27 (52%)	25 (48%)	0.79 (0.31-2.04)	1.03 (0.38-2.80)	..
Mafambisse	12 (46%)	14 (54%)	1.0
Time from enrolment to result (days)					
0-28	113 (62%)	68 (38%)	1.27 (0.67-2.40)	2.75 (1.10-6.88)	0.0311‡
≥29	38 (68%)	18 (32%)	1.0	1.0	..
Time from enrolment to result (days) × time period					0.0222
0-28, with POC	87 (66%)	44 (34%)	..	0.17 (0.04-0.78)	..
≥29, with POC	7 (54%)	6 (46%)	..	1.0	..
CD4 cell count per µL					0.9780 (unadjusted)
<100	67 (64%)	38 (36%)	0.99 (0.58-1.69)
≥100	84 (64%)	48 (36%)

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	Not lost	Lost	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p value*
(Continued from previous page)					
Between enrolment and ART					
Total	473	456			0.8199 (unadjusted)
Male	143 (50%)	141 (50%)	1.03 (0.78-1.37)
Female	330 (51%)	315 (49%)	1.0
Age					0.1056§
1-14 years	16 (50%)	16 (50%)	1.28 (0.58-2.81)	1.56 (0.68-3.56)	..
15-29 years	199 (46%)	231 (54%)	1.49 (0.98-2.25)	1.50 (0.96-2.34)	..
30-44 years	191 (55%)	156 (45%)	1.05 (0.68-1.60)	1.08 (0.69-1.70)	..
≥45 years	64 (56%)	50 (44%)	1.0	1.0	..
POC CD4 available?					<0.0001
Yes	295 (68%)	142 (33%)	0.27 (0.21-0.36)	0.27 (0.21-0.36)	..
No	178 (36%)	314 (64%)	1.0	1.0	..
Clinic					0.0104
Matola	167 (60%)	110 (40%)	0.46 (0.31-0.68)	0.59 (0.39-0.89)	..
Machava	140 (52%)	127 (48%)	0.63 (0.43-0.94)	0.81 (0.53-1.23)	..
Munhava	99 (45%)	123 (55%)	0.87 (0.58-1.31)	1.06 (0.69-1.64)	..
Mafambisse	67 (41%)	96 (59%)	1.0	1.0	..

POC CD4=point-of-care CD4 cell count. ART=antiretroviral therapy. *p values are adjusted except when the independent variable was not statistically significant, as stated. †Unadjusted p=0.0009. ‡Unadjusted p=0.4605. §Unadjusted p=0.0196.

Table 2: Results from a multivariable logistic regression analysis of the effect of independent variables on loss to follow-up before CD4 staging and initiation of antiretroviral therapy at primary health clinics in Mozambique

eligibility for treatment within 90 days of enrolment. Eligibility was defined by a documented CD4 cell count of fewer than 250 cells per μL for patients aged 15 years and older, fewer than 350 cells per μL for patients aged 4-14 years, and fewer than 750 cells per μL for patients aged 1-3 years, in accordance with the national guidelines for eligibility in Mozambique. Loss to follow-up before CD4 staging was defined as failure to complete a CD4 staging visit. Treatment initiation was defined as documentation of dispensed antiretroviral drugs within 60 days of a staging visit and patients were considered lost to follow-up if they had not started treatment during this period. Preliminary data collected in 12 months before the study at these sites showed that 87% of staging occurred within 90 days of enrolment and 86% of treatment initiation occurred within 60 days of staging. The duration and associated loss to follow-up were calculated for the following pretreatment stages; from enrolment to CD4 staging visit, from staging to treatment initiation for eligible patients, and from enrolment to initiation of antiretroviral treatment.

We compared the study outcomes for enrolled patients before and after the introduction of point-of-care testing using the χ^2 test for nominal variables and the Mantel-Haenszel χ^2 test for ordinal data, in a bivariate analysis. A multivariable logistic regression was then used to estimate the odds ratio and 95% CIs for the effect of point-of-care testing adjusted for only those factors that were identified to be significant from the bivariate analysis. We compared the time from enrolment to initiation of antiretroviral treatment before and after the introduction of point-of-care testing using the Kaplan-

Meier method. All data were analysed with STATA (version 10.0) software.

Role of the funding source

UNITAID provided funding for test instruments and supplies. Absolute Return for Kids supported test supplies, and study operational and human resource costs. The sponsors of the study had no role in study design or data collection, analysis, or interpretation. The corresponding author had access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

For the cohort before the introduction of point-of-care CD4 testing, a total of 534 patients were enrolled at the four sites (table 1). Of these patients, 492 (92%) were included in the analysis (figure 1). The remainder were excluded because they were younger than 12 months ($n=31$, 6%) or were transferred to another facility ($n=11$, 2%). After the implementation of point-of-care testing, a total of 487 patients were enrolled at the four sites. Of these patients, 437 (90%) were included in the analysis and the remainder were excluded because they were younger than 12 months ($n=44$, 9%) or were transferred to another facility ($n=6$, 1%). There were no significant differences in sex, median age, proportion of patients younger than 18 years, or CD4 cell count between the study participants before and after the introduction of point-of-care testing (table 1). Additionally, there were no differences in these variables, or in rates of loss to follow-up and initiation of

	Pre-POC CD4 test	Post-POC CD4 test
Total	492	437
Male	161 (33%)	123 (28%)
Female	331 (67%)	314 (72%)
Age (%)		
1–14 years	12 (3%)	20 (5%)
15–29 years	232 (47%)	198 (46%)
30–44 years	181 (37%)	166 (38%)
≥45 years	65 (13%)	49 (11%)
Clinic (%)		
Matola	134 (27%)	143 (33%)
Machava	132 (27%)	135 (31%)
Munhava	117 (24%)	105 (24%)
Mafambisse	109 (22%)	54 (12%)
Lost to follow-up between enrolment and CD4 staging		
Yes	278 (57%)	92 (21%)
No	214 (44%)	345 (79%)
CD4 level ≤ART threshold		
Yes	93 (19%)	144 (33%)
No	399 (81%)	293 (67%)
Number of visits for initial CD4 test (%)		
No CD4 recorded	246 (50%)	91 (21%)
One	140 (29%)	240 (55%)
Two or more	106 (22%)	106 (24%)
Lost to follow-up between CD4 staging and ART initiation		
Yes	36 (39%)	50 (35%)
No	57 (61%)	94 (65%)
Initiated ART		
Yes	57 (12%)	94 (22%)
No	435 (88%)	343 (78%)
Median (IQR) days from enrolment to test	10 (6–16)	1 (0–3)
Median (IQR) days from test to result	17.5 (9–29)	0.5 (0–9)
Median (IQR) days from enrolment to result	32 (19–64)	3 (0–13)
Median (IQR) days from result to ART initiation	5 (0–19)	6 (0–22)
Median (IQR) days from enrolment to ART initiation	48 (34–80)	20 (10–31)

POC CD4=point-of-care CD4 cell count. ART=antiretroviral therapy.

Table 3: Study population characteristics before and after the introduction of point-of-care CD4 tests at primary health clinics in Mozambique

antiretroviral treatment, between patients enrolled at the four sites 1 year before this study and those enrolled in the study before the introduction of point-of-care testing. The patients' records were almost complete, with less than 0.6% of patients missing demographic data and less than 5% missing dates of steps in the pretreatment process. The characteristics (age, sex, CD4 cell count, and site) of patients with missing data did not differ significantly from those with complete records. A small number of patients, 7 (1.4%) in the baseline cohort and 3 (0.7%) in the point-of-care cohort, started antiretroviral therapy without a CD4 cell count—these patients were not classed as lost to follow-up in our analysis.

The introduction of point-of-care CD4 tests was followed by a significant reduction in loss to follow-up. Total losses

between enrolment and antiretroviral therapy initiation dropped from 64% to 33% (adjusted odds ratio [OR] 0.27, 95% CI 0.21–0.36) (table 2), a difference of 31.3% (95% CI 25.2–37.5). This effect was due mainly to a reduction in loss to follow-up before completion of CD4 staging, which decreased from 57% to 21% (OR 0.2, 95% CI 0.15–0.27) (table 2 and table 3), a difference of 35.5% (95% CI 29.6–41.3). After implementation of point-of-care CD4 testing the proportion of enrolled patients who initiated ART increased from 12% to 22% (OR 2.05, 95% CI 1.42–2.96), a difference of 9.9% (95% CI 5.2–14.6) (figure 2). Loss to follow-up between staging and antiretroviral therapy initiation for treatment-eligible patients did not change significantly after the introduction of point-of-care CD4 testing (table 2).

After the introduction of point-of-care CD4 tests, the median time from enrolment to antiretroviral treatment initiation dropped from 48 days (IQR 34–80) to 20 days (IQR 10–31, $p < 0.0001$). The most substantial reduction was in the median time between enrolment and completion of CD4 staging, which dropped from 32 days (IQR 19–64) to 3 days (IQR 0–13), whereas the median time between staging and ART initiation did not change significantly. Before the introduction of point-of-care CD4 tests, to obtain a CD4 result involved several steps each with delays. To have samples drawn and CD4 tests completed at the laboratory took a median of 10 days (IQR 6–16) after enrolment. The staging visit, in which the patient received the test result, took an additional 17.5 days (IQR 9–29). Point-of-care CD4 testing was done on the same day as enrolment for 30% of patients and on the following day for an additional 22%. 90% of those given point-of-care CD4 tests were tested within 5 days of enrolment. Once tested, 50% of patients then completed their staging on the same day as they were tested. However, only 21% of enrolled patients completed both their point-of-care CD4 testing and their staging consultation on the same day as enrolment. There was no significant difference in loss to follow-up between staging and ART initiation for patients who successfully completed their CD4 test and staging the same day as enrolment compared with those who did not (OR 2.2, 95% CI 0.96–5.06), although the sample size of initiated patients who did not complete their CD4 test and staging on the same day was small ($n=35$, 8%). Additionally, there was no significant difference in loss to follow-up between staging and antiretroviral therapy initiation for patients with low CD4 cell counts (<100 cells per μL), compared with those with high counts (100–250 cells per μL) (OR 0.69, 95% CI 0.32–1.48).

Before point-of-care CD4 testing, ART-eligible patients who completed CD4 staging within 14 days of enrolment were as likely to be lost between CD4 staging and ART initiation as patients who completed staging over longer periods (OR 0.66, 95% CI 0.2–2.19). The number of visits that eligible patients made to complete CD4 staging did not affect their success in initiation of antiretroviral

therapy (OR 0.57, 95% CI 0.25–1.33). Loss to follow-up was not influenced by sex with or without point-of-care CD4 tests (table 2). Older patients were less likely to be lost before completion of staging than younger patients; particularly, loss to follow-up was higher in the age group 15–29 years than in other age groups both before and after the introduction of point-of-care CD4 tests.

Discussion

The introduction of point-of-care CD4 tests was associated with increased retention of patients and increased ART initiation. The improvements were probably because of a reduction in the time taken to stage patients—from more than 1 month to 3 days—which reduced the opportunities for loss to follow-up and increased the number of treatment-eligible patients who progressed to treatment. For some patients, a point-of-care CD4 test might have simply postponed loss to follow-up to a later time; longer-term studies are needed to assess this possibility. Nevertheless, clinics could counsel and treat patients who would have been lost to follow-up earlier, which might help to reduce subsequent attrition.

The revised WHO antiretroviral therapy guidelines²⁴ for resource-limited settings recommend ART initiation at a CD4 cell count of 350 cells per μL . Untreated patients with CD4 cell counts below this value are at high risk of HIV-related morbidity and mortality,^{19,25} and patients who start treatment closer to this threshold have decreased mortality with ART.^{20,26} However, median CD4 cell counts at ART initiation are low; for example, median CD4 cell count was 136 cells per μL in a study of eight sub-Saharan countries.²⁷ Point-of-care CD4 tests might enable more patients to initiate ART with cell counts closer to 350 cells per μL by increase of the number of patients who are successfully staged and by reduction of pretreatment loss to follow-up. Modelling results show that expansion of access to ART initiation below CD4 cell counts of 350 cells per μL is cost-effective and provides a substantial survival advantage compared with other WHO ART recommendations.²⁸ In our study, if the threshold of 350 cells per μL had been used for patients aged older than 15 years the proportion of patients eligible for ART would have increased from 45% to 64% in the baseline cohort, and from 42% to 59% in the point-of-care CD4 cohort.

The retrospective, observational, and non-randomised nature of our study is a limitation and hence the results should be interpreted with caution. We took steps to reduce sources of bias; however, our findings might have been subject to confounders for which we did not control in our adjusted analysis. Although the study was done at clinics with well organised data management systems, inaccurate records might have affected the study outcomes. The time between study cohorts might have allowed secular changes, for example in clinic operations or the population of patients, to contribute to the observed outcomes. However, characteristics of patients, enrolment rates, and clinic procedures (other than point-of-care CD4

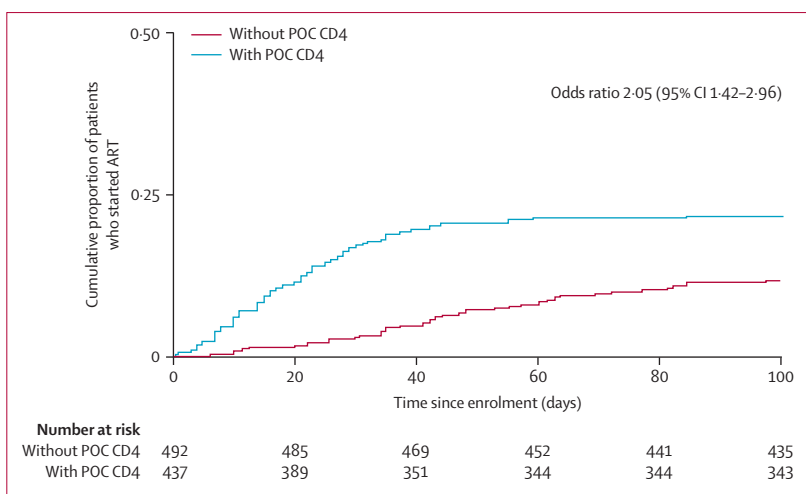


Figure 2: Kaplan-Meier estimate of time from enrolment into HIV care to initiation of antiretroviral therapy before and after the use of POC CD4 for immunological staging at primary health care clinics ($p=0.0001$) ART=antiretroviral therapy. POC CD4=point-of-care CD4 cell count.

tests) were similar in both study groups. Patients' characteristics and rates of loss to follow-up and ART initiation at these clinics had not changed in the 12 months before the start of the study. The study clinics were broadly representative of health centres in Mozambique in terms of numbers of patients, staff structures, clinic systems, and HIV management algorithms (based on WHO ART guidelines, which are widely adopted in resource-limited countries). Baseline loss to follow-up was also similar to that reported in other sub-Saharan countries.^{15–21} A study in Mozambican primary health clinics reported a 23% loss to follow-up between enrolment and CD4 staging, and 69% between staging and initiation.¹⁸ Studies in South Africa reported 37% loss to follow-up between diagnosis and CD4 staging,²¹ and 39% loss to follow-up between staging and ART initiation.¹⁷ The study clinics might not have been representative of rural health centres because only one site (Mafambisse) was rural, and they were not representative of clinics with on-site conventional CD4 laboratories, which might deliver test results quickly and have less loss to follow-up than clinics without these facilities. Lastly, the new point-of-care CD4 test device might have misclassified eligibility for ART. However, this technology had been previously assessed in Mozambique and found to be accurate compared with laboratory-based CD4 tests.²⁹ Misclassification at the 250 cells per μL threshold was less than 6%, mainly in favour of ART, which is similar to misclassification by conventional laboratory CD4 cell count instruments.

Point-of-care CD4 tests are not a solution for all causes of pretreatment loss to follow-up. Although our study did not assess patient losses between diagnosis and enrolment into HIV care, another study in Mozambique estimated that about 44% of diagnosed patients did not enrol for care.¹⁸ Offering of a point-of-care CD4 test immediately after HIV diagnosis might help to reduce this loss.

Panel: Research in context**Systematic review**

We searched the PubMed and Cochrane Library databases up to Aug 8, 2011, for full studies reporting randomised controlled trials, cross-sectional and observational cohort studies, systematic reviews, or meta-analyses published in English using the search terms “HIV loss-to-follow-up”, “HIV retention”, “HIV antiretroviral loss-to-follow-up”, “HIV antiretroviral retention” and “point-of-care CD4”. Our search identified no studies or meta-analyses describing the effect of point-of-care CD4 tests on loss to follow-up before or during HIV antiretroviral treatment. Although loss to follow-up of patients after the initiation of antiretroviral treatment has been well studied and reviewed in recent meta-analyses, pretreatment loss to follow-up has been less well studied. Observational studies from South Africa, Mozambique, Uganda, and Ethiopia, and one systematic review were available but no meta-analyses have been published. These studies report loss to follow-up at various stages between HIV diagnosis and the initiation of antiretroviral treatment in similar settings to our study, and suggest that loss to follow-up was large between HIV diagnosis and enrolment for HIV care, between enrolment and CD4 staging, and between staging and treatment initiation. On average, about 30–60% of patients were lost during each of these steps, though these estimates are not standardised. The estimates of loss to follow-up in our study were within this range.

Interpretation

Point-of-care CD4 tests reduce loss of patients to follow-up between enrolment and immunological staging, one of the major sources of pretreatment loss to follow-up. Patients receiving point-of-care CD4 staging also begin antiretroviral therapy faster than those undergoing conventional CD4 tests. These findings need confirmation by studies in other settings, as well as assessment of longer-term benefits and cost-effectiveness. Nevertheless, these results suggest that point-of-care CD4 tests should be more widely implemented as an important method to both increase access to treatment and improve the efficiency of antiretroviral therapy delivery.

Second, even after receiving point-of-care CD4 tests, 21% of patients failed to complete staging, a loss of limited clinic and diagnostic resources. For those staged, the process was not efficient in our study; 79% of patients failed to complete their CD4 test and staging on the same day as enrolment. Some patients might have refused to be tested and logistic challenges might have also had a role. Enrolment, point-of-care CD4 test, and staging were conducted separately; patients had to move between three different locations. Transit and waiting times between rooms might have provided a reason for some patients to defer their test or staging. Integration of HIV test, enrolment, CD4 test, and staging into a single consultation, improved counselling after HIV-screening and enrolment,

improved clinic workflow, and better staffing to accommodate spikes in numbers of patients might increase the effect of point-of-care diagnostics on retention and treatment initiation. Lastly, point-of-care CD4 tests did not improve the proportion of staged and antiretroviral therapy-eligible patients who initiated treatment, despite the possibility that access to improved testing services and prompt staging might encourage patients to continue accessing services and initiate treatment. The reasons for this lack of effect are unclear but might be related to the fact that patients had to visit the clinic an additional two or three times to complete antiretroviral therapy preparation, counselling, and other laboratory tests. Other initiatives are needed to mitigate loss to follow-up in these patients. Previous studies have identified factors contributing to pretreatment loss to follow-up, such as distance to the clinic, mechanism of referral of patients, non-disclosure of HIV status to family members, unemployment, and sex.^{15–17} Interventions for post-treatment loss to follow-up—which is also related to the direct and indirect costs to the patient of access to care^{30–33}—might be useful for pretreatment patients, for example education, transport, and food subsidies or tracing of patients in the community (eg, via mobile phones), but their cost-effectiveness should be assessed before broad implementation. Streamlined counselling and point-of-care chemistry and haematology tests to reduce the length and number of visits between staging and initiation might also be effective.

In conclusion, we have described the use of a diagnostic test intervention to substantially improve antiretroviral therapy-related retention and access to treatment. Our study is also one of the first to describe the use of a diagnostic test to improve HIV treatment efficiency (panel). Point-of-care CD4 testing directly targets one of the primary causes of loss to follow-up and empowers peripheral clinics in the management of their patients. Reduction of loss to follow-up with point-of-care CD4 testing might also help to increase the likelihood that patients start treatment at higher CD4 cell counts, thereby reducing one of the largest causes of HIV-related mortality. Our study shows that point-of-care diagnostics have the potential to bring substantial benefit to health systems in resource-limited settings, especially in primary health care, which faces myriad challenges in the provision of basic medical care.

Contributors

IVJ, NES, JDL, JIQ, BMR, and TFP oversaw the design and conduct of the study and participated in writing the report. ERA and PLC oversaw the CD4 tests and data management at the clinic sites and monitored quality control. IVJ, NES, BMR, JIQ, JDL, and TFP oversaw the collection and analysis of data, and interpretation of results.

Conflicts of interest

We declare that we have no conflicts of interest.

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