Screen-and-Treat Approaches for Cervical Cancer Prevention in Low-Resource Settings

A Randomized Controlled Trial

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Context Non–cytology-based screen-and-treat approaches for cervical cancer prevention have been developed for low-resource settings, but few have directly addressed efficacy.

Objective To determine the safety and efficacy of 2 screen-and-treat approaches for cervical cancer prevention that were designed to be more resource-appropriate than conventional cytology-based screening programs.

Design, Setting, and Patients Randomized clinical trial of 6555 nonpregnant women, aged 35 to 65 years, recruited through community outreach and conducted between June 2000 and December 2002 at ambulatory women's health clinics in Khayelitsha, South Africa.

Interventions All patients were screened using human papillomavirus (HPV) DNA testing and visual inspection with acetic acid (VIA). Women were subsequently randomized to 1 of 3 groups: cryotherapy if she had a positive HPV DNA test result; cryotherapy if she had a positive VIA test result; or to delayed evaluation.

Main Outcome Measures Biopsy-confirmed high-grade cervical cancer precursor lesions and cancer at 6 and 12 months in the HPV DNA and VIA groups compared with the delayed evaluation (control) group; complications after cryotherapy.

Results The prevalence of high-grade cervical intraepithelial neoplasia and cancer (CIN 2+) was significantly lower in the 2 screen-and-treat groups at 6 months after randomization than in the delayed evaluation group. At 6 months, CIN 2+ was diagnosed in 0.80% (95% confidence interval [CI], 0.40%-1.20%) of the women in the HPV DNA group and 2.23% (95% CI, 1.57%-2.89%) in the VIA group compared with 3.55% (95% CI, 2.71%-4.39%) in the delayed evaluation group ($P<.001$ and $P=.02$ for the HPV DNA and VIA groups, respectively). A subset of women underwent a second colposcopy 12 months after enrollment. At 12 months the cumulative detection of CIN 2+ among women in the HPV DNA group was 1.42% (95% CI, 0.88%-1.97%), 2.91% (95% CI, 2.12%-3.69%) in the VIA group, and 5.41% (95% CI, 4.32%-6.50%) in the delayed evaluation group. Although minor complaints, such as discharge and bleeding, were common after cryotherapy, major complications were rare.

Conclusion Both screen-and-treat approaches are safe and result in a lower prevalence of high-grade cervical cancer precursor lesions compared with delayed evaluation at both 6 and 12 months.

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EACH YEAR 471 000 CASES AND 233 000 deaths occur from cervical cancer worldwide, of which 80% occur in less-developed countries that have access to less than 5% of global cancer treatment resources.[1] The lifetime risk of a woman developing cervical cancer in a low-resource setting is approximately 2% to 4%.[2-4] Cytology-based screening programs have markedly reduced the incidence of cervical cancer in developed countries that have the infrastructure to support these programs.[5] However, screening programs have proven difficult to implement in low-resource settings. There are 2 predominant reasons why cytology-based programs have proven difficult to implement and sustain in low-resource settings. One is the nature of the screening test.[6] High-quality cytology laboratories are difficult to maintain and there are often substantial delays before the results become available.[7] Another is the extensive workup that is typically used for women with abnormal cytological results. In developed countries, women with abnor-

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mal cytological results are usually referred for colposcopy with biopsy before initiating treatment.[8] Although this helps ensure that only women with high-grade cervical cancer precursors receive treatment, colposcopy services and histopathologic laboratories often are not available in low-resource settings.

Recently, a novel approach to cervical cancer prevention has been proposed that avoids the complex health infrastructure required by traditional approaches.[9,10] This approach incorporates non–cytology-based screening methods such as human papillomavirus (HPV) DNA testing or visual inspection with acetic acid (VIA) followed by treatment using cryotherapy of all eligible women with positive test results. Both of these approaches perform as well as or better than cytology-based screening for identifying high-grade cervical cancer precursor lesions and cryotherapy is a relatively low-technology treatment method that is highly efficacious and has minimal morbidity.[11-13]

The screen-and-treat approaches described herein have advantages for low-resource settings because they are not cytology-based screening programs and they do not require colposcopy services, which overcome 2 of the greatest barriers to cervical cancer prevention. However, the efficacy of the screen-and-treat approaches has not yet been established, and there are only limited safety data.[9]

METHODS

Study Design

Our study was designed to measure the impact of the screen-and-treat approach on the prevalence of high-grade cervical intraepithelial neoplasia and cancer (CIN 2+). The randomized clinical trial described herein compared 2 screen-and-treat groups (HPV DNA testing and VIA) with a control group that received delayed evaluation. The primary outcomes were biopsy-confirmed CIN 2+ at 6 months and significant complications within 6 months of randomization.

Participants and Clinical Examinations

Never screened, nonpregnant women aged 35 to 65 years were enrolled at 3 clinical sites in close proximity in Khayelitsha, South Africa. All women provided informed consent, completed a questionnaire, received counseling for confidential human immunodeficiency virus (HIV) testing, a pregnancy test if not postmenopausal, anonymous HIV serotesting, and a vaginal speculum examination performed by nurses trained in VIA (also referred to as direct visual inspection as previously described[14]). Cervical specimens were obtained for testing for *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and high-risk types of HPV, and cytology. The cervix was washed with 5% acetic acid and inspected for gross abnormalities or areas of acetowhitening and a 35-mm photograph was taken.

Women with significant cervicitis or vulvovaginitis were treated using the syndromic approach.[15] Women who had positive test results for *N gonorrhoeae* or *C trachomatis* received appropriate treatment. A positive VIA test result was defined as any acetowhite lesion and no attempt was made to differentiate the acetowhitening of metaplasia from CIN.[16] A total of 451 women were excluded because they had lesions suspicious for cancer (n=46), large acetowhite lesions extending over 70% of the cervix (n=17) or into endocervical canal (n=14), or were ineligible for cryotherapy due to severe atrophy (n=83), polyps (n=135), cervix distorted (n=86), cervix not adequately visualized (n=55), and other reasons (n=15). These excluded women were referred for a colposcopy. Cervical cancer was detected in 23 of these women, of whom 20 had a grossly visible lesion.

Women returned 2 to 6 days later for randomization to either the (1) HPV DNA group in which all women with positive HPV DNA test results received cryotherapy; (2) VIA group in which all women with positive VIA test results received cryotherapy; or (3) delayed evaluation (control) group. Randomization was done using a computer-generated randomization schedule with group assignments provided to the clinics in sealed envelopes. Randomization schedules were generated in batches of 300 to maintain a 1:1:1 ratio between groups during study enrollment. Cryotherapy was performed by nurses using nitrous oxide and a cryosurgical unit (Wallach Surgical Devices, Orange, Conn) with two 3-minute freezes.[17] Both treated and untreated women were asked to return at 4 weeks to complete a questionnaire.

At 6 months, a colposcopy was performed by a physician blinded to group assignment and clinical information. All acetowhite lesions required biopsy and all women irrespective of whether a lesion was observed underwent an endocervical curettage. Women with CIN 2+ were treated appropriately. Assessment and treatment of women who became pregnant during the study was postponed until 3 months postpartum. Blood for anonymous HIV serotesting was obtained. All women who had either HPV DNA or VIA positive test results at enrollment and a subset who had either HPV DNA or VIA negative test results (all women enrolled in 2002) were scheduled for repeat colposcopy at 12 months.

The study was approved by the institutional review boards of Columbia University (New York, NY) and the University of Cape Town (Cape Town, South Africa). All participants provided written informed consent. A data and safety monitoring board monitored the trial.

Laboratory Testing

The Hybrid Capture 2 assay and high-risk probe mixture (Digene Corp, Gaithersburg, Md) was used at the University of Cape Town for HPV DNA testing. Biopsies were processed at Columbia University and evaluated by a single pathologist who was blinded to the study randomization.[18] Endocervical curettages containing high-grade cervical neoplasia were classified as positive for CIN 2+. At the end of the study, all biopsies classified as CIN and all biopsies originally classified as normal from

women who had an HPV DNA positive test result or who had a cytological result of low-grade squamous intraepithelial lesion or greater at enrollment were rereviewed by the same pathologist at Columbia University. If the second review did not result in the same assessment as the first review, slides were reviewed by another pathologist for a final diagnosis (concordance on 2 of 3 reviews). Among the 611 women for whom biopsies were blindly reviewed, the reviews were concordant in 491 (97%) of 506 originally classified as not having CIN 2+ and 100 (95%) of 105 originally classified as having CIN 2+. The κ coefficient agreement between the 2 reviews was 0.89.[19] In 6 discordant cases there remained a discrepancy after the third independent review that was resolved in conference.

Statistical Analysis

For power calculations, the prevalence of CIN 2+ in the population was estimated to be 3%.[20,21] Based on 80% power with a 1-sided α of .05 indicating significance and using a Bonferroni correction for 3 pairwise comparisons and 1-tail testing, it was calculated that 1664 participants per group were needed to detect a reduction of greater than 50% in CIN 2+ at 6 months in treatment groups compared with the delayed evaluation group. One-tail testing was used because there is little biological basis to expect the interventions to increase disease relative to the delayed evaluation group. This meant screening 7200 women, assuming that 70% would be eligible for the study and would be followed up at 6 months. Statistical power to evaluate complications of therapy varied with the expected prevalence of the end point. For HIV seroconversion, the trial had sufficient power to detect an increase of more than 2-fold in seroconversion across groups at 6 months, assuming a 1.5% seroconversion rate in the delayed evaluation group.

The prevalence of CIN 2+ detected by 6 months in each of the 3 groups was compared between the groups using χ^2 tests (2-sided); 95% confidence intervals (CI) around the proportions were calculated using a binomial estimate. A stratified analysis by HIV serostatus was preplanned. The efficacy of each screen-and-treat approach was quantified as the percentage difference in CIN 2+ attributable to the approach (disease prevalence in the delayed evaluation [control] group minus that in the treatment group divided by that in the delayed evaluation group). The cumulative prevalence of CIN 2+ by 12 months in each group was calculated as a weighted-average of the Kaplan-Meier life-table estimate in the stratum with positive test results for HPV DNA or VIA and the stratum with negative test results for HPV DNA or VIA, weighting each stratum-specific estimate by the proportion in each stratum at randomization. The 95% CIs were calculated using the stratum-specific SEs from the Kaplan-Meier life-table estimate.[22]

The safety analyses compared the occurrence of specific outcomes between groups and among those who did and did

Table 1. Sociodemographic Characteristics and Risk Factors for Cervical Disease at Enrollment*

	HPV DNA Group (n = 2163)	VIA Group (n = 2227)	Delayed Evaluation (Control) Group (n = 2165)
Age, mean (SD), y	43.3 (6.9)	43.3 (7.2)	43.4 (7.3)
Age, y			
35-39	818 (37.8)	862 (38.7)	866 (40.0)
40-49	924 (42.7)	935 (42.0)	870 (40.2)
50-65	422 (19.5)	430 (19.3)	429 (19.8)
Positive test result			
Human papillomavirus†	474 (21.9)	483 (21.7)	446 (20.6)
Visual inspection with acetic acid	467 (21.6)	492 (22.1)	500 (23.1)
Cytology			
LSIL on Papanicolaou test	134 (6.2)	158 (7.1)	134 (6.2)
Chlamydia trachomatis and *Neisseria gonorrhoeae*‡	117 (5.4)	118 (5.3)	104 (4.8)
Trichomonas vaginalis	236 (10.9)	245 (11.0)	221 (10.2)
Human immunodeficiency virus	268 (12.4)	252 (11.3)	264 (12.2)
Moderate to severe vaginal discharge	500 (23.1)	517 (23.2)	498 (23.0)
Treated for cervicitis or vulvovaginitis	554 (25.6)	546 (24.5)	546 (25.2)
Married	1097 (50.7)	1116 (50.1)	1104 (51.0)
Age <16 y at first sexual intercourse	731 (33.8)	777 (34.9)	738 (34.1)
≥5 Lifetime sex partners	740 (34.2)	753 (33.8)	743 (34.3)
≥2 Sex partners during previous month	30 (1.4)	36 (1.6)	28 (1.3)
Current smoker	160 (7.4)	183 (8.2)	165 (7.6)
No. of live births			
None	76 (3.5)	73 (3.3)	82 (3.8)
1-4	1395 (64.5)	1441 (64.7)	1431 (66.1)
≥5	692 (32.0)	713 (32.0)	652 (30.1)
Education			
No school	203 (9.4)	218 (9.8)	197 (9.1)
Some primary school	813 (37.6)	831 (37.3)	799 (36.9)
Some high school	956 (44.2)	1022 (45.9)	989 (45.7)
High school graduate	188 (8.7)	154 (6.9)	180 (8.3)
Currently employed	575 (26.6)	537 (24.1)	520 (24.0)
Current contraceptive use			
Injectable	318 (14.7)	379 (17.0)	325 (15.0)
Oral	32 (1.5)	51 (2.3)	43 (2.0)

Abbreviations: HPV, human papillomavirus; LSIL, low-grade squamous intraepithelial lesion; VIA, visual inspection with acetic acid.
*Values are expressed as number (percentage) unless otherwise indicated. $P>.05$ for comparisons across all 3 groups.
†Identified by using Hybrid Capture 2 (Digene Corp, Gaithersburg, Md).
‡Test results were not available until several weeks after randomization. More than 60% of these women were asymptomatic and were not treated prior to randomization using the syndromic approach.[15]

not undergo cryotherapy within a group. Comparisons were made using χ^2 tests. SAS statistical software version 8.0 (SAS Institute Inc, Cary, NC) was used.

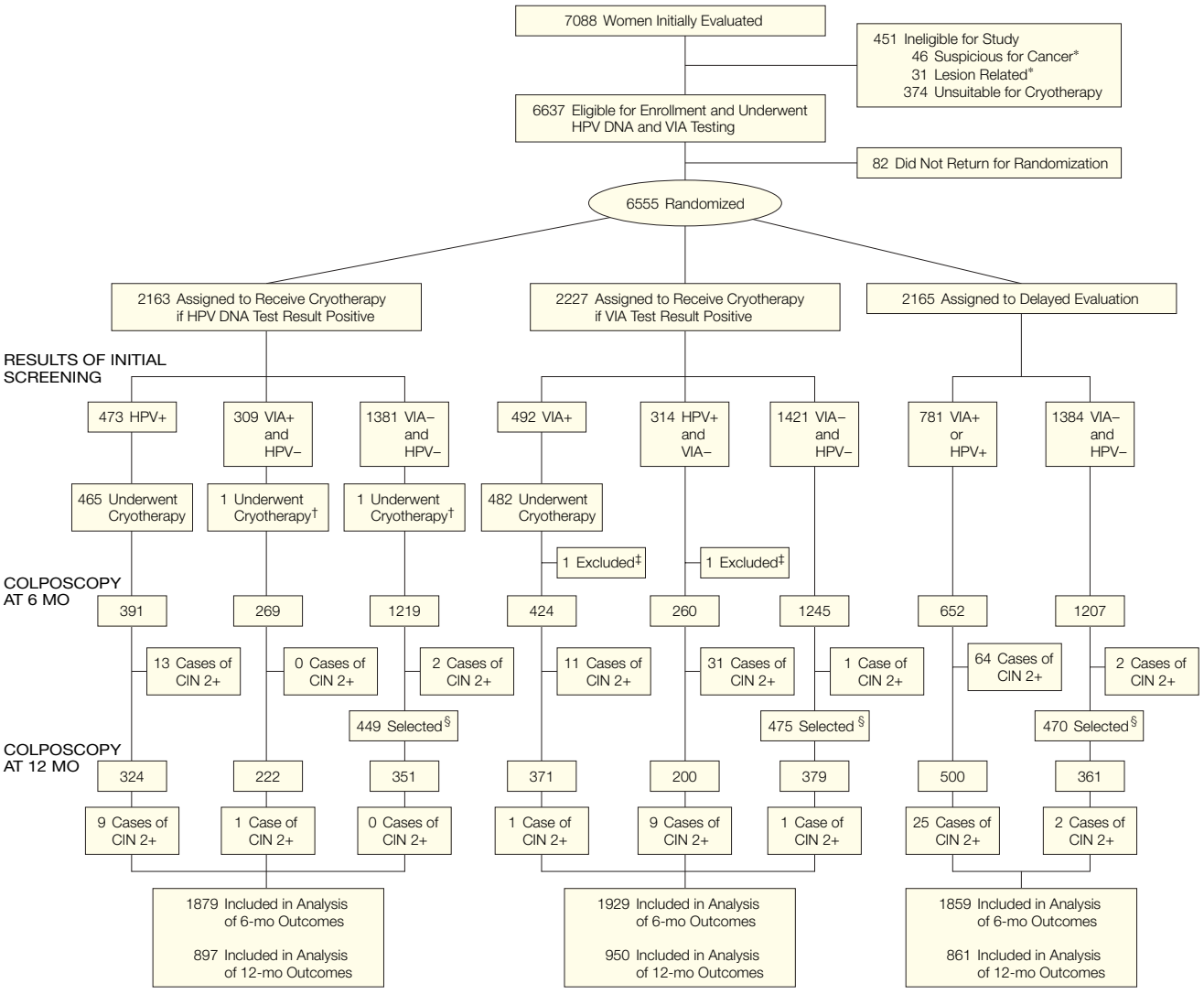
RESULTS

Participant Profile and Protocol Adherence

A total of 7088 women were evaluated; 6637 (94%) met the eligibility criteria and underwent a complete examination between June 2000 and December 2002. Of these, 6555 (99%) returned 2 to 6 days later for randomization. There were no significant differences in sociodemographic characteristics or risk factors for CIN between groups at enrollment (TABLE 1).

Of 2163 women in the HPV DNA group, 467 (22%) underwent cryotherapy. Of 2227 women in the VIA group, 482 (22%) underwent cryotherapy. Cryotherapy was not performed in 18 women due to pregnancy (n=3), delay due to bleeding or infection and subsequently lost to follow-up (n=6), clinician error (n=5), and ineligibility (n=4). Of 949 cryotherapy procedures, 877 (92%) were performed on the day of randomization. Cryotherapy for 28 women in the HPV DNA group and 44 in the VIA group ($P=.07$) was delayed due to infection (n=37), bleeding (n=9), and other reasons (n=26). Of women undergoing cryotherapy, 136 (29%) in the

Figure 1. Distribution of Participants



CIN 2+ indicates high-grade cervical intraepithelial neoplasia and cancer; HPV, human papillomavirus; VIA, visual inspection with acetic acid.
*Considered ineligible for enrollment because VIA showed either a cervical mass or an acetowhite lesion inappropriate for cryotherapy.
†Received cryotherapy in error.
‡Cancer detected based on postrandomization assessment of cervical photographs and cytology.
§A subset of women who had negative test results for both VIA and HPV DNA were selected for 12-month follow-up.

HPV DNA group and 143 (30%) in the VIA group received antibiotic or antifungal medication at the initial screening for cervicitis or vulvovaginitis.

Impact of Screen-and-Treat Approach at 6 and 12 Months

Six-month outcome data were obtained in 5667 women (86% of those randomized; FIGURE 1). Follow-up rates did not significantly differ between groups ($P=.60$) or between those who did or did not undergo cryotherapy ($P=.39$). The interval between enrollment and the 6-month follow-up visit was also similar between groups (mean [SD],188 [49] days for the HPV DNA group; 188 [48] days for the VIA group; and 190 [55] days for the delayed evaluation group). There were significant but small differences in baseline HPV and HIV status but not in other characteristics (TABLE 2).

Compared with the delayed evaluation group, the prevalence of biopsy-confirmed CIN 2+ at 6 months was significantly less in both the HPV DNA ($P<.001$) and VIA groups ($P=.02$). At 6 months, CIN 2+ was diagnosed in 0.80% (95% CI, 0.40%-1.20%) of the women in the HPV DNA group and 2.23% (95% CI, 1.57%-2.89%) in the VIA group compared with 3.55% (95% CI, 2.71%-4.39%) in the delayed evaluation group. Thus, the screen-and-treat approach using HPV DNA testing was associated with a 77% lower prevalence of CIN 2+ than in the delayed evaluation group at 6 months, whereas the screen-and-treat approach using VIA was associated with a 37% lower prevalence (TABLE 3).

The prevalence of CIN 2+ in the HPV DNA group at 6 months remained significantly lower than that in the delayed evaluation group if the analysis was confined to HIV-seronegative women alone, but the difference associated with the VIA-based strategy did not. Among women HIV-seronegative at randomization (n=5001), CIN 2+ was diagnosed in 0.85% (95% CI, 0.40%-1.29%) in the HPV DNA group compared with 2.11% (95% CI, 1.42%-2.79%) in the VIA group and 2.75% (95% CI, 1.96%-3.54%) in the delayed evaluation group. No significant differences in the effect of either screen-and-treat approach were observed between the 3 clinical sites.

If CIN 3+ (CIN 3 and cancer) was used as the study end point at 6 months, a significant effect was seen in the HPV DNA group ($P<.001$) but not in the VIA group ($P=.11$). If CIN 1+ (all grades of CIN and cancer) was used as the study end point, the magnitude of the effect in the HPV DNA group was less but remained significant ($P<.001$); no significant effect was observed in the VIA group ($P=.36$) (FIGURE 2).

To investigate whether participants lost to follow-up may have biased our findings, we calculated what the expected effect of the 2 screen-and-treat interventions would have been if all women who had cytology results of low-grade squamous intraepithelial lesion or greater at enrollment and who were lost to follow-up (23 in the HPV DNA group, 21 in the VIA group, and 20 in the delayed evaluation group) had returned and had CIN 2+ at 6 months, regardless of whether they had received cryotherapy (ie, the intervention completely failed among those lost to follow-up). Under these assumptions the prevalence of CIN 2+ in the HPV DNA group would have been 1.76%; VIA group, 2.88%; and delayed evaluation group, 3.97%. Compared with the delayed evaluation group, there would have been a 56% reduction in the prevalence of CIN 2+ in the HPV DNA group and a 27% reduction in the VIA group.

We also investigated whether the lower prevalence of CIN 2+ at 6 months in the screen-and-treat groups was due to changes in sexual behavior as a function of participating in the study or knowledge of HIV status. This was done by comparing the prevalence of CIN 2+ at 6 months among women in the HPV DNA group who had positive test results at enrollment and received cryotherapy with that of women in the delayed evaluation group who had HPV but who did not receive cryotherapy. When stratified by sexual activity and condom use, similar effects of treatment were observed in all strata.

Clinical trials of therapies for CIN have typically followed up women for 12 months or longer. Therefore, all

Table 2. Follow-up Rates at 6 Months

	No. (%) of Participants	*P* Value
Randomization group		
HPV DNA	2163 (86.9)	.60
VIA	2227 (86.6)	
Delayed evaluation (control)	2165 (85.9)	
Cryotherapy		
Received	949 (85.6)	.39
Did not receive	5606 (86.6)	
Baseline Results		
Papanicolaou test		
≥LSIL	5920 (86.5)	.15
<LSIL	412 (83.9)	
HPV DNA test		
Positive	1402 (83.2)	<.001
Negative	5150 (87.3)	
VIA test		
Positive	1459 (85.1)	.09
Negative	5096 (86.8)	
HIV test		
Positive	782 (83.6)	.01
Negative	5760 (86.8)	
Sociodemographic Characteristics		
Age, y		
35-39	2544 (85.9)	.002
40-49	2729 (88.1)	
50-65	1282 (84.2)	
Status		
Married	3317 (85.8)	.14
Unmarried	3238 (87.1)	
Age at first sexual intercourse		
<16 y	2246 (86.2)	.66
≥16 y	4309 (86.6)	
No. of lifetime sex partners		
≥5	2233 (87.4)	.12
<5	4322 (86.0)	
No. of live births		
None	232 (87.5)	.10
1-4	4267 (87.0)	
≥5	2056 (85.1)	
Education		
No school	620 (83.7)	.20
Some primary school	2444 (86.8)	
Some high school	2968 (86.6)	
High school graduate	523 (87.4)	
Current contraceptive use		
None	5340 (86.0)	.05
Injectable	1022 (88.6)	
Oral	124 (83.9)	
Other*	69 (92.8)	

Abbreviations: HIV, human immunodeficiency virus; HPV, human papillomavirus; LSIL, low-grade squamous intraepithelial lesion; VIA; visual inspection with acetic acid.
*Implantable intrauterine devices and condoms.

women who had positive test results for HPV DNA or VIA at enrollment, as well as a subset of women who had negative test results for HPV DNA and VIA, were scheduled for a repeat colposcopy at 12 months. Because CIN 2+ was rarely detected in women who had negative test results for both HPV DNA and VIA, this approach allowed us to model the impact of screen-and-treat approaches at 12 months (Figure 1). Data were obtained from 2708 women (74% of those scheduled to be examined) and the cumulative prevalence of CIN 2+ by 12 months in both screen-and-treat groups continued to be lower than in the delayed evaluation group. In the HPV DNA group, 1.42% (95% CI, 0.87%-1.97%) had CIN 2+ by 12 months compared with 2.91% (95% CI, 2.12%-3.69%) in the VIA group and 5.41% (95% CI, 4.32%-6.50%) in the delayed evaluation group (Table 3). This translates into 1 case of CIN 2+ being averted for every 25 women enrolled in the HPV DNA group and 1 case being averted for every 40 women enrolled in the VIA group.

Complications of Screen-and-Treat Approaches

Many women reported pain or lightheadedness during the procedure and most had abnormal vaginal discharge afterward (TABLE 4). Some had abdominal pain or bleeding in the month after the procedure, which frequently resulted in consultation with a clinician. One serious adverse event occurred 2 weeks after cryotherapy. An HIV-positive woman developed severe cervical bleeding requiring hospitalization.

Twenty-seven women were recalled some weeks after randomization because their cervical cytology or photograph obtained at screening was suspicious for cancer. Twenty-four women returned for evaluation and 2 cases of invasive cancer were identified (both in the VIA group). One woman had not received cryotherapy because the cancer was in the endocervical canal and not visible, the other woman had received cryotherapy.

There were no differences in HIV-seroconversion rates 6 months after randomization: 1.06% (95% CI, 0.59%-1.53%) in the HPV DNA group; 0.99% (95% CI, 0.52%-1.46%) in the VIA group; and 1.17% (95% CI, 0.66%-1.68%) in the delayed evaluation group. This was also true 12 months after randomization: 1.76% (95% CI, 0.99%-2.53%) in the HPV DNA group; 1.90% (95% CI, 1.12%-2.68%) in the VIA group; and 1.95% (95% CI, 1.14%-2.76%) in the delayed evaluation group. Approximately half of the women who underwent cryotherapy had sexual intercourse within 1 month of the procedure and about 60% of those women used condoms (Table 4).

Differential Performance of HPV DNA and VIA Screen-and-Treat Approaches

The efficacy of the screen-and-treat approach depends on both the sensitivity of the screening test as well as the efficacy of the treatment. The reasons for the lower prevalence of CIN 2+ in the HPV DNA group compared with the VIA group were investigated by comparing specific subsets of women within groups (TABLE 5). Among HPV-positive women at enrollment, there was a 74% difference in cumulative prevalence of CIN 2+ by 12 months in the HPV DNA group compared with the delayed evaluation group. Among women with positive VIA test results at enrollment, there was a 78% difference between the VIA group and the delayed evaluation group. Therefore, the efficacy of cryotherapy was similar in the HPV DNA and VIA groups. The lower prevalence of CIN 2+ in the HPV DNA group compared with the VIA group was attributable to initial HPV DNA testing correctly identifying more women with CIN 2+ at enrollment. This interpretation is further supported by the

Table 3. Pathological Diagnoses of Cervical Intraepithelial Neoplasia

	HPV DNA Group	VIA Group	Delayed Evaluation (Control) Group
Cumulative Prevalence at 6 or 12 mo After Randomization			
CIN 2+ Total No.	25	54	93
% (95% CI)*	1.42 (0.87-1.97)	2.91 (2.12-3.69)	5.41 (4.32-6.50)
At 6 mo After Randomization			
Evaluated, No.	1879	1929	1859
CIN 1	45	58	44
Neoplasia in endocervical curettage	4	5	5
CIN 2	4	20	33
CIN 3	7	18	27
Cancer	0	0	1
CIN 2+ Total No.	15	43	66
% (95% CI)	0.80 (0.40-1.20)	2.23 (1.57-2.89)	3.55 (2.71-4.39)
At 12 mo After Randomization†			
Evaluated, No.	897	950	861
CIN 1	21	27	25
CIN 2	7	8	18
CIN 3	2	3	8
Cancer	1	0	1
CIN 2+ Total No.	10	11	27

Abbreviations: CI, confidence interval; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; VIA, visual inspection with acetic acid.
*Calculated as a weighted average of the stratum-specific Kaplan-Meier estimates of the cumulative proportions with CIN 2+ by 12 months per 100 women.
†According to the study design, only women who were free of CIN 2+ at 6 months, who had positive test results for VIA or HPV DNA testing at baseline, and a proportionate sampling of women who had negative test results for VIA and HPV DNA at baseline were eligible for 12-month follow-up. Of 1218 women in the HPV DNA group, 897 (74%) underwent assessment; 950 (77%) of 1237 women in the VIA group; and 861 (73%) of 1187 women in the delayed evaluation (control) group. The number of mean (SD) days between enrollment and the 12-month follow-up visit were similar among the groups (HPV DNA group: 385 [48]; VIA group: 388 [51]; delayed evaluation (control) group: 387 [49]).

findings among women in the delayed evaluation group. At enrollment, 84 (90%) of the 93 women subsequently identified with CIN 2+ by 12 months had positive HPV DNA test results whereas only 51 (55%) had positive VIA test results.

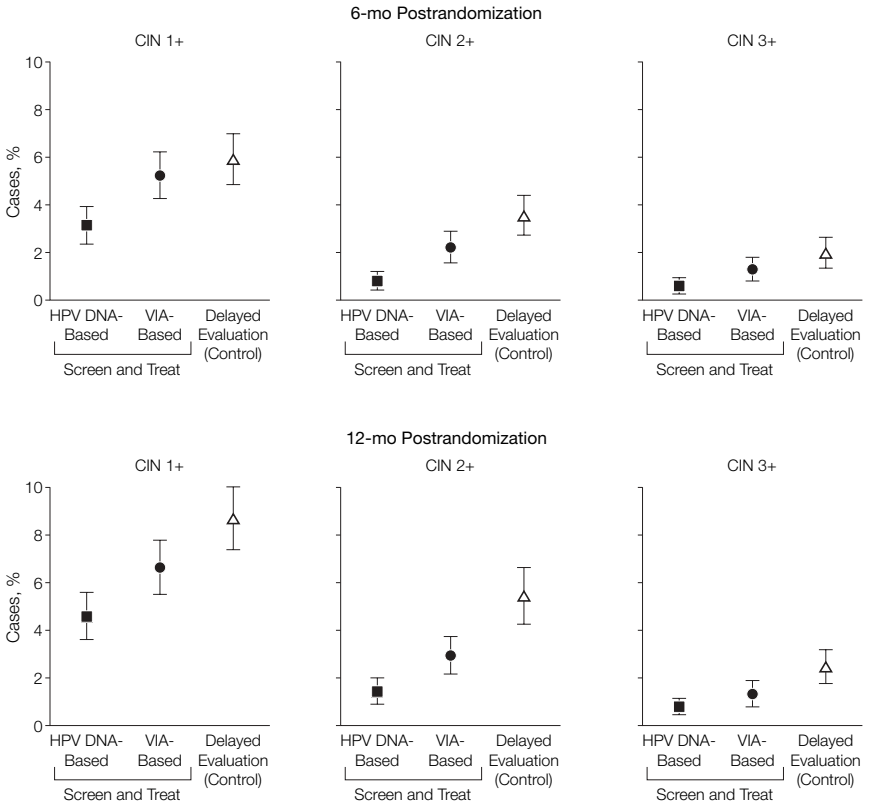
COMMENT

This trial demonstrates that screen-and-treat approaches to cervical cancer prevention, which overcome many of the limitations inherent in traditional cytology-based screening programs, are both safe and efficacious. The HPV DNA–based screen-and-treat group had up to a 77% lower prevalence of CIN 2+ compared with the delayed evaluation group at 6 months and a substantial difference was maintained at 12 months. The VIA-based screen-and-treat approach also had a significant, but lesser, impact on CIN 2+. Our results underestimate the full effect that would be obtained in a screening program because an additional 23 cancer cases and 15 cases of CIN 2+ were identified during screening among the 482 women who were ineligible for enrollment into the trial and referred for further evaluation. The differential in performance of the VIA-based approach compared with the HPV DNA-based approach is due to the identification of fewer cases of CIN 2+ by VIA rather than a differential efficacy of cryotherapy. This is consistent with a recent evaluation of the performance of VIA in 11 different cross-sectional clinical studies that reported a pooled sensitivity of 76.8% for CIN 2+.[23] In contrast, a sensitivity of greater than 90% has been reported by most large screening trials evaluating HPV DNA testing.[12]

The risk-to-benefit ratio of the screen-and-treat approaches appear to be highly favorable. There was only a single serious complication that occurred in an immunosuppressed HIV-positive patient and 99% of participants stated they would recommend this type of screening program to friends and family. A recent demonstration project from Thailand of a screen-and-treat approach also found a low rate of significant complications and a high rate of participant satisfaction.[9] Although we observed a significant impact on the prevalence of CIN 2+ with 2 screen-and-treat approaches, the magnitude of the impact that such programs will have on cervical cancer can only be established through long-term prospective studies.

There is considerable interest in addressing inequalities in global health.[24] Interest has been focused predominantly on infectious diseases that are considered more easily remedied than many other conditions. Even though cervical cancer is the leading cause of cancer-related death in women in many developing countries, cervical cancer screening is often perceived as being too difficult to implement or sustain to be included in the package of services being made available for the world's poorest countries.[25,26] The favorable results obtained in the current trial suggest that this perception may be wrong. A screen-and-treat approach lacks many of the drawbacks of cytology-based screening programs. Screening and cryotherapy can be carried out by mid-level nurses in a primary care setting. Cytology laboratories, which are difficult to sustain and are often of poor quality in low-resource settings, are not needed.[7] With visual screening methods, the entire program can be administered in 1 visit. As a result, a screen-and-treat approach should be considerably less expensive and easier to implement than traditional cytology-based screening programs. We previously evaluated the cost-effectiveness of screen-and-treat strategies if conducted in South Africa.[10] Both 1- and 2-visit strategies using HPV DNA or VIA were not only highly attractive

Figure 2. Biopsy-Confirmed Cervical Intraepithelial Neoplasia at 6 and 12 Months



Error bars indicate 95% confidence intervals. CIN 1+ indicates all grades of cervical intraepithelial neoplasia and cancer. CIN 2+ indicates CIN 2, CIN 3, and cancer. CIN 3+ indicates CIN 3 and cancer. HPV indicates human papillomavirus; VIA, visual inspection with acetic acid.

Table 4. Complications of Cryotherapy*

	HPV DNA Group		VIA Group		Delayed Evaluation (Control) Group; No Cryotherapy (n = 2165)
	Cryotherapy (n = 467)	No Cryotherapy (n = 1696)	Cryotherapy (n = 482)	No Cryotherapy (n = 1745)	
Pain, light-headedness, or other complaint	168 (36)		171 (36)		
Within 1 mo					
Unscheduled visit†	39 (9)	6 (0.4)‡	53 (11)	9 (0.5)‡	14 (0.7)
Hospital admission	1 (0.2)	3 (0.2)	1 (0.2)	4 (0.2)	4 (0.2)
Participants followed up at 1 mo	449 (96)	1646 (97)	470 (98)	1695 (97)	2096 (97)
New and troubling symptoms†	120 (27)	160 (10)‡	119 (25)	162 (10)‡	223 (11)
Consulted clinician	93 (21)	286 (17)	108 (23)	307 (18)‡	401 (19)
Vaginal discharge†	353 (79)	429 (26)‡	389 (83)	401 (24)‡	558 (27)
Abnormal bleeding	64 (14)	108 (7)‡	66 (14)	105 (6)‡	142 (7)
Abdominal pain	144 (32)	340 (21)‡	138 (29)	353 (21)‡	460 (22)
Sex since last visit†§	216 (48)	1044 (63)‡	249 (53.0)	1090 (64)‡	1341 (64)
Used male or female condoms most of the time or always†	121 (56)	176 (17)‡	149 (60)	170 (16)‡	236 (18)
Would recommend program to their friends and relatives	448 (99.9)	1644 (99.9)	470 (100)	1693 (99.9)	2092 (99.8)
Prior to 6 mo					
Cervical cancer‖	0	0	1	1	0

Abbreviations: HPV, human papillomavirus; VIA, visual inspection with acetic acid.
*Values are expressed as number (percentage).
†$P<.05$ for comparisons across the 3 groups.
‡$P<.05$ for comparisons of women receiving cryotherapy and those not receiving cryotherapy.
§After treatment, women were instructed to abstain from vaginal intercourse, douching, or using intravaginal products for 4 weeks and given condoms to use if sexually active.
‖Two cancers were missed on initial screening but were later detected prior to the 6-month study visit based on review of enrollment cytology and photographs.

Table 5. Cumulative Probability of CIN 2+ by 12 Months

	CIN 2+ by 12 mo	
Randomization Group	No. of Participants	% (95% CI)*
HPV DNA (n = 2163)		
Cryotherapy	22	5.86 (3.47-8.25)
No cryotherapy	3	0.31 (0-0.69)
VIA (n = 2227)		
Cryotherapy	12	2.73 (1.20-4.26)
No cryotherapy	42	3.74 (2.49-4.99)
Delayed evaluation (control) (n = 2165)		
No cryotherapy	93	3.55 (2.71-4.39)
HPV		
Positive	84	23.00 (18.60-27.40)
Negative	9	1.10 (0.33-1.87)
VIA		
Positive	51	12.50 (9.28-15.70)
Negative	42	4.20 (2.79-5.61)

Abbreviations: CIN 2+, high-grade cervical intraepithelial neoplasia and cancer; HPV, human papillomavirus; VIA, visual inspection with acetic acid.
*Calculated as the stratum-specific Kaplan-Meier estimates of the cumulative proportions with CIN2+ by 12 months per 100 women.

compared with traditional cytology-based approaches, but also had cost-effectiveness ratios comparable with well-accepted health interventions, such as childhood vaccines. Now that the safety and efficacy of screen-and-treat programs have been demonstrated, the next step should be to conduct large-scale public health intervention projects to better define the operational aspects of these programs. Such studies also should evaluate reductions in cervical cancer through long-term monitoring of treated populations.

The key strengths of the trial are (1) the randomized design, which ensures that any effect of participating in the trial are shared across all groups; (2) that it targeted women aged 35 years or older, which is the optimal age to initiate cervical cancer screening in low-resource settings[2,4]; and (3) that all participants underwent colposcopy and histological sampling at 6 months with blinded review of all results making ascertainment bias unlikely.

The study also has several potential limitations. One limitation is the length of follow-up for the primary end point. To measure the impact of screen-and-treat approaches it was important to have a delayed evaluation group. However, follow-up of this delayed evaluation group for longer than 6 months without treating women with CIN 2+ was unacceptable. Another limitation is our power for detecting increases in HIV seroconversions after treatment. Although the finding of no excess of HIV seroconversions in the HPV DNA and VIA groups is reassuring, the study is underpowered to detect small increases and larger trials are need to more fully investigate the impact of cryotherapy on HIV transmission. We also did not conduct the

screen-and-treat approaches in a single visit. Instead, women returned several days after initial screening for treatment. Although we obtained high rates of follow-up, lower follow-up might occur in a real-world service delivery setting. This would reduce the efficacy of the HPV DNA–based strategy compared with the VIA-based strategy, which can be administered in a single visit. Moreover, the study was neither powered nor designed to detect differences in cancer rates.

This trial has shown that screening and treating women based on the results of 2 alternative screening tests to cytology, HPV DNA testing and VIA, is safe and has a significant impact on the prevalence of CIN 2+ among women participating in such a program. In low-resource settings, screen-and-treat approaches may be able to reduce the risk of a common and easily preventable cancer in women.

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Study concept and design: Denny, Kuhn, Pollack, Wright.
Acquisition of data: Denny, DeSouza, Dupree, Wright.
Analysis and interpretation of data: Denny, Kuhn, Wright.
Drafting of the manuscript: Denny, Kuhn, Pollack, Wright.
Critical revision of the manuscript for important intellectual content: DeSouza, Dupree, Wright.
Statistical analysis: Kuhn, Wright.
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Study supervision: Wright.
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