## Title

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# SEARCH Human Immunodeficiency Virus (HIV) Streamlined Treatment Intervention Reduces Mortality at a Population Level in Men With Low CD4 Counts

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***Background.*** We tested the hypothesis that patient-centered, streamlined human immunodeficiency virus (HIV) care would achieve lower mortality than the standard treatment model for persons with HIV and CD4 ≤ 350/uL in the setting of population-wide HIV testing.

***Methods.*** In the SEARCH (Sustainable East Africa Research in Community Health) Study (NCT01864603), 32 communities in rural Uganda and Kenya were randomized to country-guided antiretroviral therapy (ART) versus streamlined ART care that included rapid ART start, visit spacing, flexible clinic hours, and welcoming environment. We assessed persons with HIV and CD4 ≤ 350/uL, ART eligible in both arms, and estimated the effect of streamlined care on ART initiation and mortality at 3 years. Comparisons between study arms used a cluster-level analysis with survival estimates from Kaplan-Meier; estimates of ART start among ART-naive persons treated death as a competing risk.

***Results.*** Among 13 266 adults with HIV, 2973 (22.4%) had CD4 ≤ 350/uL. Of these, 33% were new diagnoses, and 10% were diagnosed but ART-naive. Men with HIV were almost twice as likely as women with HIV to have CD4 ≤ 350/uL and be untreated (15% vs 8%, respectively). Streamlined care reduced mortality by 28% versus control (risk ratio [RR] = 0.72; 95% confidence interval [CI]: .56, .93; $P$ = .02). Despite eligibility in both arms, persons with CD4 ≤ 350/uL started ART faster under streamlined care versus control (76% vs 43% by 12 months, respectively; $P$ < .001). Mortality was reduced substantially more among men (RR = 0.61; 95% CI: .43, .86; $P$ = .01) than among women (RR = 0.90; 95% CI: .62, 1.32; $P$ = .58).

***Conclusions.*** After population-based HIV testing, streamlined care reduced population-level mortality among persons with HIV and CD4 ≤ 350/uL, particularly among men. Streamlined HIV care models may play a key role in global efforts to reduce AIDS deaths.

**Keywords.** advanced HIV-disease; mortality; population-based HIV testing; streamlined care.

Mortality related to human immunodeficiency virus (HIV) has fallen worldwide with antiretroviral therapy (ART) scale-up, but 690 000 people with HIV (PWH) died in 2019 [1]. Globally, only 59% of PWH are estimated to have viral suppression [1]. Thus, the full individual and public health gains from effective treatment for all PWH have yet to be fully realized [2]. The maximum benefits of ART are achieved when people are tested early in disease, rapidly start ART, are retained in care, and are virally suppressed [3]. New approaches to eliminating AIDS deaths must address many barriers in the HIV testing and care cascade, including lack of knowledge of HIV status among some populations, low rates of linkage to care, delays in ART initiation upon linkage, imperfect retention in care, and absence of patient-centered delivery systems responsive to gender-specific needs [1, 4–10]. Qualitative research has shown that men have complex hegemonic masculinity constructs that contribute to lower uptake of HIV services compared to women [11, 12].

Clinic-based studies report mortality reductions with ART rollout, but these studies have been limited by lack of full ascertainment of mortality among patients lost to follow-up and have only included those persons who have been enrolled in HIV care [3]. Few studies have examined population-level mortality with ART scale-up or interventions to reduce HIV-associated deaths among "late-presenters," persons remaining undiagnosed despite low CD4 count, or persons previously diagnosed and not linked to care or lost from care [3, 13–15].

Many HIV-associated deaths are among late-presenters [15–18]. In Uganda, 20–25% of newly identified PWH present with advanced disease, defined as baseline CD4 < 200/μL. Moreover, at Mulago Hospital (the largest public hospital in Uganda), the majority of patients infected with HIV and hospitalized with acute illnesses were aware of their HIV-infected status but were not enrolled in HIV care, either because they had never linked to care or had become disengaged from care

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[16]. In this hospitalized population with HIV and a median CD4 cell count of 64 cells/mL, we found a 33% ART-naive, pre-ART mortality within 2 weeks among those who were eligible for rapid ART start.

Reducing preventable HIV-associated deaths requires strategies for identifying, engaging, linking, and retaining PWH who are not previously in care or have fallen out of care [2]. These populations need to be engaged in care before they present with advanced disease and critical illnesses. Comprehensive population-based HIV testing and linkage provides a means to actively find and engage these challenging populations [9]. Moreover, providing patient-centered streamlined care models to reduce patient-level barriers is associated with high viral suppression and retention [8, 10].

We evaluated the effect of streamlined ART delivery for PWH with CD4 ≤ 350/uL in the cluster randomized Sustainable East Africa Research in Community Health Study (SEARCH; NCT:01864603). Because this analysis focuses on patients with CD4 ≤ 350/uL, ART eligibility was equivalent across both study arms. PWH in the intervention arm received a patient-centered streamlined HIV care delivery strategy, whereas patients in the control arm received standard country-guided ART delivery. We hypothesized that the SEARCH streamlined care intervention would reduce mortality among PWH with CD4 ≤ 350/uL in the setting of population-wide HIV testing.

## METHODS

### SEARCH Study Design and Population

The SEARCH "test and treat" trial was a pair-matched, community-randomized study of 32 rural communities conducted in Eastern and Western Uganda and in Kenya from 2013 through 2017 [19]. This 3-year trial compared an intervention strategy consisting of annual population-wide HIV testing via multidisease health campaigns and universal ART delivery via a patient-centered streamlined care model, to a control strategy consisting of baseline population-wide HIV testing and ART offered according to country guidelines. Details of randomization, census, community health campaigns, and other trial methods are described elsewhere [8, 19–21]. Briefly, we randomized 32 communities into 16 intervention and 16 control communities. We conducted door-to-door census enumeration of all residents living in all 32 communities followed by 2-week multidisease health campaigns that offered universal HIV testing together with additional health services for participants. Adult (≥15 years old) residents who did not attend the campaigns were offered HIV testing at home or at locations of their choice, as previously described [20]. Digital biometric fingerprint measurement supplemented by name matching were used to link residents to study data as they participated in testing and care activities in the community.

In intervention communities, repeat health campaigns were conducted annually, and all HIV-positive persons were offered ART regardless of $CD4^+$ cell count. In control communities, population-wide HIV testing was performed at baseline and after 3 years; adults with HIV were offered ART according to country guidelines, which changed over the course of the study from CD4 ≤ 350/uL at baseline to <500/uL within 1 year of follow-up, and finally to universal treatment prior to study close [19]. Thus, in both arms, all PWH with CD4 ≤ 350/uL were ART-eligible from the study start. At study baseline in both arms, all PWH (regardless of their CD4 count) received a transport voucher to facilitate linkage to care. After 3 years, campaigns were conducted in all communities for endpoint measurement as described previously [19]. Our study population for this analysis were PWH who were aged ≥15 and who had CD4 ≤ 350/uL at baseline.

### SEARCH Streamlined Care Intervention

The SEARCH streamlined care intervention was developed to address the barriers to linkage, ART start, retention, and viral suppression and has been previously described [19]. Streamlined care was offered to all PWH in intervention communities. PWH not in active care were offered a "warm handoff" where a clinic representative met or spoke to the client upon baseline testing and provided a mobile phone number to call with questions. The streamlined care model also included same-day accelerated ART start through a structured protocol, flexible clinic hours, friendly providers and a welcoming environment, structured viral load results delivery and viral load counseling, and mobile phone based appointment reminders [8]. HIV care was delivered in a multidisease, chronic care model that provided integrated care for HIV, diabetes, and hypertension for PWH as well for individuals without HIV.

### Measurements

Demographic measures were collected at census and at time of baseline HIV testing as previously described [19]. Participants with a confirmed HIV antibody test result, detectable HIV RNA, or a Ministry of Health record of prior HIV care were considered PWH. Plasma human immunodeficiency virus type 1 (HIV-1) RNA level (viral load [VL]) was measured on all PHW at baseline. Viral suppression at was defined as VL ≤ 500 copies/mL.

### Vital Status Ascertainment

We performed a second census in communities at the year 3 end of the study to ascertain vital status on all household members enumerated at baseline. Comprehensive key informant interviews were performed during the population-based health fairs and home testing at year 3 to ascertain mortality on all persons, irrespective of HIV status. Individuals not seen in person at year 3 were tracked, and vital status was obtained via interview

of household member, neighbor or community leader, either in person or by phone interview. Causes of death were classified as due to illness, childbirth, suicide, or accident.

### STATISTICAL ANALYSES

This was a prespecified analysis in the SEARCH trial. The primary mortality outcome was all-cause mortality by year 3. Mortality among PWH with CD4 ≤ 350/uL at study baseline (2013) was compared between arms using a 2-stage approach [22]. First, Kaplan-Meier estimators were used to calculate the risk of death by 36 months in each community, right censoring at time of migration out of the community. Outmigration was defined as living outside of the community ≥6 months prior to year 3 or 12 months continuous stay outside the community during the study. Second, community-level, targeted maximum likelihood estimation (TMLE) with data-adaptive selection of prespecified adjustment variables was used to compare mortality between arms, accounting for the pair-matched design [23]. Analogous methods were used to compare cumulative incidence of ART initiation by 1, 12, and 24 months among PWH with CD4 ≤ 350/uL not on ART at baseline, censoring at outmigration and treating death due to any cause as a competing risk. Individual-level TMLE was used to estimate adjusted predictors of mortality. Gender was evaluated in prespecified subgroup analyses. For context, we also calculated mortality rates among adult residents of the 32 SEARCH communities with baseline HIV status measured, stratified by baseline HIV status, and compared mortality between study arms using an analogous 2-stage approach [19]. When calculating mortality rates, person-time-at-risk began at the start of baseline HIV testing and ended at death or the close of HIV testing for the study.

#### Ethical Considerations

The study was approved by the Makerere University School of Medicine Research and Ethics Committee, the Uganda National Council for Science and Technology, the University of California, San Francisco Committee on Human Research, and the Kenya Medical Research Institute Ethical Review Committee. Verbal consent was obtained at enrollment; written consent was obtained for persons in the intervention arm receiving ART not yet indicated by country guidelines.

#### Role of the Funding Source

The funders played no role in the design of the study, data collection and analysis, interpretation, manuscript preparation, or submission.

## RESULTS

#### Study Population

Overall there were 143 870 stable adult residents aged 15 years and older in the 32 communities; baseline HIV status was measured among 91% (130 874/143 870) of these individuals (Figure 1). Baseline HIV prevalence was 10% (13 266/143 870) overall, 20% (8934/45 742) in Kenya, 7% (2783/42 004) in West

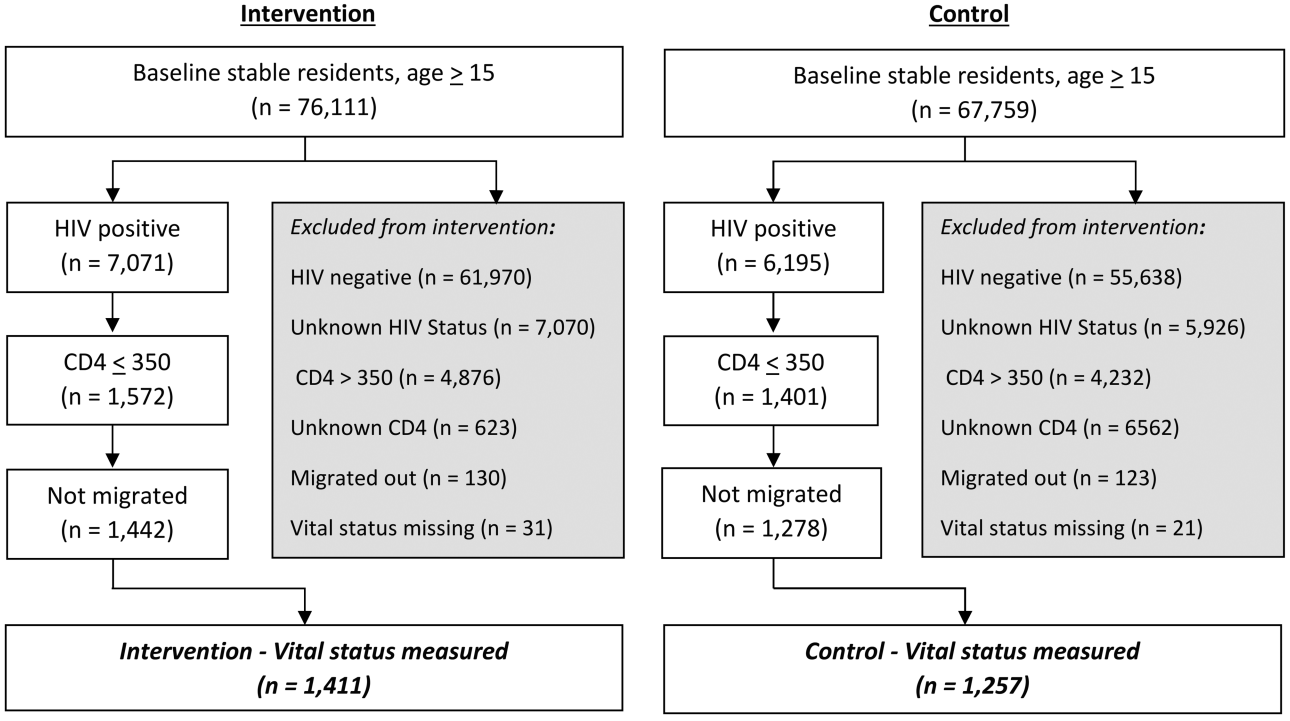


**Figure 1.** Participant flow chart. Abbreviation: HIV, human immunodeficiency virus.

Uganda, and 4% (1549/43 128) in East Uganda. Of the 91% (12 081/13 266) of PWH with baseline CD4 measures, 67% (8070/12 081) were women, and 33% (4011/12 081) were men. Among these, 25% (2973/12 081) had CD4 ≤ 350/uL: 35% of men (1384/4011) and 20% of women (1589/8070). Men with HIV were twice as likely as women with HIV to both have CD4 ≤ 350/uL and not be on ART: 15% (603/4011) versus 8% (680/8070), respectively.

Among the 2973 PWH with baseline CD4 ≤ 350/uL, 47% (1384/2973) were male, 7% (211/2973) were single, 56% (1663/2973) were farmers, and 20% (588/2973) were 50 years of age or older; 63% (1862/2973) were resident in Kenya, 24% (715/2973) in West Uganda, and 13% (396/2973) in East Uganda (Table 1; characteristics by study arm are provided in the Supplementary Table). Forty-three percent (1283/2973) of PWH with CD4 ≤ 350/uL were ART naive; of these 78% (995/1283) were new diagnoses, whereas 22% (288/1283) had a prior HIV diagnosis but no prior or current ART use. Seventy-seven percent (1301) of the 1690 low-CD4 participants with ART experience had a measured viral load; of these, 27% (347/1301) were unsuppressed.

Comparing sexes, men were more likely than women to be over 50 years of age (26% vs 15%, respectively), to have CD4 < 150/uL (21% vs 17%, respectively), and to have baseline HIV RNA > 100 000 copies/mL (28% vs 19%, respectively), placing men at elevated risk of HIV progression and death (Table 1).

**Table 1. Characteristics of People With Human Immunodeficiency Virus (HIV) and CD4 ≤ 350 cells/mL at Study Baseline, Stratified by Sex**

| | Male | Female | All |
|---|---|---|---|
| n | 1384 | 1589 | 2973 |
| Age category, y (%) | | | |
| 15–20 | 17 (1.2) | 61 (3.8) | 78 (2.6) |
| 21–49 | 1012 (73.1) | 1295 (81.5) | 2307 (77.6) |
| >50 | 355 (25.7) | 233 (14.7) | 588 (19.8) |
| Marital status (%) | | | |
| Single | 101 (7.3) | 110 (6.9) | 211 (7.1) |
| Married, not polygamous | 910 (65.8) | 644 (40.5) | 1554 (52.3) |
| Married, polygamous | 239 (17.3) | 288 (18.1) | 527 (17.7) |
| Widowed, divorced, separated | 132 (9.6) | 547 (34.4) | 679 (22.9) |
| Occupation (%) | | | |
| Farming | 733 (53.0) | 930 (58.5) | 1663 (56.0) |
| Nonfarming | 606 (43.8) | 530 (33.4) | 1136 (38.2) |
| No job or disabled | 44 (3.2) | 129 (8.1) | 173 (5.8) |
| Educational level (%) | | | |
| Below primary school | 950 (68.9) | 1257 (79.3) | 2207 (74.5) |
| Completed primary school | 160 (11.6) | 183 (11.5) | 343 (11.6) |
| Any secondary school or higher | 268 (19.4) | 146 (9.2) | 414 (14.0) |
| Household wealth index quintile (%) | | | |
| First, indicating least wealth | 230 (17.0) | 302 (19.3) | 532 (18.2) |
| Second | 228 (16.8) | 256 (16.4) | 484 (16.6) |
| Third | 239 (17.6) | 283 (18.1) | 522 (17.9) |
| Fourth | 296 (21.8) | 354 (22.7) | 650 (22.3) |
| Fifth, indicating most wealth | 362 (26.7) | 367 (23.5) | 729 (25.0) |
| Residents with prevalent hypertension | 108 (7.9) | 136 (8.7) | 244 (8.3) |
| CD4 = 150 | 288 (20.8) | 267 (16.8) | 555 (18.7) |
| VL > 100 000 | 312 (28.5) | 226 (18.9) | 538 (23.5) |

Abbreviation: VL, viral load.

### Study Follow-Up

Median observation time was 1108 days among 1572 individuals in intervention and 1112 days among 1401 individuals in the control communities. Outmigration was balanced between the intervention and control communities: 130/1572 (8%) outmigrated from intervention communities and 123/1401(9%) outmigrated from control communities (Figure 1). Among persons who did not outmigrate, vital status at 3 years was ascertained in 98%: 1411/1442 (98%) in the intervention arm and 1257/1278 (98%) in the control communities.

### ART Start Among ART-Naive PWH and CD4≤350

The intervention accelerated ART initiation among the 1283 PWH with low CD4 count not on ART at baseline; of these, 76% (95% confidence interval [CI]: 71%, 81%) in the intervention versus 43% (95% CI: 38%, 48%) in the control arm had initiated ART by 12 months (risk ratio [RR]: 1.78; 95% CI: 1.60, 1.98, $P < .001$). ART initiation by 12 months within arms was similar between men (N = 603) and women (N = 680) who were ART-naive at baseline; however, both men and women initiated ART more rapidly in the intervention versus control arm (Figure 2).

### Mortality

Two hundred and eleven participants died by the end of year 3: 94 in intervention and 117 in control communities. The 3-year risk for mortality among persons with low CD4 count was 28% lower in the intervention arm (6.2%, 95% CI: 5.0%, 7.4%) than in the control arm (8.6%, 95% CI: 6.4%, 10.9%; RR: 0.72; 95% CI: .56, .93; $P = .02$; Figure 3).

When stratified by gender, the effect of intervention on risk of 3-year mortality persisted among men with low CD4 count: 6.6% (95% CI: .052, .079) in intervention and 11% (95% CI: .081, .135) in control arms (RR: 0.61; 95% CI: .43, .86; $P = .01$) but not among women (RR: 0.90; 95% CI: .62, 1.32, $P = .58$) (Figure 3). Although men with CD4 ≤ 350 /uL were older than women with CD4 ≤ 350 /uL, the gender difference in effect size persisted after adjustment for age. Among persons with ART experience at baseline, the intervention reduced mortality among men, although among women there was no significant difference (men: RR = 0.57; 95% CI: 0.34, 0.98; $P = .04$; women: RR = 1.11; 95% CI: .57, 2.19; $P = .73$).

After adjustment for other risk factors, in the control arm being male and being ART-naive were significantly associated with increased risk of mortality. In the intervention arm, these factors were no longer associated with excess mortality (Figure 4).

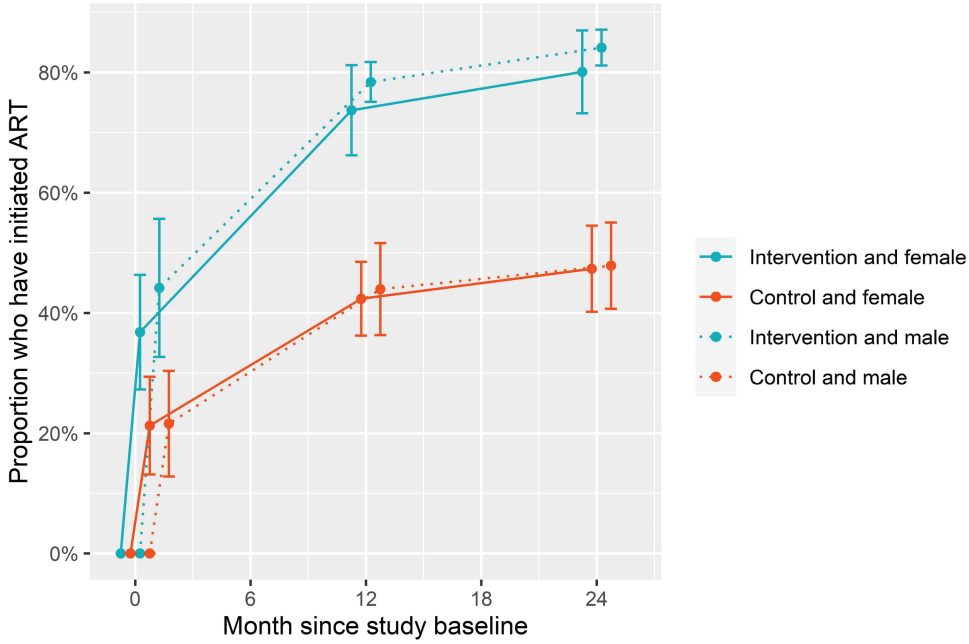


**Figure 2.** Cumulative probability of initiating ART by 1, 12, and 24 months among PWH with CD4 ≤ 350 cells/ml not on ART at baseline (N = 1283), stratified by sex (680 women, 603 men). Estimated for each community censored at outmigration and treated death as a competing risk; ART initiation between arms was compared using community-level TMLE. Error bars indicate 95% CIs for each sex-arm strata. Abbreviations: ART, antiretroviral therapy; CI, confidence interval; PWH, people with human immunodeficiency virus; TMLE, targeted maximum likelihood estimation.

For context, crude mortality rates among PWH were 1.34/100 person-years (PY) and 1.04/100 PY in the control and intervention arms of the study, respectively (RR = 0.77, 95% CI: .64, .93). Among persons without HIV, crude mortality rates were 0.55/100 PY and 0.52/100 PY, in the control and intervention arms of the study (RR = 0.95, 95% CI: .85, 1.06).

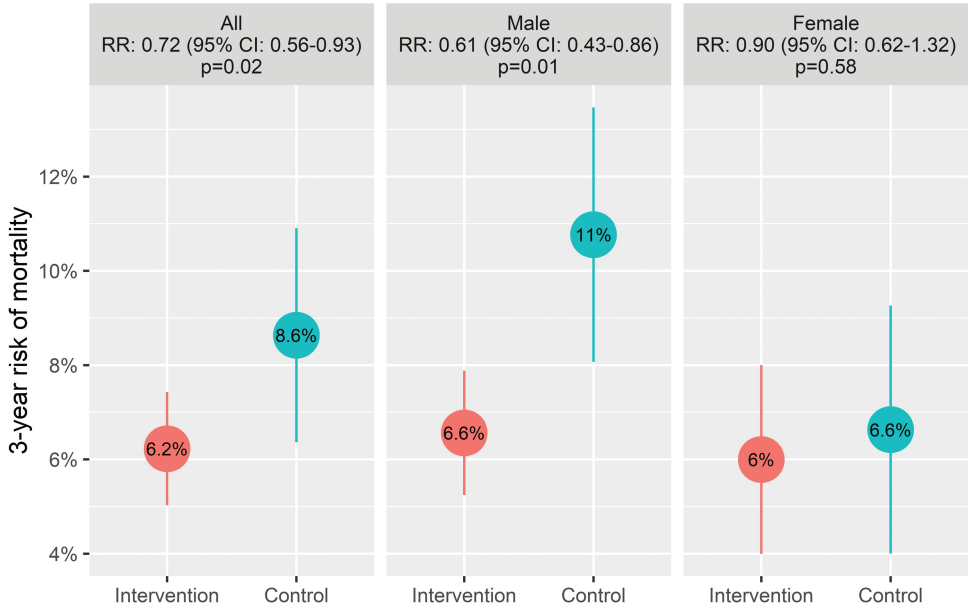


**Figure 3.** Difference in 3-year risk of mortality among PWH with CD4 ≤ 350 cells/mL (N = 2973), overall and stratified by sex (1384 women, 1589 men). Cumulative risk of death was estimated for each community censoring at outmigration; mortality between arms was compared using community-level TMLE. Abbreviations: CI, confidence interval; PWH, people with human immunodeficiency virus; RR, risk ratio; TMLE, targeted maximum likelihood estimation.

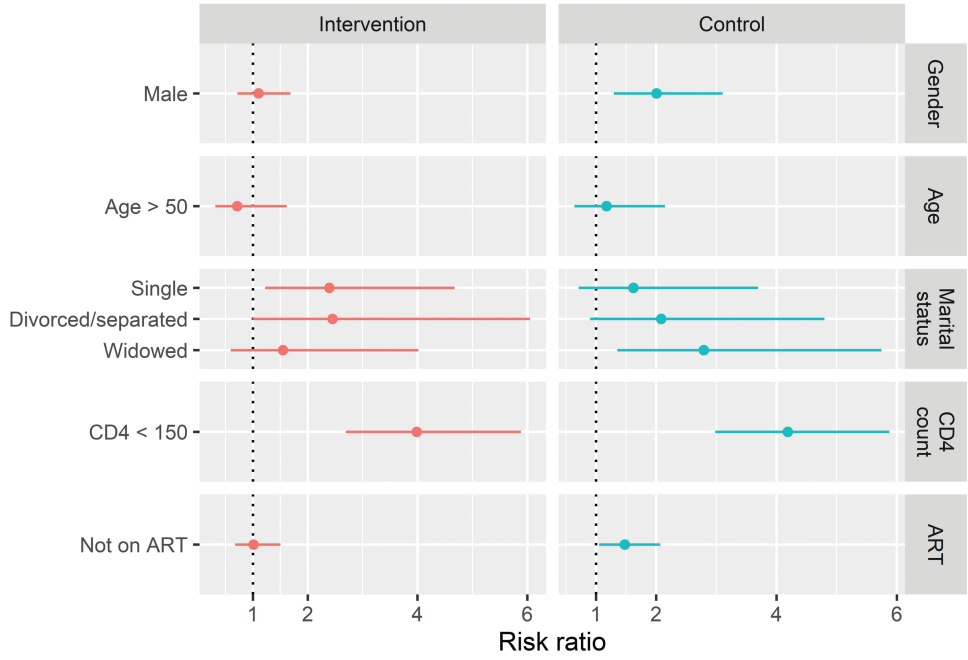


**Figure 4.** Multivariable predictors of mortality among PWH with CD4 ≤ 350 cells/mL (N = 2973), stratified by intervention arm (N = 1572 intervention arm, 1401 control arm). Adjusted relative risks were estimated using individual-level TMLE. Abbreviations: ART, antiretroviral therapy; PWH, people with human immunodeficiency virus; TMLE, targeted maximum likelihood estimation.

## DISCUSSION

In our analysis of mortality in the SEARCH trial, population-based HIV testing reached a substantial number of PWH who were ART-naive patients with low CD4 counts. Men with HIV were more likely to have both a low CD4 count and be ART-naive than women with HIV. Upon HIV diagnosis, SEARCH streamlined care accelerated ART start and reduced mortality by 28% among PWH with CD4 ≤ 350/uL, particularly among men. Higher baseline viral load and lower CD4 count among newly diagnosed men compared to women may have placed men at elevated risk for HIV progression and death.

Our results show that mortality among populations without HIV was similar in intervention versus communities (~0.5 deaths/100 PY); however, among PWH, population mortality was significantly lower in the intervention (1.04/100 PY) versus the control (1.34/100 PY) arm. HIV treatment programs have substantially reduced adult mortality in Africa, but mortality rates among PWH are still markedly higher than among persons without HIV. The 2016 Kenya health and demographic surveillance system (HDSS) data showed that the excess mortality among PWH was approximately 3 times the mortality in the population without HIV (1.59/100 PY vs 0.57/100 PY, respectively) [14] and roughly 60% higher than the mortality seen among PWH who received the SEARCH intervention, suggesting that there is still substantial room to capture increased benefits of ART. We found that persons living with HIV with low CD4 count who are not on ART can be reached through population-level testing and linked to care and that this intervention could reduce population level mortality among PWH, particularly those with low CD4 count. If these low CD4 populations are not identified, they are likely to develop clinical symptoms and either die at home or appear at health facilities as "late presenters" with advanced disease and a high risk of death [15–18].

Our data suggest that the SEARCH streamlined care intervention reduced mortality among PWH with low CD4 count via 2 mechanisms. First, ART initiation was significantly accelerated among ART-naive low CD4 persons. Second, in a separate analysis, we previously showed that among PWH with low CD4 count who linked to care (streamlined care provided in the intervention arm but not in the control arm) resulted in higher rates of care engagement (81% vs 73%, as defined by the proportion of time that patients adhered to visit schedules) and viral suppression (67% vs 47%) for ART-experienced patients with baseline viremia [24].

Extensive literature reports excess mortality among men [25]. Advanced HIV disease, male sex, and older age have been reported to be independent risk factors for early mortality following ART initiation [3, 25–29], suggesting that more aggressive efforts are needed to reach male PWH and retain them in care [30]. In control communities, being male and not being on ART were risk factors for death; however, they were no longer risk factors for death in the intervention communities. These results show that with widescale HIV testing, linkage, and treatment interventions, excess mortality among patients not on ART

and among men can be significantly reduced. Although men have a lower uptake of HIV testing services as described above [31], our previously published social science studies from the SEARCH trial [32, 33]provide potential pathways for reduced mortality among men, as compared to women. Specifically, men in the SEARCH study were more socially supported following their HIV diagnosis, and the SEARCH intervention facilitated subsequent linkage to care and retention. Furthermore, men reported fewer financial, social, and partner-level challenges related to their HIV disclosure and care seeking, which all may have facilitated clinic attendance, better health outcomes, and thus, decreased mortality.

In contrast to men, our streamlined care intervention was not associated with a statistically significant reduction in mortality among women with low CD4 count. Our linkage to care and chronic care interventions in the intervention communities were the same for women and men. The proportion of PWH with low CD4 count who were ART-naive at study baseline was the same among men (44%) and women (43%), and time to ART initiation among ART naive persons was similar between men and women within each arm. At baseline in both control and intervention communities, men as compared to women were more likely to be over 50 years of age. However, the gender difference in effect size remained after age adjustment. A potential explanation for more pronounced effect of the intervention among men was that among PWH with CD4 ≤ 350/uL, men were more likely to have CD4 < 150/uL, to be ART naive, and to have baseline VL > 100 000 copies/mL. Thus, men with low CD4 count may have been at elevated risk of HIV progression and death compared to women.

Limitations of our study are that we did not establish highly detailed causes of death, although in sensitivity analyses (data not shown) results were similar after excluding deaths due to suicide, trauma, and childbirth. Because we delivered patient-centered streamlined care as a multicomponent package intervention, we could not assess which specific components of the streamlined care system (eg, flexible hours, reduced visit frequency) were central to its overall success. However, the full multicomponent package was explicitly designed to be feasible, low cost, and synergistic; cost of the full multicomponent streamlined care program was in the range of other and PEPFAR sponsored programs [34].

In conclusion, after population-based HIV testing, SEARCH streamlined care accelerated ART initiation and reduced mortality at a population level among PWH with CD4 ≤ 350/uL, particularly among men. Finding PWH with low CD4 count in the community presents an opportunity to prevent HIV-related mortality. In our study and others, population-based universal testing provided a crucial means to reach this challenging population. Population-based testing, combined with streamlined care delivery, may play a key role in meeting the UNAIDS goal of eliminating all AIDS-related deaths.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

## Notes

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