

Effect of point-of-care CD4 cell count results on linkage to care and antiretroviral initiation during a home-based HIV testing campaign: a non-blinded, cluster-randomised trial



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Summary

Background HIV disease staging with referral laboratory-based CD4 cell count testing is a key barrier to the initiation of antiretroviral treatment (ART). Point-of-care CD4 cell counts can improve linkage to HIV care among people living with HIV, but its effect has not been assessed with a randomised controlled trial in the context of home-based HIV counselling and testing (HBCT).

Methods We did a two-arm, cluster-randomised, controlled efficacy trial in two districts of western Kenya with ongoing HBCT. Housing compounds were randomly assigned (1:1) to point-of-care CD4 cell counts (366 compounds with 417 participants) or standard-of-care (318 compounds with 353 participants) CD4 cell counts done at one of three referral laboratories serving the study catchment area. In each compound, we enrolled people with HIV not engaged in care in the previous 6 months. All participants received post-test counselling and referral for HIV care. Point-of-care test participants received additional counselling on the result, including ART eligibility if CD4 was less than 350 cells per μL , the cutoff in Kenyan guidelines. Participants were interviewed 6 months after enrolment to ascertain whether they sought HIV care, verified through chart reviews at 23 local clinics. The prevalence of loss to follow-up at 6 months (LTFU) was listed as the main outcome in the study protocol. We analysed linkage to care at 6 months (defined as 1-LTFU) as the primary outcome. All analyses were by intention to treat. This trial is registered at ClinicalTrials.gov, number NCT02515149.

Findings We enrolled 770 participants between July 1, 2013, and Feb 28, 2014. 692 (90%) had verified linkage to care status and 78 (10%) were lost to follow-up. Of 371 participants in the point-of-care group, 215 (58%) had linked to care within 6 months versus 108 (34%) of 321 in the standard-of-care group (Cox proportional multivariable hazard ratio [HR] 2.14, 95% CI 1.67–2.74; log rank $p < 0.0001$).

Interpretation Point-of-care CD4 cell counts in a resource-limited HBCT setting doubled linkage to care and thereby improved ART initiation. Given the substantial economic and logistic hindrances to providing ART for all people with HIV in resource-limited settings in the near term, point of care CD4 cell counts might have a role in prioritising care and improving linkage to care.

Funding US Centers for Disease Control and Prevention.

Introduction

The benefits of antiretroviral therapy (ART) for HIV control are now well documented by the Strategic Timing of AntiRetroviral Treatment (START), TEMPRANO, and HPTN052 trials. After a long debate on when to initiate ART, these trials prompted WHO to issue in 2015, HIV treatment guidelines recommending treatment for all, regardless of CD4 lymphocyte count. The Vancouver Consensus Statement at the 2015 International AIDS Society Conference sought the political will and resources needed to meet the updated WHO guideline and related UNAIDS 90-90-90 by 2020 goal of diagnosing infections among 90% of people infected with HIV, initiating 90% of those diagnosed on ART, and achieving viral suppression in 90% of those who initiate ART.

The magnitude of the challenge ahead is formidable.¹ Although about 18 million people living with HIV are now receiving ART, the 2016 UNAIDS update estimated

that fewer than half of people living with HIV know their HIV status, 46% receive ART, and fewer than 40% have suppressed viral loads. The delays and hurdles along the HIV care continuum continue to result in late presentation for ART enrolment by most people with HIV, especially in low-resource settings. Bridging such a wide gap to meet UNAIDS 90-90-90 goals will require strategies beyond further expansion of the clinic-based infrastructure, such as community-based HIV care delivery, particularly early in the HIV care continuum. The median CD4 cell count at first presentation to HIV care or at ART initiation in the traditional clinic-based HIV care system has not improved over the last decade in sub-Saharan Africa. The value has remained near 250 cells per μL at linkage to HIV care and 150 cells per μL at ART initiation,² indicating advanced HIV disease, and the long duration with unsuppressed viral load and its attendant transmission potential.

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Research in context

Evidence before this study

HIV burden remains high and its control is quite poor in sub-Saharan Africa. This might be a result of barriers in the early stages of the care continuum. Despite impressive expansion of clinic-based national antiretroviral therapy (ART) programmes, UNAIDS estimates that nearly half the 37 million people living with HIV do not know their HIV infection status, and less than one-third have a suppressed viral load. Expansion of community-based HIV care programmes is a key strategy in identifying people infected with HIV. Once identified as HIV-infected, linkage to HIV care and ART initiation are crucial to realising the benefits of HIV viral load suppression. In 2015, WHO recommended initiating ART soon after diagnosis for all people with HIV. In most resource-constrained settings, however, people with more advanced immune suppression, typically based on CD4 cell count criteria, are prioritised for initiation of ART. For people with HIV, counselling on more advanced HIV disease is a powerful motivator for initiating ART, but often occurs only after disease staging steps in the care continuum after diagnosis. We searched PubMed for randomised controlled trials aimed at improving linkage to care, with the terms “point of care”, “point-of-care”, “CD4 testing”, “community-based HIV testing”, “linkage to care”, “continuum of care”, and “HIV care cascade”, from Jan 1, 2000, to Dec 31, 2015, with no language restrictions. We found three studies that showed improved linkage to care after HIV diagnosis: one with a case management approach, the second a post-test counselling combined with home visits, and

the third a point-of-care CD4 cell count test in clinic settings. We found an observational study with at home CD4 cell counts but it lacked a comparator group. No randomised controlled trials from low-resource settings have assessed interventions to improve linkage to care in combination with home-based counselling and testing (HBCT). Community-based HIV testing and care is an under-used strategy for reaching the UNAIDS 90-90-90 goals.

Added value of this study

To our knowledge, our randomised trial is the first to show improvement in linkage to care with point-of-care HBCT. In this rural Kenyan setting, we observed a near doubling in linkage to care within 6 months of HIV testing; 58% of those linked to care and eligible for ART (ie, CD4 count <350 cells per μL) initiated ART in the point-of-care group versus 34% in the standard-of-care group. We used lay operators for point-of-care testing, and showed the potential of combining HBCT with CD4 cell counts and counselling on ART eligibility. This trial confirms the benefit of completing most of the steps before starting ART outside the clinic, thus addressing a crucial barrier in the clinic-based HIV care continuum.

Implications of all available evidence

National ART programmes should do operational research on how to integrate point-of-care CD4 cell counts into HIV testing programmes. This approach is crucial to linking people with HIV to care, meeting the UNAIDS 90-90-90 goals, and realising the full potential of ART to save lives and prevent transmission.

The sum of national, bilateral, and multilateral global resources committed to HIV control falls far short of the fiscal need for universal ART access.³ Access to cost-effective, simple, and robust viral load monitoring in many resource-limited settings like Kenya remains a challenge. CD4 testing remains a practical and necessary marker for assessment of the baseline status of HIV infection before ART initiation. Unfortunately, the typical laboratory-based CD4 testing is encumbered by multiple steps prone to delay. First, a person with HIV must register for HIV care. A blood specimen is then collected, transported to, and processed at a reference laboratory. The result must be conveyed to the patient's chart in the clinic, and finally, the patient must return to the clinic. The resultant delays probably contribute to the observed high mortality during the first year after engaging in HIV care.⁴ Several point-of-care CD4 count devices have been developed to overcome this problem. In one randomised trial⁵ and two observational studies in Africa,^{6,7} use of such devices to provide CD4 cell counts for people with HIV has resulted in increased rates of linkage to care. However, none of these studies showed the effect on a large scale with lay operators in field conditions associated with home-based HIV counselling and testing (HBCT) campaigns, which was an opportune setting for assessing the effect of point-of-care CD4 testing among people not engaged in HIV care.

In Kenya, Nyanza province has the highest HIV prevalence and incidence.⁸ The Kenya Medical Research Institute (KEMRI), in cooperation with the US Centers for Disease Control and Prevention (CDC), operates a health and demographic surveillance system in western Kenya's Nyanza province. With HIV prevalence rates of 24.8% and 19.9%, Siaya and Kisumu districts in this rural province have a HIV burden nearly four times that of Kenya's average of 5.6%.⁸ We have previously shown that results of the PIMA CD4 point-of-care device, when used by lay operators with capillary blood spots, had 95% accuracy compared with venous samples when tested by laboratory technicians using the gold standard FACSCount laboratory-based CD4 assay.⁹ In the context of a large HBCT campaign in Nyanza, we did a study to determine whether provision of CD4 count results with a point-of-care device improved linkage to care among people living with HIV compared with the laboratory-based standard-of-care testing.

Methods

Study design and participants

We did a non-blinded, controlled, cluster-randomised trial with randomisation at the level of housing compounds. A cluster was defined as a housing compound in Siaya and Kisumu districts and comprised multiple related

nuclear family dwellings around a courtyard. The population under surveillance included 220 000 people, served by 23 health-care facilities. HIV care is integrated into primary care and supported by three referral laboratories, where routine CD4 testing is done with FACSCount (Becton Dickinson Biosciences, Franklin Lakes, NJ, USA). We enrolled trial participants between July 1, 2013, and Feb 28, 2014. Trial staff worked with HBCT staff to assign compounds randomly to receive either point-of-care CD4 cell counts at home (PIMA; Alere, Waltham, MA, USA) after confirmatory positive rapid HIV testing as per Kenya's national algorithm or standard-of-care CD4 cell counts at one of three referral laboratories serving the study catchment area. Referral for standard-of-care testing was generated by the HBCT staff at the referral laboratories on a walk-in basis, without compensation as per routine. Participants of all ages were eligible for enrolment if they tested positive for HIV during HBCT, and denied receipt of HIV care for the previous 6 months. Adults gave informed consent before enrolment, in their choice of Luo, Swahili, or English, and children younger than 18 years gave their assent along with parental consent for study participation.

Randomisation and masking

Each compound in the areas targeted for the HBCT campaign was randomly assigned (1:1) to a trial group using a unique numeric compound identifier generated by the health and demographic surveillance system, with odd numbers assigned to the point-of-care group and even numbers assigned to the standard-of-care group. Whereas randomisation was at the compound level, eligibility determination, refusal, and enrolment occurred at the participant level. We used cluster randomisation to ensure that all people living with HIV in a compound received CD4 testing by the same method. Compounds were randomly assigned before visiting them to plan the field deployment of point-of-care testing devices and lay health workers. Participants were masked to their CD4 cell count method allocation until after the positive HIV test result had been delivered.

Procedures

All participants received standard dual rapid testing with the Determine HIV-1/2 rapid test (Alere, Waltham, MA, USA) as the screening test and the Uni-Gold HIV rapid test (Trinity Biotech, Wicklow, Ireland) as the confirmatory test. Participants received standard, scripted post-test counselling and referral for HIV care. HBCT staff notified trial staff by mobile phone of individuals meeting these two eligibility criteria for potential enrolment. Intervention group participants received point-of-care CD4 cell count testing and additional counselling on the result by trial staff, including their ART eligibility on the basis of CD4 criteria at that time (<350 cells per μ L). At the 23 ART clinics

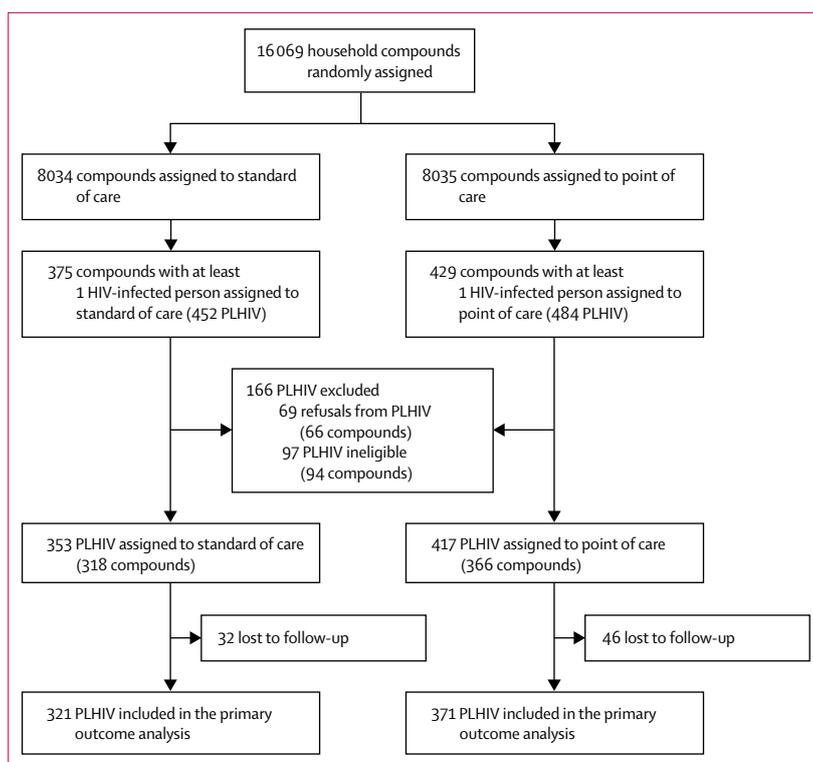


Figure 1: Trial profile
PLHIV=people living with HIV.

	Standard of care (n=321)	Point of care (n=371)	Overall (n=692)
Sex			
Male	108 (34%)	127 (34%)	235 (34%)
Female	213 (66%)	244 (66%)	457 (66%)
Age (years)			
<18	24 (7%)	26 (7%)	50 (7%)
18–24	49 (15%)	43 (12%)	92 (13%)
25–34	107 (33%)	122 (33%)	229 (33%)
35–80	141 (44%)	180 (49%)	321 (46%)
Education*			
Primary	277 (86%)	327 (88%)	604 (87%)
Secondary	41 (13%)	43 (12%)	84 (13%)
Marital status†			
Married	199 (62%)	235 (63%)	434 (63%)
Single	45 (14%)	52 (14%)	97 (14%)
Other	73 (23%)	82 (22%)	155 (22%)
Employment*			
No	112 (35%)	109 (29%)	221 (32%)
Yes	206 (65%)	261 (70%)	467 (68%)

Data are n (%). Standard of care is referral to clinic for CD4 count. Point of care is the use of a point-of-care device to determine CD4 count and counselling after positive HIV test. *Four missing. †Five missing.

Table 1: Demographic characteristics of participants with HIV who completed follow-up, by study group at enrolment

	Linkage to care (%)	Univariable HR (95% CI)	p value	Multivariable HR (95% CI)	p value
Standard-of-care group (n=321)	108 (34%)	1	..	1	..
Point-of-care group (n=371)	215 (58%)	2.04 (1.60–2.60)	<0.0001	2.14 (1.67–2.74)	<0.0001
Sex					
Male	105/235 (45%)	1	..	1	..
Female	218/457 (48%)	1.05 (0.84–1.33)	0.66	1.00 (0.78–1.30)	0.99
Age (years)	0.14	..	0.14
<18	29/50 (58%)	1	..	1	..
18–24	37/92 (40%)	0.56 (0.35–0.92)	..	0.50 (0.27–0.94)	..
25–34	111/229 (48%)	0.75 (0.50–1.12)	..	0.63 (0.35–1.14)	..
35–80	146/321 (45%)	0.67 (0.45–1.00)	..	0.55 (0.30–1.03)	..
Education					
Primary	279/604 (46%)	1	..	1	..
Secondary	43/84 (51%)	1.12 (0.82–1.53)	0.49	1.17 (0.85–1.62)	0.33
Marital status	0.75	..	0.49
Married	203/434 (47%)	1	..	1	..
Single	47/97 (48%)	1.10 (0.79–1.52)	..	0.76 (0.46–1.24)	..
Other	71/155 (46%)	0.95 (0.73–1.25)	..	0.93 (0.70–1.25)	..
Employment					
No	116/221 (52%)	1	..	1	..
Yes	206/467 (44%)	1.26 (0.99–1.58)	0.05	1.29 (0.99–1.68)	0.06

Standard of care is referral to clinic for CD4 count. Point of care is the use of a point-of-care device to determine CD4 count and counselling after positive HIV test. HR=hazard ratio.

Table 2: Cox proportional hazards univariable and multivariable analyses of demographic variables affecting linkage to HIV care

serving the study catchment area, operating hours and workflow were not altered as a result of this trial, except for the instruction to clinic providers that point-of-care participants arriving with a CD4 cell count printed from the PIMA device should have those results recorded and acted upon the same as if the test result was provided by the referral laboratory. ART initiation for point-of-care group participants required meeting the same standards as others receiving care at the clinic.

We completed laboratory validation and field feasibility of the PIMA device in this setting before trial launch, and have presented the results elsewhere.⁹ The performance of PIMA in use by lay counsellors was comparable to that of the laboratory reference standard FACSCalibur, and consistent with previous reports. CD4 testing with finger-prick capillary blood compared with venous blood, resulted in a small but acceptable misclassification rate of 5.4% at the CD4 count threshold of 350 cells per μL used in Kenya at the time of this study.

6 months after enrolment we interviewed participants at home to ascertain whether and where they sought care. We attempted up to three follow-up home visits within 2 weeks after 6 months had elapsed from enrolment. Final follow-up visits were completed by Sept 30, 2014. When available in the clinic charts, we abstracted HIV-related variables including the referral

laboratory CD4 cell counts and ART regimens. The institutional review boards at CDC and KEMRI approved the study protocol.

Outcomes

The prevalence of loss to follow-up (LTFU) at 6 months was listed as the main outcome in the study protocol. We analysed the prevalence of linkage to care within 183 days after enrolment (defined as 1–LTFU) as the primary outcome, and time to ART initiation as a secondary outcome.

Statistical analysis

Sample size calculations were based on the primary outcome of chart-verified linkage to care within 6 months of study enrolment with a two-sided Pearson χ^2 test with a significance level of α 0.05. We assumed a 50% linkage to care rate in the standard-of-care group. At 345 participants per group, the study was powered at 80% to detect an absolute difference of 15%.

We investigated associations among demographic characteristics (and CD4 at enrolment for the point-of-care group) and linkage to care status with the study group. Demographic characteristics included sex, age stratum, education, marital status (married, single, or other, which includes widowed and divorced), employment status, ART status (at baseline), and CD4 cell count at enrolment for point-of-care participants. Multivariable analysis was done with list-wise deletion (n=686). Univariable analyses with and without children (<18 years old) did not reveal substantial differences; hence, we report multivariable results including children. For all categorical variables, we did a cluster-adjusted χ^2 test for treatment differences. All analyses were by intention to treat. We also did sensitivity analyses counting the enrolled participants lost to follow-up as not linked to care. In all models, we accounted for the cluster-randomised design by treating the compound as the cluster.

The primary analysis modelled time to linkage to care with the outcome defined as time to HIV clinic linkage from enrolment for each trial group. We calculated the log-rank test for a treatment difference and present Kaplan-Meier curves by treatment group. We used a univariable Cox proportional hazards model to estimate the hazard ratio (HR) and 95% CI and a robust SE with the compound defined as the cluster. We tested the proportional hazards assumption of the Cox model with weighted Schoenfeld residuals. Additionally, we estimated the HR and efficacy for point of care versus standard of care with a multivariable Cox model that controlled for all considered variables. The secondary analysis focused on the time to ART from both enrolment and linkage. The time to chart-verified ART initiation from linkage included only participants who were linked to care. We computed Kaplan-Meier curves for time to ART initiation by treatment group. Univariable and

multivariable Cox proportional hazards models were used to estimate the efficacy and HR for point of care compared with standard of care with the same methods described for time to linkage. SAS version 9.3 and R version 3.1.1 were used for all analyses. This trial is registered with ClinicalTrials.gov, number NCT02515149.

Role of the funding source

CDC and KEMRI staff based in Atlanta, GA, USA, and at the KEMRI–CDC Field Station in Kisumu, Kenya led the study design, data collection, data analysis, data interpretation, and manuscript writing. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication. Alere donated the study point-of-care devices but did not have any other role in the study.

Results

More than 20000 individuals living in 16069 compounds were tested between June 13, 2013, and March 7, 2014, as part of the HBCT campaign; 8034 compounds were randomly assigned to the standard-of-care group and 8035 compounds to the point-of-care group. The HBCT campaign yielded 936 HIV-infected participants in 804 compounds who were approached to join this study. Of the 804 compounds with at least one person living with HIV, 88% had only one person infected with HIV. We enrolled 770 (82%) people living with HIV from 684 compounds who met the eligibility criteria (figure 1). 69 (7%) people in 66 compounds refused participation in the trial and 97 (10%) participants in 94 compounds were ineligible, the most common reason being enrolment in HIV care within the previous 6 months. Of 353 (46%) enrolled in the standard-of-care group and of 417 (54%) in the point-of-care group, similar proportions (9% vs 11%) were lost to follow-up. The primary outcome of linkage to care was measured in 692 (90%) of enrolled participants from Jan 9, 2014, to Nov 26, 2014. Demographic characteristics were similar in the study groups (table 1), in the 692 participants, and in the 78 people lost to follow-up.

Among 321 standard-of-care participants, 108 (34%) had linked to HIV care within 6 months following study enrolment compared with 215 (58%) of 371 who linked to care in the point-of-care group ($p<0.0001$; table 2). 63 (17%) of 371 participants in the point-of-care group began ART compared with 33 (10%) of 321 in the standard-of-care group ($p=0.001$). When the data were restricted to only participants successfully linked to care, however, ART initiation by study group was similar: 33 (31%) of 108 in the standard-of-care group and 63 (29%) of 215 in the point-of-care group ($p=0.92$). Among the 75 linked participants in the point-of-care group with CD4 counts less than 350 cells per μL , 38 (51%) of 75 participants had started ART within 6 months. These data were not available for the standard-of-care group because of the low numbers of participants who had standard-of-care CD4 testing during the period of

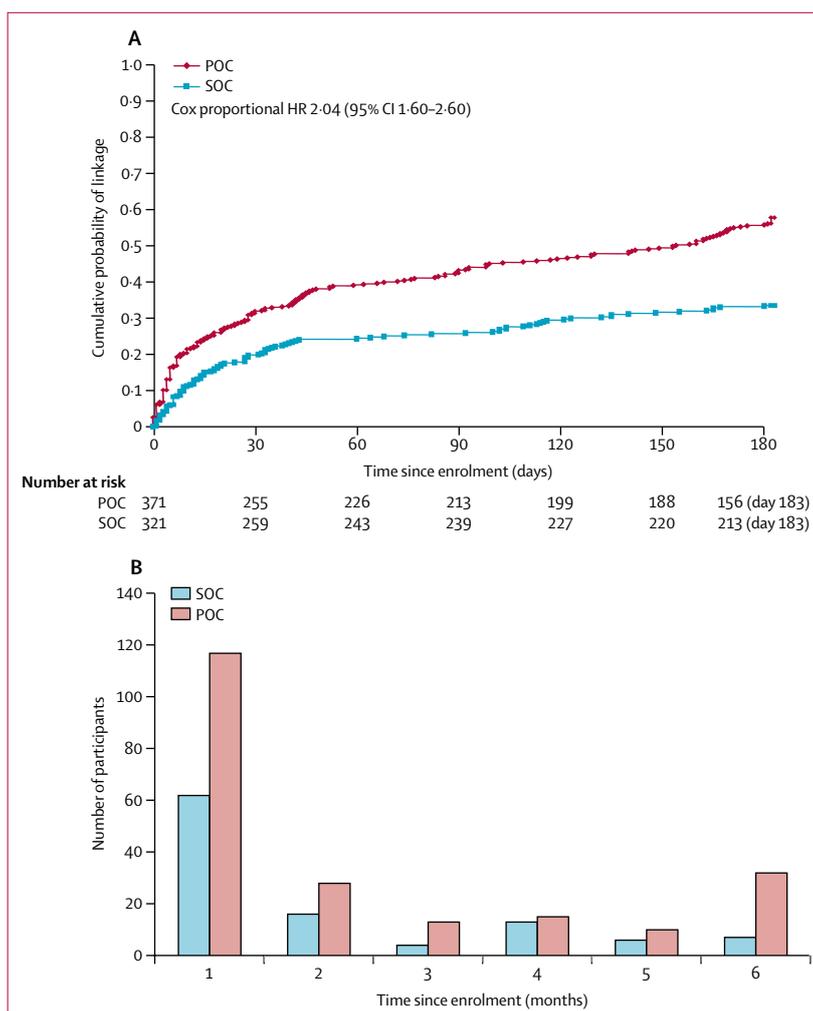


Figure 2: Linkage to HIV care after enrolment by study group

(A) Kaplan-Meier cumulative probability and (B) number of participants by month. HR=hazard ratio. POC=point-of-care CD4 testing and counselling. SOC=standard of care.

observation. Among 361 (97%) point-of-care group participants with an available CD4 test result, 126 males had a median CD4 count of 401 cells per μL (IQR 219–623) and 235 females had a median CD4 count of 500 cells per μL (315–697).

Patients in the point-of-care group were twice as likely to be linked to care as those in the standard-of-care group (figure 2). Of the 117 participants linked to HIV care in the first month in the point-of-care group, 87 (74%) were linked within 2 weeks of enrolment (figure 2). Similarly, of the 62 participants linked to HIV care in the first month in the standard-of-care group, 42 (68%) were linked within 2 weeks of enrolment. As part of the sensitivity analysis counting the 78 lost to follow-up participants (32 in the standard-of-care group and 46 in the point-of-care group) as not linked to care, the multivariable Cox proportional HR comparing point-of-care with standard-of-care groups was 1.98 (95% CI 1.55–2.53).

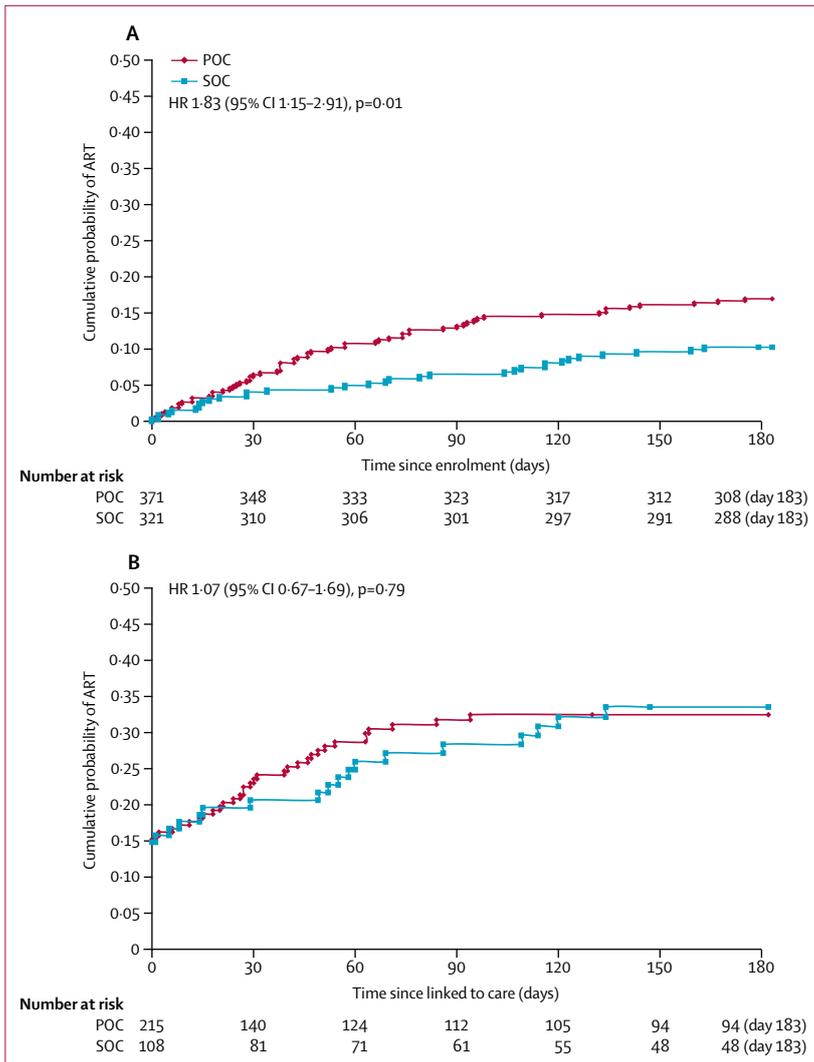


Figure 3: Kaplan-Meier cumulative probability of antiretroviral therapy initiation by group (A) After enrolment and (B) after linkage to care. ART=antiretroviral therapy. HR=hazard ratio. POC=point-of-care CD4 testing and counselling. SOC=standard of care.

The median time to ART initiation was 47 days (IQR 24–94) from enrolment in the point-of-care group and 70 days (19–122) in the standard-of-care group (figure 3). Restricting to participants linked to care though, there was no difference in time to ART initiation, as a similarly low proportion were initiated on ART in the two groups (figure 3).

Among the 215 participants in the point-of-care group linked to care, 208 (97%) of the CD4 results at enrolment were available. Point-of-care participants with CD4 counts less than 200 cells per μL were more likely to be linked to care than were those with counts of 200 cells per μL or more (figure 4). When a CD4 count cutoff of 350 cells per μL was used, although patients in the lower CD4 count cutoff groups did have higher linkage to care rates than their counterparts in the higher CD4 count categories, the difference was not significant (figure 4).

Discussion

In the setting of a HBCT campaign in rural western Kenya, when compared with standard-of-care laboratory-based CD4 cell counts, point-of-care counts improved linkage to care from 34% to 58% and led to a reduction in the time to ART initiation from a median of 70 days to 47 days after diagnosis at home. Participants in the point-of-care group benefitted from a printed CD4 result on the same day as receiving the HIV diagnosis, and received standard counselling regarding their treatment eligibility and other HIV care available to them. Compared with the standard-of-care group, they were spared the initial clinic visit (where the referral for phlebotomy would occur), the laboratory visit for phlebotomy (typically farther from home than the ART clinic), the wait for the CD4 result before the subsequent visit for counselling on the CD4 result, and the time and financial costs of this additional travel.

The greatest effect of the intervention, which included counselling regarding treatment eligibility after the CD4 test, was observed in people who needed ART the most (CD4 count <200 cells per μL), followed by the group who were ART eligible on the basis of Kenyan guidelines at the time (CD4 count <350 cells per μL). People living with HIV with low CD4 cell counts, and likely more long-standing infection, might have had previous opportunistic infections or knowledge of earlier CD4 counts, and their new knowledge of a lowered CD4 cell count could have motivated linkage to care. Additionally, people with lower CD4 cell counts could have been engaged in HIV care (including ART) more than 6 months before enrolment. Unfortunately, we did not collect results of previous HIV or CD4 testing or previous HIV care on the participants.

Since the proportions of participants starting ART in both groups were similar once they linked to care, it seems that the proportion of people started on ART was not associated with the intervention but driven almost entirely by linkage to care itself. Given the asymptotic nature of the curve (figure 2A), we believe that the length of the follow-up period was long enough to capture any effect on linkage to care and ART initiation that the intervention could be expected to have. Only 51% of people living with HIV in the point-of-care group who were eligible by the CD4 count of 350 cells per μL cutoff started ART, which, although highly successful by current statistics in Kenya, points to the need for overcoming additional barriers to ART initiation. These residual barriers could include clinic-level factors (eg, pharmacy stock-outs, scheduling challenges, and requirements for adherence counselling before initiating ART), provider-level factors (eg, inadequate experience or mistrust of the new point-of-care technology resulting in repeat testing in laboratories), and individual factors (eg, health beliefs, transportation challenges, and more pressing immediate survival challenges such as food insecurity).^{10,11} Specifically, travel time and distance to clinic have been well documented as

important barriers to initiation and retention in HIV care.¹²

There have been few randomised trials of novel interventions to improve linkage to care. The Antiretroviral Treatment Access Study¹³ done in four US cities showed that a case-management approach improved linkage to HIV clinics by 18%. Post-test counselling combined with home visits in rural Uganda showed a 29% improvement in linkage.¹⁴ A retrospective analysis from New York City showed that partner services staff improved timely linkage (within 3 months of diagnosis) by 13%, by assisting patients with newly diagnosed HIV infection with appointment scheduling and transportation.¹⁵ Only one other randomised trial has assessed the effect on linkage to care by the provision of immediate CD4 counts to people with HIV.⁵ These investigators used laboratory-based flow cytometers to measure CD4 counts among patients attending a South African clinic and also observed a doubling in linkage to care at 6 months. Another trial in South Africa showed that ART uptake improved by 36% and viral suppression by 26% among people with HIV attending the clinics when provided a rapid CD4 count at the time of the visit.¹⁶ Several other studies have reported 25–41% improvements in linkage to care with the use of point-of-care CD4 cell count devices in the context of HBCT, but none were randomised.^{7,17,18} More recently, another observational study, albeit lacking a comparator group, in two high prevalence districts in Uganda and South Africa, showed uptake of ART of up to 76% among those eligible, following a similar home-based HIV and CD4 testing and counselling process.¹⁷ Additionally, retrospective analyses from Botswana and Malawi have been presented and seem to confirm the benefit of point-of-care CD4 cell counts in reducing the time to ART initiation.^{19,20} We show a moderately large (24%) absolute improvement in linkage to care with objective verification from clinic charts in a randomised trial set within HBCT. Given that our study staff made up to three attempts at home-based follow-up to ascertain self-report of linkage to care, we had low rates of attrition from both study groups (about 10%).

Home-based HIV testing can increase uptake by first-time testers and subsequent linkage to care in settings with generalised HIV epidemics.²¹ WHO's 2015 Consolidated Guidelines on HIV Testing has now endorsed expanding the use of trained lay providers as an important strategy for reaching the first 90% goal of identifying people with HIV. Emerging evidence on the use of trained lay providers for point-of-care CD4 cell counts in non-clinic settings,²² as used in this study, supports this approach, combining HBCT and point-of-care testing. As a gateway to earlier intervention for increasing ART coverage, non-clinic, community-based HIV care services could represent the next frontier for curbing the effects of HIV morbidity and mortality and onward transmission. As important innovations for optimising the effect of ART, such as same day ART

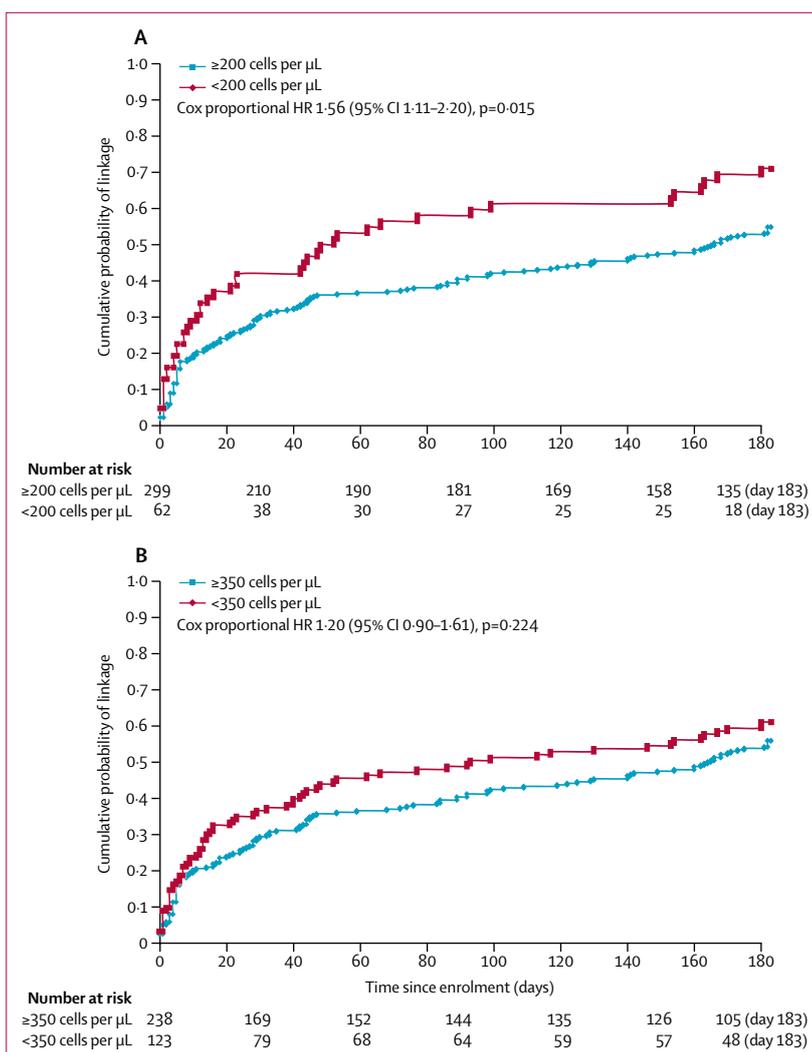


Figure 4: Cumulative probability of linkage to care among point-of-care CD4 count group participants. CD4 count cutoffs of (A) 200 cells per μL and (B) 350 cells per μL . HR=hazard ratio. POC=point-of-care CD4 testing and counselling. SOC=standard of care.

initiation (after HIV diagnosis) are developed and implemented, baseline point-of-care CD4 cell counts are likely to be a crucial inclusion in such ART delivery approaches.²³

Although the 2015 WHO ART guidelines and the 2016 Kenya ART guidelines now recommend universal ART initiation regardless of CD4 cell count, the available financial resources for ART, especially in low-resource settings, are unlikely to triple from US\$6 billion per year to the projected need for US\$20 billion per year.^{3,24} Also, the capacity for decentralisation, scale-up, and monitoring at the scale needed is likely to remain constrained. Community-based HIV care remains an under-used strategy, and might prove to be more cost-effective, especially in resource-limited settings.

Curbing the high preventable mortality from HIV means improving the implementation of existing WHO

For WHO's 2015 Consolidated Guidelines on HIV Testing see <http://www.who.int/hiv/pub/guidelines/hiv-testing-services/en>

guidelines on management of opportunistic infections. WHO recommends provision of co-trimoxazole for people living with HIV who have CD4 counts of 350 cells per μL or less to reduce mortality from malaria, severe bacterial infections, pneumocystis pneumonia, and toxoplasmosis.²⁵ Similarly, WHO also recommends prophylactic antifungal therapy with fluconazole for people with CD4 counts of 100 cells per μL or less and cryptococcal antigenaemia. Although CD4 cell counts for monitoring of people receiving ART could become unnecessary in settings where viral load testing becomes available, CD4 testing at baseline is likely to be required for routine clinical assessment and to guide crucial interventions to reduce mortality (eg, prophylaxis for active cryptococcal and mycobacterial infections).

On the basis of our findings and other studies, national ART programmes should do implementation research to better define the role of point-of-care CD4 cell counts, while recognising the need for additional innovations for reducing barriers to enrolling and retaining patients in HIV care and initiating ART. The enhanced efficacy of community outreach for engaging key populations such as female sex workers, and the access barriers faced by such key populations have been well documented.²⁶ As nearly half of people living with HIV remain unidentified, clinic-based models of HIV testing (whether voluntary or provider-initiated counselling and testing) might be approaching the limits of their yield. To reach key populations such as sex workers and drug users,^{27,28} the integration of point-of-care CD4 cell counts with non-clinic venue-based HIV and sexually transmitted infection testing, and methadone maintenance therapy, could be more acceptable and cost-effective.²⁹ Similarly, to reach more rural populations, where distances from referral laboratories are an established barrier,³⁰ point-of-care testing by trained lay providers before ART initiation is a promising solution.^{19,20}

Our findings should be interpreted with caution given the following limitations. Our study did not capture previous HIV testing or CD4 test results, which might have positively affected the motivation to link to care after receiving point-of-care CD4 cell count results in this study. Additional factors that affect linkage to care behaviour such as time and cost of travel for additional visits, and the opportunity cost of doing so (eg, missed work) were not assessed in our study. Finally, linkage to care observed during the study follow-up period does not reflect long-term retention and adherence outcomes, which would be an important question to address in future studies.

Our next steps are to complete a costing and cost-effectiveness analysis of this trial to inform Kenya's national ART programme regarding the implementation of point-of-care CD4 cell counts in non-clinic settings. Additionally, similar investigations targeting key populations such as commercial or transactional sex workers, people who inject drugs, prisoners, and in non-HIV clinic

settings such as paediatric, adolescent, and antenatal clinics could be done to further define the settings where point-of-care testing might facilitate linkage to care.

Contributors

CZ and FOO served as co-principal investigators. CZ, MAD, FOO, DOO, CER, RTC, and TS wrote the protocol. TS secured funding for the project. DOO oversaw field activities. BO and CZ oversaw laboratory analyses. MAD, FOO, DOO, BO, and RTC managed the study and ensured quality. RN managed data entry and cleaning. TW cleaned data and assisted in data analysis. CER analysed the data. MAD prepared the first draft of the manuscript. All authors contributed to the interpretation of the results and drafting of the final article, including critique of important intellectual content.

Declaration of interests

We declare no competing interests.

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