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# Scaling up cervical cancer prevention in Western Kenya: Treatment access following a community-based HPV testing approach

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## Abstract

**Objective:** To evaluate access to treatment after community-based HPV testing as testing within screen-and-treat programs has the potential to lower mortality from cervical cancer in low-resource settings.

**Methods:** A prospective cohort study was conducted in western Kenya in 2018. Women aged 25–65 years underwent HPV self-testing. HPV-positive women were referred for cryotherapy. Participant data were obtained from questionnaires during screening and treatment. The proportion successfully accessing treatment and variables associated with successful treatment was determined.

**Results:** Of the 750 women included, 140 (18.6%) tested positive for HPV. Of them, 135 were notified of their results, of whom 77 (59.2%) sought treatment and 73 (52.1%) received cryotherapy. Women who received treatment had a shorter time from screening to result notification (median 92 days, interquartile range [IQR] 84–104) compared to those who did not (97 days, IQR 89–106; $P$=0.061). In adjusted analyses, women with a history of cervical cancer screening (odds ratio [OR] 11, 95% confidence interval [CI] 1.42–85.20) and those electing result notification through a home visit (OR 4, 95% CI 1.23–14.17) were significantly more likely to acquire treatment at follow-up.

**Conclusion:** Linkage to treatment after community-based HPV screening in this population was low, highlighting the need for strategies aimed at strengthening treatment linkage in similar settings.

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Author contributions

All authors were responsible for the conception and design, data analysis and interpretation, writing the manuscript, and final approval of the manuscript.

Conflicts of interest

The authors have no conflicts of interest.

**Keywords**

Cervical cancer prevention; Cervical cancer screening; Global women's health; HPV screening; Low-income countries; See-and-treat

## 1 INTRODUCTION

Cervical cancer is the second most common cancer among women in low- and middle-income countries (LMICs) [1]. In 2018, approximately 80% of the 500 000 cases of cervical cancer and 90% of the 311 000 deaths worldwide occurred in LMICs [1]. Lack of widespread screening programs and subsequent treatment for precancerous lesions explain this disproportionate burden [2]. Although vaccination will become a powerful driver of prevention, among women above the vaccination age cohort, screening programs remain the primary strategy for prevention. A 2015 survey in Kenya found that only 16.4% of women aged 30–49 years had ever undergone cervical cancer screening [3].

Low-income countries lack the healthcare infrastructure required for cytology-based screening programs that have reduced the disease burden in high-income countries. In 2013, WHO recommended cervical cancer screening using visual inspection with acetic acid (VIA) or HPV testing in LMICs [4]. HPV-based screening is superior to VIA for the detection of precancerous lesions and reduction in mortality[5, 6], and both WHO and Kenya Cancer Screening guidelines recommend HPV testing as a primary screening test [4, 7]. HPV self-sampling is highly accurate when compared to physician-collected samples [8], is acceptable to women [9], and increases the uptake of screening, potentially widening the reach and impact of screening programs [10]. WHO recommends coupling HPV screening with immediate treatment due to limited availability of colposcopy and histopathology [4]. Data show that screen-and-treat programs that link HPV directly to cryotherapy reduce the risk of precancer and invasive cancer [5].

An alternative to facility-based cervical cancer screening is screening within the community during Community Health Campaigns (CHCs), which are high-volume, community-based screening programs [11]. Community-based cervical cancer screening via HPV self-collection addresses barriers to facility-based screening including distance, staff shortage, and a pelvic exam, and is cost-effective compared to VIA-based screening if coupled with high rates of follow-up [11]. While several studies in LMICs have reported on community-, home-, or clinic-based HPV self-sampling [10–14], few have reported on the frequency and determinants of successful acquisition of treatment among screen-positive women [14, 15], a critical step in the prevention cascade.

By offering screening at the community level and linking only those who screen positive to facility-based care, CHCs can reduce the visit burden for both women and facilities [16]. A recent randomized controlled trial found that CHC-based HPV self-testing in western Kenya was highly acceptable, and reached a higher number of women in the community (60%) compared with clinic-based screening (37%, $P<0.001$) [16]. Although CHCs can increase access to screening, limited data from LMICs evaluate the successful linkage to treatment following CHC-based screening. Understanding the determinants of successful acquisition

of treatment is a crucial part of the cervical cancer prevention cascade, without which the impact of screening programs may not be realized. The aim of the present study was to investigate the frequency and determinants of treatment acquisition among women who had HPV detected via self-sampling following a community-based screening campaign.

## 2 MATERIALS AND METHODS

Between April and May 2018, a prospective cohort study of HPV testing and follow-up was conducted in a peri-urban area of Kisumu County, Kenya. The target population was women aged 25–65 years and eligible for screening. Exclusion criteria were history of hysterectomy or diagnosis of cervical cancer. Screening of cervical cancer was nested within the CHC component of the Community Health Initiative conducted by the Family AIDS Care & Education Services (FACES) program in partnership with the Ministry of Health in Kenya. The CHCs were part of a model of HIV care which sought to achieve a population coverage of over 90% for HIV testing and linkage to care through community-based testing and included screening for HIV, diabetes, and hypertension [17]. Before the CHCs, community engagement and mobilization were carried to sensitize participants about the upcoming screening for cervical cancer.

During the CHCs, women were invited to participate in a brief cervical cancer and HPV education session. Participation was voluntary and screening was free of charge. Individual informed consent was obtained followed by a brief survey to collect demographic and reproductive health information and the preferred mode of HPV result notification. Women were then provided with the HPV testing kit, given pictorial self-collection instructions, and directed to private areas for self-collection. During self-collection, women were instructed to insert the brush into the vagina until they met resistance, rotate it several times, and then remove and place the brush into the specimen cup, which was sealed, placed in a specimen bag, and returned to study staff.

Specimens were transported to the study laboratory for processing and batch testing with the *care*HPV Test Kit (Qiagen, Germantown, MD, USA), as previously described [11]. Following processing, participants were notified of their results based on their preferred mode of notification – text message, phone call, or a home visit. At least three different active attempts were made to reach participants; after this, they could obtain their results by calling the study phone. A text notification was considered successful if transmission of the text message was confirmed by the Frontline SMS program (i.e. the phone was on, the SIM card was valid, the line was active). Phone and home visits were successful if the participant was reached in person and given her results directly by study staff. Follow-up guidelines were provided according to the Kenya Ministry of Health protocol [7].

All HPV-positive women were offered free treatment at one of two county hospitals, per WHO recommendations of screen-and-treat after a positive HPV test [4]. A pre-treatment VIA was done to determine eligibility and mode of treatment. Cryotherapy, performed by trained nurses, was offered to women with an entirely visible lesion and squamocolumnar junction, with lesions covering less than 75% of the cervix, per the Ministry of Health and WHO guidelines [4, 7]. Women whose lesions were not amenable to treatment with

cryotherapy were referred for biopsy or loop electrosurgical excision procedure (LEEP) at the local referral hospital. Following cryotherapy, a brief survey was administered eliciting participants experience with treatment.

The number and proportion of HPV-positive women who successfully received treatment 6 months after the community campaign and the percentage acquiring treatment within a single visit with a 95% confidence interval (CI) were determined. The clinical and demographic variables associated with successful treatment acquisition were examined. The average time from HPV testing and access to treatment was evaluated, as well as the patient satisfaction with cryotherapy. To test for associations between treatment acquisition and categorical explanatory variables, $\chi^2$ and Fisher exact tests were performed. For continuous explanatory predictors, two independent-sample t-tests were used to compare sample means by the outcome. Logistic regression was used to explore the association of demographic and clinical variables with the outcome of successful treatment acquisition. Variables found to be significantly associated with treatment in the bivariate analysis were considered for multivariate analysis. All data were analyzed using Stata version 15.0 (College Station, TX, USA). Institutional review board approval was obtained from the Kenya Medical Research Institute (KEMRI), the University of California San Francisco, and Duke University.

## 3 RESULTS

Among the 750 women participating in the study, 140 (18.6%) tested positive for HPV. The mean age of HPV-positive women was 35 years (SD ± 9) (Table 1). Of the HPV-positive women, 130 (92.8%) were notified of their test results by their preferred mode of notification. The remaining women did not receive their results despite multiple attempts due to non-functional phone numbers or inability of community health workers to locate them during home visits. The majority of women (88%) had a successful result notification on the first attempt (Table 2). Among the 130 women notified of their HPV results, 77 (59.2%) sought treatment and 73 (52.1%) received treatment with cryotherapy (Fig. 1).

The majority of women who screened HPV-positive were married (57.5%) and had at least some primary school education (52.1%) (Table 1). One-third of women (30.5%) self-identified as HIV-positive. The majority of HIV-positive women (97.4%) were on antiretroviral therapy at the time of screening. Of the women, 37% reported a history of cervical cancer screening and 53% endorsed prior knowledge of HPV.

In bivariate analysis, variables significantly associated with treatment acquisition included marital status ($P$=0.019), level of education ($P$=0.017), and prior screening for cervical cancer ($P$=0.023) (Table 1). Women who received treatment had a significantly shorter time from screening to result notification (median 92 days, interquartile range [IQR] 84–104) compared to those who did not receive treatment during the study follow-up (median 96 days, IQR 89–106; $P$=0.061. In adjusted multivariate logistic regression, prior cervical cancer screening (odds ratio [OR] 11.00, 95% CI 1.42–85.20) and HPV result notification through a home visit (OR 4.00, 95% CI 1.23–14.17) were statistically significantly associated with successful treatment acquisition (Table 3).

Among the 77 women who presented for treatment, four did not receive treatment. Two were referred for biopsy for lesions suspicious for cancer, one had cervicitis for which she received antibiotics and HPV treatment was deferred, and one was not eligible for treatment due to a history of total hysterectomy (Table 2). Among the 73 women who received treatment, 97.3% received treatment on the first day sought (95% CI 0.94–1.01), with all 73 receiving cryotherapy. The median time from HPV result notification to treatment was 94 days (IQR 86–106). Women traveled, on average, 27 minutes to the treatment center (SD ± 13.8), with the majority using a motorbike (52.1%) for transportation, followed by taxi (30%) and walking (17.8%). Most women (74%) denied any difficulty with transportation in accessing treatment. Women reported spending an average of 4.5 hours in accessing treatment (SD ± 2.7), with 47.9% reporting missing work to access treatment. Almost all women (97.3%) felt that the procedure was explained clearly to them. Although 45.2% (95% CI 0.34–0.57) reported feeling some pain or discomfort with the treatment, all women said that they would recommend cryotherapy to a friend. As a small pilot study, high rates of data completeness were obtained, with the rate of missing data at less than 2%.

## 4 DISCUSSION

It was found that a little over half of the women who had HPV detected via self-screening at a multi-disease CHC received treatment over a 6-month follow-up period. Although the screening occurred in a peri-urban area, and treatment was acceptable and free of charge, uptake was less than optimal. In multivariate analysis, a history of prior screening for cervical cancer and HPV result notification via a home visit, compared to text message, was associated with increased likelihood of accessing treatment. It was also found that a shorter time from screening to result notification was associated with increased odds of accessing treatment, although this was not statistically significant. While almost half of the treated women reported some pain or discomfort with treatment, all women said they would recommend treatment to a friend.

Effective secondary prevention of cervical cancer is multifaceted, comprising adequate screening coverage with an appropriate screening test, frequent screening intervals, linkage of screen-positive women to treatment, and adequate follow-up after treatment. In this cascade, successful programs must link screening to timely and appropriate treatment for screen-positive women. One factor that strongly impacts treatment uptake is the inability to deliver immediate results and offer women same-day treatment. None of the currently available HPV-testing assays used in LMICs, including the *care*HPV test kit (Qiagen, Germantown, MD, USA), which requires batch testing of approximately 90 specimens, with a processing time of approximately 3 hours [11], and the *Xpert* HPV assay (Cepheid, Sunnyvale, CA, USA), which allows for single-sample processing with results available in approximately 1 hour, can offer truly point-of-care testing [13]. In the absence of a point-of-care HPV test, minimizing the time from screening to result notification may increase uptake.

The rate of treatment uptake in the present study is similar to the rates of treatment and follow-up in studies using *careHPV* testing (45%–51%) [11, 14], but is lower compared to reported follow-up in studies using the *Xpert* HPV assay (90%–94%) [15, 18]. A study

evaluating a 2015 community-based HPV screening program in western Kenya reported that while 76% of HPV-positive women were notified of their results, 51% of those testing positive presented for treatment during the follow-up period [11]. A study in Uganda on community-based HPV self-sampling compared to clinic-based VIA found that only 45% of HPV-positive women attended a follow-up appointment for results and management [14]. In a clinic-based screen-and-treat study in Papua New Guinea (PNG) among 700 participants using HPV-self testing, 12.5% of women were HPV-positive, of whom 94% received same-day treatment [15]. Compared to the above studies, which used the *careHPV* assay, the study in PNG has a particularly high rate of treatment following HPV positivity, possibly related to use of the *Xpert* HPV assay which allows single-sample processing with results available in 1 hour [19]. This high rate of treatment uptake in the study in PNG is mirrored in another study using the *Xpert* HPV test. In Cameroon, Kunckler et al. [18] also evaluated an HPV-based see-and-treat program using clinic-based self-sampling. Among 121 screen-positive women, 110 (90.1%) received same-day treatment [18]. In the present study, it was found that a shorter time from screening to result notification resulted in higher linkage to treatment, highlighting a potential need to incorporate point-of-care HPV tests into CHCs or adopt strategies to decrease the time from screening to result notification.

Our treatment uptake rate of 52%, while lower than reported rates in the two studies using the *Xpert* HPV assay, is comparable to rates of follow-up reported in VIA-based programs in similar settings [14, 20]. However, studies show that HPV-based screening, recommended as first-line in LMICs where available, is more effective than VIA-based screening [21], and has greater reduction in mortality from cervical cancer when coupled with treatment compared to VIA [5]. Widespread use of HPV self-sampling has the potential to further increase the reach and efficacy of screening programs for cervical cancer, if timely linkage to treatment is achieved.

Efforts to address barriers to treatment uptake are crucial in strengthening the cervical cancer prevention cascade. While the model in the present study demonstrated excellent acceptability, with 100% of women treated saying they would recommend it to a friend, almost half of the women testing positive did not receive treatment within 6 months. Several studies have evaluated barriers to treatment uptake after screening for cervical cancer. A study in Cameroon found that the use of reminder phone calls coupled with peer counseling and navigation of women diagnosed with cervical precancer could be effective ways of improving adherence to follow-up [22]. The role of patient navigators in improving linkage to treatment after screening for cervical cancer has been highlighted in Tanzania [23, 24].

A limitation of the present study is its relatively small sample size. While the prevalence of HPV (18.6%) is similar to that reported by other studies from the region [11, 14, 25], the present analysis was based on 140 HPV-positive women needing treatment. Other factors, such as the distance to the treatment facility or long wait times once at the treatment facility, may have affected the uptake of treatment in the present study and were not captured in the data.

To support the cost-effectiveness of HPV-based screening, strategies to decrease loss to follow-up, such as point-of-care diagnostics with same-day treatment or faster time to result

notification, and use of patient navigators to promote adherence to follow-up need further investigation. For successful treatment linkage, the HPV result notification via home visits may be more effective compared to text messages or phone calls.

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## Synopsis

Cryotherapy after a community-based HPV self-testing program was highly acceptable, but treatment access was low, highlighting the need for strategies to strengthen linkage to treatment.

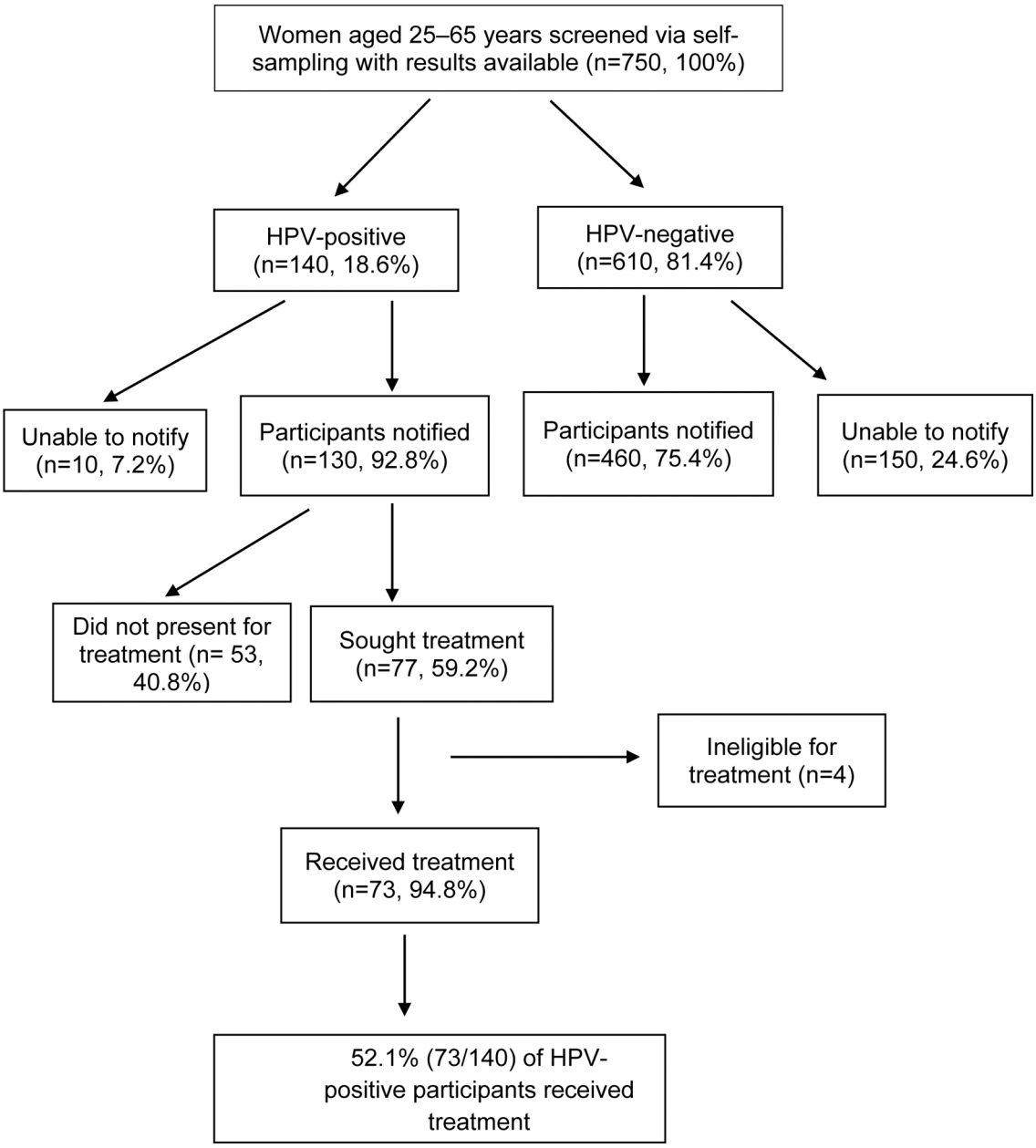


**Figure 1.**
Study flow chart.

**Table 1.**

Sociodemographic and clinical characteristics of HPV-positive women in Kisumu, Kenya by treatment uptake status.[a]

| Characteristic | Total (n=140) | Received treatment (n=73 (52%)) | Did not receive treatment (n=67 (48%)) | *P* value (t-test, $\chi^2$ or Fisher exact test) |
|---|---|---|---|---|
| Age (years) | 35.3±9.3 | 35.6±8.7 | 35.0±10.0 | 0.682 |
| *Marital status* | | | | 0.019 |
| Single | 31 (24.4) | 20 (64.5) | 11 (35.5) | |
| Married | 73 (57.5) | 33 (45.2) | 40 (54.8) | |
| Widowed | 16 (12.6) | 11 (68.8) | 5 (31.2) | |
| Divorced | 2 (1.6) | 1 (50.0) | 1 (50.0) | |
| Separated | 5 (3.9) | 0 | 5 (100.0) | |
| *Polygamous marriage* | | | | 0.743 |
| Yes | 10 (13.7) | 5 (50.0) | 5 (50.0) | |
| No | 63 (86.3) | 28 (44.4) | 35 (55.6) | |
| *Level of education* | | | | 0.017 |
| None | 18 (12.8) | 11 (61.1) | 7 (38.9) | |
| Some primary | 73 (52.1) | 30 (41.1) | 43 (58.9) | |
| Some secondary | 36 (25.7) | 21 (58.3) | 15 (41.7) | |
| Tertiary or higher | 13 (9.3) | 11 (84.6) | 2 (15.4) | |
| *Reason for attending CHC* | | | | 1.000 |
| Feeling unwell | 96 (80.7) | 49 (51.0) | 47 (49.0) | |
| Well-being check-up | 18 (15.1) | 9 (50) | 9 (50) | |
| Other[b] | 5 (4.2) | 2 (40) | 2 (60) | |
| *Self-reported HIV status* | | | | 0.934 |
| Positive | 39 (30.5) | 20 (51.3) | 19 (48.7) | |
| Negative | 78 (60.9) | 40 (51.3) | 38 (48.7) | |
| Unknown | 11 (8.6) | 5 (45.5) | 6 (54.5) | |
| Use of antiretroviral therapy at time of HPV testing (only HIV-positive) | | | | 1.000 |
| Yes | 38 (97.4) | 19 (50.0) | 19 (50.0) | |
| No | 1 (2.6) | 1 (100) | 0 | |
| *Reported HIV stigma (only HIV-positive* | | | | 1.000 |
| Yes | 4 (11.4) | 2 (50.0) | 2 (50.0) | |
| No | 31 (88.6) | 16 (51.6) | 15 (48.4) | |
| Age first sex (years) | 16.9±2.2 | 17±2.5 | 16.9±1.8 | 0.734 |
| Parity | 3±2 | 3±2 | 3±2 | 0.685 |
| *Current method of contraception* | | | | 0.193 |
| Condoms | 5 (4.2) | 4 (80) | 1 (20) | |
| Injectable | 21 (17.6) | 9 (42.9) | 12 (57.1) | |
| Implant | 84 (70.6) | 41 (48.8) | 43 (51.2) | |

| Characteristic | Total (n=140) | Received treatment (n=73 (52%)) | Did not receive treatment (n=67 (48%)) | *P* value (t-test, $\chi^2$ or Fisher exact test) |
|---|---|---|---|---|
| Other[c] | 9 (7.6) | 7 (77.8) | 2 (22.3) | |
| *Reported prior screening for cervical cancer* | | | | 0.023 |
| Yes | 12 (37.5) | 11 (91.7) | 1 (8.3) | |
| No | 20 (62.5) | 10 (50.0) | 10 (50.0) | |
| *Prior knowledge of HPV testing* | | | | 0.169 |
| Yes | 17 (53.1) | 13 (76.5) | 4 (23.5) | |
| No | 15 (46.9) | 8 (53.3) | 7 (46.7) | |
| *Result notification method* | | | | 0.141 |
| Text message | 15 (19.5) | 7 (46.7) | 8 (53.3) | |
| Phone call | 15 (19.5) | 12 (80.0) | 3 (20.0) | |
| Home visit | 47 (61.0) | 26 (55.3) | 21 (44.7) | |
| *Number of notification attempts* | | | | 1.000 |
| 1 | 120 (88.9) | 65 (54.2) | 55 (45.8) | |
| 2 | 7 (5.2) | 4 (57.1) | 3 (42.9) | |
| 3 | 6 (4.4) | 3 (50) | 3 (50) | |
| 4 | 2 (1.5) | 1 (50) | 1 (50) | |
| *Result notification on first attempt* | | | | 0.951 |
| Yes | 120 (88.9) | 65 (54.2) | 55 (45.8) | |
| No | 15 (11.1) | 8 (53.3) | 7 (46.7) | |
| Time from screening to notification (days) | 94 (86–106) | 92 (84–104) | 97 (89–106) | 0.061 |

Abbreviation: CHC, Community Health Campaign.

[a]Values are given as number (percentage), mean ± SD, or median (interquartile range).

[b]Other = Someone recommended the visit, curious about services, other reasons.

[c]Other = oral contraceptive pill, intrauterine device, sterilization, lactational amenorrhea.

**Table 2.**

HPV-positive women's experience in accessing treatment after self-screening.[a]

| Characteristic | Treatment acquisition Yes (%) (n=73) | 95% CI |
|---|---|---|
| Time from notification to treatment (days) | 13 (1–50) | |
| *Treatment received on first day sought* | | |
| Yes | 97.3 | 0.91–1.00 |
| No | 2.7 | 0.00–0.10 |
| Travel time to treatment center (min) | 27.04±13.80 | |
| *Type of transport to clinic* | | |
| Motorbike | 52.1 | |
| Taxi | 30.1 | |
| Walking | 17.8 | |
| Cost of transport to treatment (US$) | 075±0.46 | |
| *Difficulty with transport to treatment* | | |
| Yes | 26.03 | 0.16–0.38 |
| No | 73.97 | 0.62–0.84 |
| Missed work in order to access treatment | | |
| Yes | 47.89 | 0.36–0.60 |
| No | 52.11 | 0.40–0.64 |
| Hours used in accessing treatment | 4.53±2.72 | |
| *Did you need childcare to attend treatment?* | | |
| Yes | 26.03 | 0.16–0.38 |
| No | 73.97 | 0.62–0.84 |
| *Was the treatment procedure explained clearly?* | | |
| Yes | 97.26 | 0.90–1.00 |
| No | 2.74 | 0.00–0.10 |
| *Type of treatment received* | | |
| Cryotherapy | 100 | |
| *Reason not treated after presenting for treatment* | | |
| Referred for biopsy | 2 (50) | |
| Cervicitis | 1 (25) | |
| Had received total hysterectomy | 1 (25) | |
| Was treatment uncomfortable or painful? | | |
| Yes | 45.21 | 0.34–0.57 |
| No | 54.79 | 0.43–0.66 |
| Would you recommend the treatment to a friend? | | |
| Yes | 100 | |
| No | 0 | |

[a]Values are given as number (percentage), mean ± SD, or median (interquartile range).

**Table 3.**

Odds ratios for successful treatment acquisition.[a]

| Patient factor | Category | Treated | Not treated | Unadjusted OR | 95% CI of unadjusted OR | Adjusted OR | 95% CI of adjusted OR |
|---|---|---|---|---|---|---|---|
| Age (years) | ------ | 33 (28–41) | 31 (28–38) | 1.01 | 0.97–1.04 | 1.09 | 0.78–1.52 |
| Marital status | Not partnered | 36 (65) | 19 (35) | 1.00[b] | | | |
| | Partnered | 36 (44) | 46 (56) | 0.41 | 0.20–0.84[c] | 0.78 | 0.51–1.21 |
| Level of education | None | 3 (50) | 3 (50) | 1.00[b] | | | |
| | Primary | 32 (42) | 44 (58) | 0.73 | 0.14–3.84 | | |
| | Secondary | 25 (61) | 16 (39) | 1.56 | 0.28–8.72 | | |
| | Post-secondary | 12 (86) | 2 (14) | 6.00 | 0.67–53.68 | | |
| Parity | ------ | 2 (1–3) | 3 (1–5) | 0.75 | 0.47–1.19 | | |
| Reported prior cervical cancer screening | No | 10 (50) | 10 (50) | 1.00[b] | | | |
| | Yes | 11 (92) | 1 (8) | 11.00 | 1.19–101.98[c] | 11.00 | 1.42–85.20[c] |
| Prior knowledge of HPV testing | No | 8 (53) | 7 (47) | 1.00[b] | | | |
| | Yes | 13 (76) | 4 (24) | 2.84 | 0.63–12.89 | | |
| Result notification method | Text message | 7 (47) | 8 (53) | 1.00[b] | | | |
| | Phone call | 26 (55) | 21 (45) | 1.41 | 0.44–4.54 | 1.24 | 0.70–2.20 |
| | Home visit | 12 (80) | 3 (20) | 4.57 | 0.90–23.14 | 4.00 | 1.23–14.17[c] |
| Number of notification attempts | > 1 | 8 (40) | 12 (60) | 1.00[b] | | | |
| | 1 | 65 (54) | 55 (46) | 1.77 | 0.68–4.65 | | |
| Time from screening to notification (days) | ------ | 92 (84–104) | 97 (89–106) | 0.98 | 0.96–1.00[c] | 1.19 | 0.84–1.68 |

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Values are given as number (percentage), mean ± SD, or median (interquartile range).

[b]Reference category.

[c]Statistically significant at 95% CI.