Efficacy of human papillomavirus-based screen-and-treat for cervical cancer prevention among HIV-infected women

Louise Kuhn[a,b], Chunhui Wang[c], Wei-Yann Tsai[d], Thomas C. Wright[c] and Lynette Denny[e]

Background: Cervical cancer prevention should be provided as part of primary healthcare services for HIV-infected women but conventional screening programs are difficult to implement in low-resource settings. Here, we evaluate the efficacy among HIV-infected women of a simpler, screen-and-treat strategy in which all women with a positive screening test are treated with cryotherapy.

Methods: We conducted a randomized clinical trial of two screen-and-treat strategies among 6555 women in Cape Town, South Africa, among whom 956 were HIV-positive. Women were randomized to screen-and-treat utilizing either human papillomavirus DNA testing or visual inspection with acetic acid as the screening method or to a control group. Women were followed for up to 36 months after randomization with colposcopy and biopsy to determine the study endpoint of cervical intraepithelial neoplasia grade 2 or higher.

Results: In the control group, HIV-positive women had higher rates of cervical intraepithelial neoplasia grade 2 or higher detected by 36 months (14.9%) than HIV-negative women (4.6%) ($P = 0.0006$). Screen-and-treat utilizing human papillomavirus DNA testing significantly reduced cervical intraepithelial neoplasia grade 2 or higher through 36 months in both HIV-positive (relative risk = 0.20, 95% confidence interval 0.06–0.69) and HIV-negative women (relative risk = 0.31, 95% confidence interval 0.20–0.50). Reductions in the visual inspection with acetic acid-and-treat group were less marked. Complications of cryotherapy were mostly minor and did not differ in frequency between HIV-positive and HIV-negative women.

Conclusion: Screen-and-treat using human papillomavirus testing is a simple and effective method to reduce high-grade cervical cancer precursors in HIV-infected women.

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Introduction

It is well established that HIV-infected women have high rates of human papillomavirus (HPV) infections and are at increased risk of developing high-grade cervical cancer precursors and invasive cervical cancer [1,2]. Rollout of HIV care and treatment programs in sub-Saharan Africa have helped strengthen ambulatory services for chronic care and could provide a platform for effective cervical cancer prevention programs. Most HIV treatment

[a]Gertrude H. Sergievsky Center, College of Physicians and Surgeons, [b]Department of Epidemiology, Mailman School of Public Health, [c]Department of Pathology, College of Physicians and Surgeons, [d]Department of Biostatistics, Mailman School of Public Health, Columbia University, New York, New York, USA, and [e]Department of Obstetrics and Gynaecology, University of Cape Town, Cape Town, South Africa.

Correspondence to Louise Kuhn, PhD, Gertrude H. Sergievsky Center, College of Physicians and Surgeons, Columbia University, 630W 168th Street, New York, NY 10032, USA.

Tel: +1 212 305 2398; fax: +1 212 305 2426; e-mail: lk24@columbia.edu
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programs have expanded to provide better diagnosis and treatment of tuberculosis and there is burgeoning interest in putting in place programs for cervical cancer screening [3,4]. Antiretroviral therapy (ART) does not mitigate the need for screening [1]. Rather as HIV-infected women live longer and healthier lives due to access to ART, it is likely that more of these women will develop cervical cancer unless effective prevention programs can be established.

It has proven difficult to establish conventional cytology-based screening programs in low-resource settings where the prevalence of HIV infection is greatest because of the infrastructure requirements of cytology (Pap smears) and pathology (biopsies) as well as the advanced clinical expertise required to perform colposcopy [5,6]. In response, our group and others have been investigating simpler cervical cancer prevention strategies that utilize noncytological screening methods, namely HPV DNA testing or visual inspection with acetic acid (VIA), and those which immediately treat women with positive screening test results (referred to as 'screen-and-treat') [7–12]. The screen-and-treat approach contrasts with conventional screening approaches in that it eliminates the requirement to confirm a diagnosis prior to treatment. This greatly reduces the need for colposcopy and cervical biopsy, which are expensive, labor-intensive and reliant on well functioning clinical, laboratory and referral systems. In practice, these additional and expensive steps introduce opportunity for loss to follow-up and delay treatment and, because of low sensitivity, lead to under-treatment and missed disease.

Little is known about the safety and efficacy of screen-and-treat when used in HIV-infected women. We conducted a randomized cervical cancer prevention trial in South Africa that evaluated two screen-and-treat approaches: HPV-based screen-and-treat and VIA-based screen-and-treat. Because of the high HIV seroprevalence among the general population in South Africa, our trial included 956 HIV-positive women. Here, we report on the safety and efficacy of screen-and-treat among HIV-positive women.

Method

Study design

We conducted a randomized clinical trial to evaluate the safety and efficacy of two screen-and-treat strategies for cervical cancer prevention. Over 7000 previously unscreened, nonpregnant women aged 35–65 years were recruited at three ambulatory women's health clinics in Khayelitsha, Cape Town, South Africa, between January 2000 and December 2002. Women with cervical lesions detected through visual inspection of the cervix that were suspected of being cancerous, or with large acetowhite lesions extending over 70% of the cervix or into the endocervical canal, or who were considered by clinicians to be inappropriate for cryotherapy for various other reasons were not eligible to be enrolled in the study. These criteria excluded 6% of women screened [7]. Eligible women were randomized to one of three study arms: HPV-and-treat in which women with positive HPV test underwent cryotherapy; VIA-and-treat, in which women with positive VIA tests underwent cryotherapy; or control group in which evaluation or treatment was delayed for 6 months. All women were followed at 6 months after randomization with colposcopy and biopsy to determine the study endpoint of cervical intraepithelial neoplasia grade 2 or higher (CIN2+) and a predetermined subset underwent additional colposcopy and biopsy at 12, 24 and 36 months.

Study procedures

At enrollment, all women were screened using an HPV DNA test (Hybrid Capture 2; Qiagen Corp., Germantown, Maryland, USA) that detects 13 HPV types considered high risk for the development of cervical cancer (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) on cervical samples and had a VIA examination done by specially trained nurses. Women completed questionnaires on sociodemographic characteristics and sexual history and had samples collected for cervical cytology (Pap smear), *Neisseria gonorrhea*, *Chlamydia trachomatis* and *Trichomonas* infections and were tested for HIV. Women were asked to return 2–6 days later to obtain their screening test results and randomization was done if they returned for this follow-up visit. Study clinicians opened opaque envelopes at the randomization visit in which the assignment had been concealed. Assignments had been prepared by the study statistician in blocks of size 100 per site. Cryotherapy was then performed if indicated at this follow-up visit by nurses using nitrous oxide and a commercially available cryosurgical unit (Wallach Surgical Devices, Orange, Connecticut, USA) with two 3-min freezes. Women undergoing cryotherapy were counseled to refrain from sexual intercourse for 1 month and were provided female or male condoms if intercourse did occur.

Complaints and side effects were documented at the time of the cryotherapy procedure and all women (whether or not they underwent cryotherapy) returned at 1 month after randomization at which time a questionnaire on symptoms and sexual behaviors was administered. Women were encouraged to return to the study site at any time in the event of complications and information on how to contact the principal investigator was recorded on patient-retained records to be presented at emergency or other health services.

All women were followed with a colposcopy examination by a study physician blinded to clinical information 6 months after randomization. All acetowhite lesions

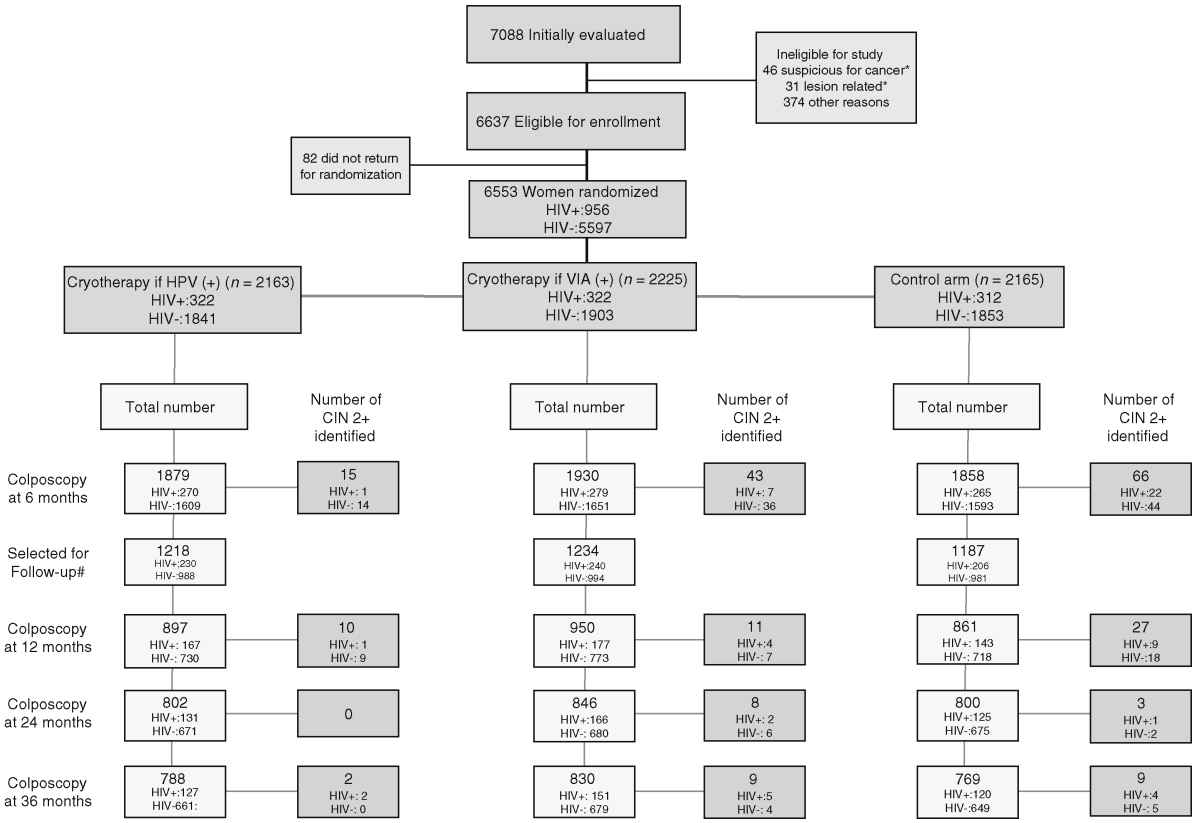

Fig. 1. Consort diagram for the study. *Considered ineligible for enrollment because VIA showed either a cervical mass or an acetowhite lesion inappropriate for cryotherapy, #all HPV-positive or VIA-positive women and a subset of women who were both VIA-negative and HPV-negative were selected for 36-month follow-up.

were biopsied and all women had an endocervical curettage (ECC) collected regardless of whether a lesion was observed. A systematic sample of the cohort was selected for extended follow-up at 12, 24 and 36 months. This sample included all women who were either HPV-positive or VIA-positive at enrollment as well as about a third of the women who tested negative for both HPV and VIA at enrollment (all those recruited in 2002). The study was designed in this way to reduce costs, as the occurrence of the study endpoint among HPV-negative and VIA-negative women is extremely rare. Colposcopy with histological sampling was done as described above and follow-up continued through June 2006 (Consort, Fig. 1). Women with biopsy-identified or ECC-identified CIN2+ at 6 months or later were treated with large loop electrosurgical excision and exited the study. Biopsies were processed at Columbia University and were evaluated independently by two pathologists. Consensus diagnoses were used for the study. The study design and primary findings have been reported elsewhere [7].

HIV status

The trial collected data on HIV status of the participants at baseline, 6, 12, 24 and 36 months. All women consented to have their blood drawn and to have their HIV results recorded in the study database unlinked to personal identifiers. HIV-positive and HIV-negative women were not distinguished during the study and all were randomized and followed as part of the larger group as described above. A voluntary HIV counseling and testing service was included as part of the study and women were strongly encouraged to learn their HIV results and be referred to the available HIV services in the community. At the time of the study, antiretroviral treatment was not routinely available in the public sector in South Africa and HIV-related tests, such as CD4 cell count and viral load, were not done as part of the study, nor was information on HIV treatment captured. Because of the high prevalence of HIV in this community, 956 (14.6%) of the women randomized had a positive HIV antibody test at one of these visits.

Here, we compare the effects of the screen-and-treat programs among women ever testing HIV-positive compared with women who remained negative throughout follow-up. Because of the randomized design of the original trial, HIV-positive women were evenly distributed in each of the three groups used in the trial (Consort, Fig. 1). This study was approved by the institutional review boards at Columbia University and the University of Cape Town. All participants provided

written informed consent. A data safety monitoring committee monitored the trial during the fieldwork phase. The study was registered in clinical trials.gov (NCT00233727).

Statistical analysis

Intent-to-treat analyses stratified by HIV status were conducted. The primary endpoint was CIN2+ confirmed on biopsy or ECC through 36 months. Given the study design that targeted a specific subset of participants for long-term follow-up, proportional weighting was used to generate 36-month estimates to represent the baseline population and standard errors were calculated using the delta method. Kaplan–Meier methods were used to calculate the cumulative proportions with CIN2+ and groups were compared using log-rank tests [13]. Rate ratios were calculated to describe the efficacy of the interventions and the risk difference was used to describe the number of cases of CIN2+ prevented per 100 women screened.

To examine the performance characteristics of HPV DNA testing and VIA conducted at the enrollment examination, standard test metrics [sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV)] were calculated among women enrolled in the control arm. Sensitivity utilized the total number of women with CIN2+ and with CIN3+ detected by 36 months as the denominator. Specificity included all women free of any CIN2+ through 36 months who had normal colposcopy results at 6 months. NPV and PPV were calculated using Kaplan–Meier methods to generate the risk of disease in screen-positive and screen-negative women, respectively. Statistical analyses were done using SAS 9.1.3 (SAS Institute Inc., Cary, North Carolina, USA) software.

Results

Study population

Nine hundred and fifty-six HIV-positive and 5596 HIV-negative women were enrolled in the trial. HIV-positive women tended to be younger (40.5 vs. 43.8 years old), less likely to be married (32.3 vs. 53.7%), more likely to have had their first sexual intercourse before the age of 16 years (38.8 vs. 33.5%), more likely to have five or more lifetime sex partners (47.7 vs. 31.7%) and less likely to have had more than four live births (18.4 vs. 33.5%) than HIV-negative women. At enrollment, HIV-positive women were more likely to have a cytological diagnosis of ASCUS+ (22.8%) than HIV-negative women (10.9%), were more likely to test positive for HPV DNA (45.9% of HIV-positive vs. 17.2% of HIV-negative) and were more likely to have a positive VIA test (30% of HIV-positive vs. 20% of HIV-negative). Among HIV-positive and HIV-negative women separately, baseline characteristics were similar between randomized groups (Table 1). At 6 months, retention in the cohort was excellent with 85.1% of HIV-positive and 86.7% of HIV-negative women evaluated. Retention declined to 63.0 and 69.5% among HIV-positive and HIV-negative women, respectively, by 36 months (Consort, Fig. 1).

Complications of cryotherapy

Among HIV-positive women, 148 in the HPV-and-treat group and 104 in the VIA-and-treat group had a positive test result and underwent cryotherapy. Among HIV-negative women, 319 in the HPV-and-treat group and 377 in the VIA-and-treat group had a positive test result and underwent cryotherapy. Combining those who underwent cryotherapy in the two screen-and-treat arms, there were no significant differences between HIV-positive and HIV-negative women in rates of complications and side effects (Table 2). In both HIV-positive and HIV-negative women who underwent cryotherapy, unscheduled clinic visits and reports of symptoms (vaginal discharge, abdominal pain and abnormal bleeding) were higher than among nontreated women. Although women who received cryotherapy were advised to refrain from sexual intercourse for a month, about half still reported having sex and less than 60% reported using male or female condoms most of the time or always. Despite reported complaints and troubling symptoms, nearly all women reported that they would recommend this program to their friends and relatives. There was one serious complication among an HIV-positive participant who reported severe bleeding about a week after cryotherapy and had to be transfused. No other serious complications were noted.

Efficacy of screen-and-treat

Screen-and-treat utilizing HPV DNA testing was highly effective in reducing the risk of CIN2+ by 36 months among both HIV-positive [relative risk (RR) = 0.20, 95% confidence interval (CI) 0.06–0.69] and HIV-negative women (RR = 0.31, 95% CI 0.20–0.50). The benefit of VIA-and-treat was less marked and only reached statistical significance in HIV-positive women (RR = 0.51, 95% CI 0.29–0.89) and not in HIV-negative women (RR = 0.76, 95% CI 0.52–1.1). As HIV-positive women had a higher CIN2+ rate, both screen-and-treat programs had a stronger impact at the population level in HIV-positive women than in the HIV-negative women. For every 100 women screened, HPV-and-treat program could prevent 11.9 CIN2+ cases in HIV-positive women and 3.1 CIN2+ cases in HIV-negative women, whereas VIA-and-treat program could prevent 7.4 cases in HIV-positive women and 1.1 cases in HIV-negative women.

In the control group, HIV-positive women had higher rates of CIN2+ detected by 36 months (14.9%) than HIV-negative women (4.6%) ($P = 0.0006$). In both the HIV-positive and HIV-negative women, the rate of

Table 1. Baseline characteristics of study participants by HIV serostatus and randomized group.

	HIV-positive ($n=956$)			HIV-negative ($n=5596$)		
	HPV group ($n=322$)	VIA group ($n=322$)	Controls ($n=312$)	HPV group ($n=1841$)	VIA group ($n=1903$)	Controls ($n=1852$)
Age (years)						
35–39	181 (56.2)	189 (58.7)	181 (58.0)	636 (34.5)	673 (35.4)	684 (36.9)
40–49	111 (34.5)	107 (33.2)	106 (34.0)	813 (44.2)	827 (43.5)	764 (41.2)
50–65	30 (9.3)	26 (8.1)	25 (8.0)	392 (21.3)	402 (21.1)	405 (21.9)
Education						
No school	19 (5.9)	20 (6.2)	19 (6.1)	185 (10.1)	198 (10.4)	178 (9.6)
Some primary school	111 (34.5)	107 (33.2)	109 (34.9)	703 (38.2)	723 (38.0)	690 (37.2)
Some high school	133 (41.3)	132 (41.0)	118 (37.8)	701 (38.1)	754 (39.6)	746 (40.3)
High school graduate	59 (18.3)	63 (19.6)	66 (21.2)	252 (13.7)	227 (11.9)	239 (12.9)
Currently employed	75 (23.3)	70 (21.7)	67 (21.5)	500 (27.2)	466 (24.5)	452 (24.4)
Married	107 (33.2)	107 (33.2)	95 (30.4)	989 (53.7)	1008 (53.0)	1010 (54.5)
Age <16 years at first sexual intercourse	112 (34.8)	135 (41.9)	124 (39.7)	618 (33.6)	641 (33.7)	614 (33.2)
≥5 Lifetime sex partners	143 (44.4)	151 (46.9)	162 (51.9)	596 (32.4)	601 (31.6)	579 (31.3)
≥2 Sex partners during previous month	8 (2.5)	12 (3.7)	8 (2.6)	22 (1.2)	24 (1.3)	19 (1.0)
Current smoker	25 (7.8)	28 (8.7)	31 (9.9)	134 (7.3)	154 (8.1)	133 (7.2)
Current contraceptive use						
Injectable	62 (19.3)	74 (23.0)	63 (20.2)	255 (13.9)	305 (16.0)	262 (14.1)
Oral	3 (0.93)	7 (2.2)	13 (4.2)	29 (1.6)	43 (2.3)	30 (1.6)
No. of live births						
None	13 (4.0)	9 (2.8)	16 (5.1)	62 (3.4)	65 (3.4)	67 (3.6)
1–4	246 (76.4)	256 (79.5)	240 (76.9)	1150 (62.4)	1183 (62.2)	1190 (64.2)
≥5	63 (19.6)	57 (17.7)	56 (18.0)	629 (34.2)	654 (34.4)	596 (32.2)
C. trachomatis or *N. gonorrhoeae*	32 (9.9)	31 (9.6)	24 (7.7)	85 (4.6)	87 (4.6)	79 (4.3)
Trichomonas vaginalis	37 (11.5)	46 (14.3)	40 (12.8)	199 (10.8)	199 (10.5)	181 (9.8)
Cytology ASCUS+	70 (21.7)	78 (24.2)	70 (22.4)	199 (10.8)	219 (11.5)	193 (10.4)
Screen test results						
HPV DNA	149 (46.3)	150 (46.6)	140 (44.9)	324 (17.6)	332 (17.4)	306 (16.5)
VIA	88 (27.3)	105 (32.6)	98 (31.4)	379 (20.6)	386 (20.3)	401 (21.6)

Combining HIV-positive and HIV-negative women across the three arms, there were significant differences by serostatus in all characteristics shown above except smoking and contraceptive use. Within HIV-positive and HIV-negative women separately, there were no significant differences across the three arms. HPV, human papillomavirus; VIA, visual inspection with acetic acid.

CIN2+ was significantly reduced in the HPV-and-treat group (to 3.1% in HIV-positive women, $P<0.0001$; and to 1.4% in HIV-negative women, $P<0.0001$) (Fig. 2). Reductions in CIN2+ detected by 36 months in the VIA-and-treat group (to 7.6% in HIV-positive women, $P=0.002$; and to 3.5% in HIV-negative women, $P=0.08$) were less marked. The VIA-and-treat strategy was significantly less effective than the HPV-and-treat

Table 2. Complications of cryotherapy in HIV-positive and HIV-negative women.

	HIV-positive ($n=956$)		HIV-negative ($n=5604$)	
	Cryotherapy[a] ($n=252$)	No cryotherapy[b] ($n=704$)	Cryotherapy[a] ($n=696$)	No cryotherapy[b] ($n=4900$)
Pain, light headedness or other complaint during the procedure	82 (32.5)	0	257 (36.9)	0
Within 1 month				
Unscheduled visit	23 (9.1)	5 (0.7)	69 (9.9)	24 (0.5)
Hospital admission	1 (2.1)	0	3 (2.5)	1 (0.5)
Participants followed up at 1 month				
New and troubling symptoms	66 (27.2)	92 (13.5)	175 (25.8)	455 (9.6)
Consulted clinician	57 (23.5)	148 (21.7)	145 (21.4)	855 (18.0)
Vaginal discharge	201 (82.7)	216 (31.6)	543 (80.1)	1179 (24.8)
Abnormal bleeding	32 (13.2)	55 (8.1)	98 (14.5)	301 (6.3)
Abdominal pain	79 (32.5)	144 (21.1)	204 (30.1)	1012 (21.2)
Sex since last visit	120 (49.4)	428 (62.7)	347 (51.2)	3055 (64.1)
If yes, used male or female condoms most of the time or always[c]	69 (57.5)	128 (29.9)	201 (57.9)	454 (14.9)
Would recommend program to their friends and relatives	243 (100)	681 (99.7)	677 (99.9)	4757 (99.9)

[a]Among women who underwent cryotherapy, there were no statistically significant difference between HIV-positive and HIV-negative women.
[b]Among women without cryotherapy, HIV-positive women were more likely to have new and troubling symptoms, to have consulted a clinician, to have vaginal discharge and more likely to use condoms ($P<0.05$).
[c]The differences between women who did and did not undergo cryotherapy were not affected by HIV status, except for condom use. Among HIV-positive women, those who had cryotherapy were 1.92 (95% CI 1.56–2.38) times more likely to use condoms, whereas among HIV-negative women, those who had cryotherapy were 3.9 (95% CI 3.45–4.41) times more likely to use condoms (P value for interaction = 0.0002).

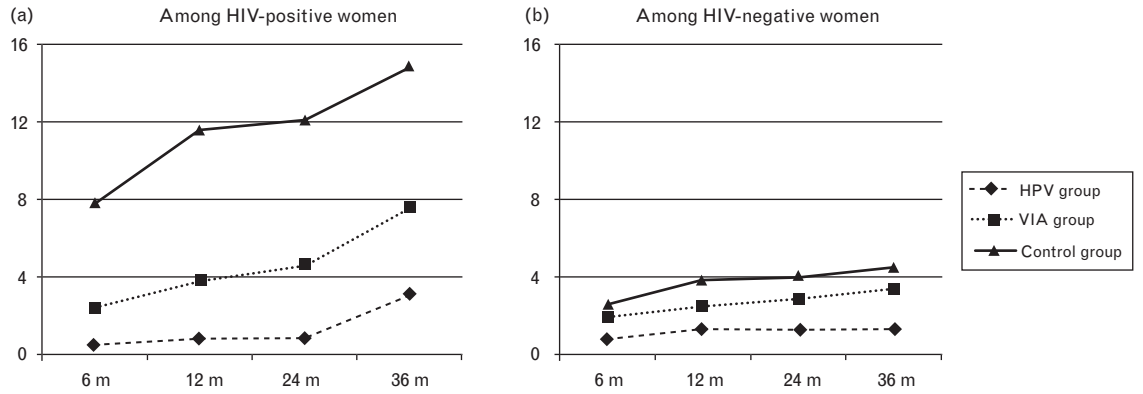

Fig. 2. Cumulative incidence of cervical intraepithelial neoplasia grade 2 or higher among HIV-positive and HIV-negative women in each randomization group. There was a significant reduction in CIN2+ in the HPV-and-treat group relative to controls in both HIV-positive (RR = 0.20, 95% CI 0.06–0.69, $P < 0.0001$) and HIV-negative women (RR = 0.31, 95% CI 0.20–0.50, $P < 0.0001$). The benefit of VIA-and-treat reached statistical significance in HIV-positive women (RR = 0.51, 95% CI 0.29–0.89, $P = 0.002$) but not in HIV-negative women (RR = 0.76, 95% CI 0.52–1.1, $P = 0.08$). CI, confidence interval; CIN2+, cervical intraepithelial neoplasia grade 2 or higher; HPV, human papillomavirus; RR relative risk; VIA, visual inspection with acetic acid.

strategy in both HIV-positive ($P = 0.005$) and HIV-negative women ($P = 0.002$) (Fig. 2). These results were similar if restricted to prevalent HIV-infected cases (women HIV-positive at baseline). In this subset, CIN2+ was detected by 36 months among 3.4, 11.4 and 19.8% of women in the HPV-and-treat, the VIA-and-treat and control group, respectively.

Cumulative CIN2+ rates increased steadily during the 36 months of follow-up in all three groups of HIV-negative women, from 2.6% at 6 month to 4.6% in the control group by 36 months. However, in HIV-positive women in the HPV-and-treat and VIA-and-treat groups, the increase between 12 and 36 months was more marked than among comparable HIV-negative women (Fig. 2). Benefits of screen-and-treat did not extend to CIN1 in the HIV-positive group. For the HIV-negative women, significant reductions in CIN1, CIN2 and CIN3 were evident (Table 3).

Performance characteristics of human papillomavirus and visual inspection with acetic acid as screening tests

In the control group, the sensitivity of HPV DNA testing at enrollment to detect CIN2+ through 36 month was 87.0% in HIV-negative women and 94.4% in HIV-positive women, whereas the sensitivity of the VIA test was 47.8% in HIV-negative women and 63.9% in HIV-positive women. The PPV for HPV testing was only slightly higher among HIV-positive women (29.9% who were HPV-positive at baseline had CIN2+ detected by 36 months) than among HIV-negative women (22.7%

Table 3. Severity of cervical lesions detected by 36 months by HIV serostatus and randomization group.

HIV-positive women	Controls ($n = 322$)	HPV group ($n = 322$)	*P* value HPV vs. control†	VIA group ($n = 312$)	*P* value VIA vs. control†
CIN1	38 (18.4)	42 (18.7)	0.95	52 (22.6)	0.99
CIN1 *P* value HIV+ vs. HIV−*	<0.0001	<0.0001		<0.0001	
CIN2	24 (10.4)	3 (2.7)	0.006	14 (5.9)	0.99
CIN2 *P* value HIV+ vs. HIV−*	0.0004	0.32		0.02	
CIN3	12 (5.1)	1 (0.4)	0.008	4 (1.7)	0.98
CIN3 *P* value HIV+ vs. HIV−*	0.04	0.66		0.83	
HIV-negative women	Controls ($n = 1841$)	HPV group ($n = 1903$)		VIA group ($n = 1852$)	
CIN1	56 (4.7)	29 (2.2)	0.003	42 (2.9)	0.034
CIN2	39 (2.6)	14 (0.9)	0.0003	30 (2.0)	0.17
CIN3	30 (2.0)	9 (0.6)	0.0006	23 (1.5)	0.31

CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; VIA, visual inspection with acetic acid.
**P* values compare HIV-positive to HIV-negative women within columns.
†*P* values compare screen-and-treat groups with controls within rows.

Table 4. Cryotherapy failures in the screen-and-treat groups and among comparable untreated women in the control group.

	HIV-positive women	HIV-negative women	*P* value HIV-positive vs. HIV-negative women
HPV+ at baseline			
In HPV-and-treat group (treated)	*N* = 149	*N* = 324	
CIN2+ by 36 months	2.8 (0.8–7.4)	7.1 (4.5–10.6)	0.05
CIN1 by 36 months	27.8 (19.8–36.3)	6.0 (3.5–9.3)	<0.0001
In control group (untreated)	*N* = 140	*N* = 306	
CIN2+ by 36 months	29.9 (21.6–38.7)	22.7 (17.8–28.0)	0.16
CIN1 by 36 months	33.0 (23.2–43.1)	15.6 (11.1–20.9)	0.002
VIA+ at baseline			
In VIA-and-treat group (treated)	*N* = 105	*N* = 386	
CIN2+ by 36 months	4.8 (1.5–11.1)	2.8 (1.4–4.9)	0.43
CIN1 by 36 months	26.0 (17.2–35.7)	3.0 (1.5–5.2)	<0.0001
In control group (untreated)	*N* = 98	*N* = 401	
CIN2+ by 36 months	27.5 (18.3–37.5)	9.6 (6.8–13.0)	0.0006
CIN1 by 36 months	28.4 (18.0–39.7)	7.0 (4.5–10.2)	0.0002

CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; VIA, visual inspection with acetic acid.

HPV-positive at baseline had CIN2+ detected by 36 months) (Supplementary Table, http://links.lww.com/QAD/A68). For the VIA test, the PPV in HIV-positive women was nearly three times higher than in HIV-negative women. This was explained by the fact that 62.2% of HIV-positive women with positive VIA tests also had HPV DNA detected vs. 26.6% of HIV-negative women.

Cryotherapy failure

We compared cryotherapy failure rates between HIV-positive and HIV-negative women (Table 4). In the HPV-and-treat group, there was a slightly lower rate of CIN2+ after cryotherapy among HIV-positive (2.8%) vs. HIV-negative (7.1%) women but this difference was of borderline significance ($P = 0.05$). In the VIA-and-treat group, CIN2+ failure rates after cryotherapy were similar in HIV-positive (4.8%) and HIV-negative (2.8%) women. Relative to comparable untreated controls, CIN2+ was significantly reduced by cryotherapy in both HIV-positive and HIV-negative women. In both screen-and-treat groups, CIN1 postcryotherapy was significantly more common among HIV-positive than HIV-negative women. For example, 27.8% of HIV-positive women who were also HPV-positive and underwent cryotherapy in the HPV-and-treat group were diagnosed with CIN1 vs. only 6.0% of similar HIV-negative women. Moreover, CIN1 was not significantly reduced by cryotherapy in HIV-positive women but was reduced in HIV-negative women (Table 4).

Discussion

Our data provide proof-of-principle that HPV-based screen-and-treat is safe and effective in HIV-positive women. A single round of screening with an HPV test followed by cryotherapy of all screen-positive women reduced high-grade cervical cancer precursors (CIN2+) by 80% and this reduction was sustained through 36 months. The benefit of HPV-based screen-and-treat in HIV-positive women was of a similar magnitude to that observed among HIV-negative women. VIA-based screen-and-treat was significantly less effective, although better than no intervention in HIV-positive women.

Other investigators [14–16] have reported relatively high rates of failure/recurrence after treatment of CIN in HIV-positive women. For example, Heard *et al.* [17] reported that the rate of recurrence of CIN after treatment was 22.3 per 100 person-years among HIV-positive women, which was higher than the recurrence rate in the general population. Similarly Massad *et al.* [15] reported that the failure rate after treatment of CIN was 46% in HIV-positive women compared with 33% in women in the general population. Failure rates in HIV-positive women have been reported to be particularly high after the use of cryotherapy [16]. There are a number of possible explanations for the apparent discrepancy between these other results and ours. One is that as we performed colposcopic examinations with biopsies during follow-up, we can differentiate CIN 1 from CIN2+. This has not been possible in many other studies, which have either been of limited size or had only cytologic (Pap) follow-up. When we use biopsy-confirmed CIN1 as the endpoint, rather than CIN2+, our results become similar to those reported by others. Treatment produced no significant reduction in CIN1 among HIV-positive women, but produced a significant reduction in CIN1 in HIV-negative women. A less advanced stage of HIV disease may be another possible explanation for the better than expected efficacy of screen-and-treat observed in our trial. HIV-positive participants in our study were relatively old (35–65 years of age) and were enrolled through community outreach rather than from HIV clinics. At the time enrollment took place, the prevalence of HIV was increasing dramatically in South Africa. Thus, it is likely that many of the HIV-positive women in our study were either recently infected or not yet profoundly

immunosuppressed. Both risk of CIN and treatment failure/recurrence in HIV-positive women have been related to the degree of immunosuppression in other cohorts [15,18].

Our data are able to inform several aspects of the relationship between HIV, HPV and cervical disease. They confirm that HIV-positive women are at high risk of HPV infection and histologically confirmed CIN. The prevalence of the 13 high-risk HPV types was 46% in HIV-positive vs. 17% in HIV-negative women and, in the control group, 15% of HIV-positive women had CIN2+ detected by biopsy compared with 5% of HIV-negative women. These rates are somewhat lower than has been reported in some other sub-Saharan African populations of HIV-positive women [19–22]. This is likely explained by our recruitment from the general population, rather than from HIV clinics more likely to overrepresent women with more advanced HIV disease. The lower HPV prevalence is also most likely explained by the age cutoffs in our study that recruited only women who are 35–65 years old. Although age trends are not well described in HIV-positive populations; in uninfected populations, there is a clear and strong relationship between HPV infection and age with the highest HPV prevalence observed among young women in the years soon after the initiation of sexual intercourse [23,24]. Interestingly, among untreated women in our study, the risk of CIN2+ was not elevated in HIV-positive relative to HIV-negative women conditioning on HPV status. These results are consistent with some studies from the United States [25,26] but others have shown increased risks of progression in HIV-positive women with HPV infection [18]. Our data also confirm that the sensitivity of screening tests is not compromised by HIV status, although specificity is worse among HIV-positive women. These results are consistent with a recent multisite evaluation of the performance of different screening tests among HIV-positive women [27].

Our study has both strengths and limitations. Its strengths include the randomized design and utilization of consensus diagnosis of CIN on biopsy as the endpoint. Biopsy confirmation is essential when studying cervical disease as surrogate endpoints defined on clinical or cytologic grounds are known to be prone to measurement error and complicate the interpretation of studies [28,29]. Moreover, women underwent multiple colposcopies during up to 3 years of follow-up as it is now established that a single colposcopy/biopsy may miss at least a third of true disease [29]. A limitation of our study is that we did not collect data on CD4 cell count, viral load or other markers of HIV-related disease progression. The community-based source of our study population suggests that women with advanced and symptomatic HIV disease are likely to have been underrepresented. We were also only able to maintain modest follow-up by 36 months (~65%). Thus, it is important to confirm these findings in a larger population of HIV-infected women to determine whether our promising results can be generalized to women with more advanced immunosuppression or those whose HIV-related immunosuppression has been partially corrected with ART. Although it is controversial whether or not ART reduces the elevated risk of cervical disease among HIV-positive women, it would be useful when considering implementation of screen-and-treat programs as part of HIV care to know the impact of ART [1,2,30].

Our trial advances the field by providing a randomized evaluation of a new screening approach that has the potential to expand access to cervical cancer prevention in low-resource settings. Economic analyses have demonstrated the favorable cost-effectiveness parameters of screen-and-treat for cervical cancer prevention in low-resource settings [31]. These strategies become even more attractive with new generation HPV tests, which are more robust, easier to use and less expensive [32]. Although the trial was not designed specifically to address the efficacy of screen-and-treat in HIV-positive women, the results suggest that an HPV-based screen-and-treat program could substantially reduce CIN2+ in HIV-positive women. HIV-positive women are at greatly elevated risk for cervical disease and HIV care and treatment programs could provide a useful platform in which to nest women's preventive services. Therefore, priority should be given to better understanding of the safety and efficacy of screen-and-treat programs in HIV-positive women and the impact of factors such as degree of immunosuppression and ART.

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EDITORIAL COMMENT

The prevention of cervical cancer in HIV-infected women

Silvia Franceschi[a] and Guglielmo Ronco[b]

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HIV-infected women have a substantially increased risk of human papillomavirus (HPV) infections compared to HIV-uninfected women [1,2]. The reasons for this finding have been debated for some time. HPV infection is predominantly acquired through heterosexual intercourse, as, in the vast majority of women worldwide, is HIV infection. A confounding effect of sexual behaviour was, therefore, evoked as a possible explanation of the excess of HPV infections and HPV-related anogenital cancers in HIV-infected women [3]. However, certain features of HPV infection in HIV-infected women cannot be explained by increased HPV exposure alone.

For example, both the prevalence and the incidence of HPV in HIV-infected women are inversely associated with $CD4^+$ cell level [1]. Moreover, new HPV infections appear in the absence of recent sexual activity much more often in HIV-infected than HIV-uninfected women, most probably a result of reactivation of latent infections [1,4]. Finally, HIV-infected women are more likely than HIV-uninfected women to harbour multiple-type infections [1,2] and to develop high-grade cervical lesions from oncogenic types other than HPV16 [1,2].

The relative risk for HPV infection among HIV-infected compared to HIV-uninfected women is consistent across different populations (between 2 and 4, depending on the degree of immunosuppression [1,2]). The relative risk for cervical cancer, however, varies enormously (from less than 2 to over 20), as it is affected by premature death from other causes or early detection and treatment of cervical precancerous lesions [5,6]. Unfortunately, cervical cancer prevention in HIV-infected women is lagging behind even in the highest-resource countries [5]. For instance, a combined analysis of 13 North American cohort studies of HIV-infected women ($n = 16\,467$) showed that between 1995 and 2007, cervical cancer incidence was 10-fold higher among HIV-infected women than the general female population, despite the widespread use of HAART and substantial screening efforts [7].

This raises the important question of whether the vast progresses in the understanding of cervical cancer screening in the general female population [8] can also be applied to HIV-infected women. There is no doubt about the equal importance of high coverage and follow-up of screening-positive women [8]. More recently, however, large randomized clinical trials from high-resource and low-resource countries have shown that in the general female population HPV test-based screening allows for earlier detection of precancerous lesions (cervical intraepithelial neoplasia, CIN, 2 and 3). Hence, it confers longer protection against CIN2 or worse (+) and cervical cancer than does cytology [9–13] or visual inspection with acetic acid (VIA) [12]. In addition, HPV testing is less dependent on high standards of quality assurance than cytology or VIA [8].

No recommendations exist for the use of HPV testing for primary screening or triage in HIV-infected women [14],

[a]International Agency for Research on Cancer, Lyon, France, and [b]Centre for Cancer Prevention, Piemonte, Turin, Italy.
Correspondence to Dr Silvia Franceschi, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon cedex 08, France.
Tel: +33 472738402; fax: +33 472738345; e-mail: franceschi@iarc.fr

G.R. was a visiting scientist at the International Agency for Research on Cancer during the preparation of this work.
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and concerns have been raised about its low specificity [15,16]. But support for the use of HPV testing to screen HIV-infected women has now been provided for the first time in an important article in the current issue of *AIDS* [17]. The article shows the outcome of a large randomized trial carried out in South Africa, which included 6553 women aged 35–65 years, of whom 956 were infected with HIV. One of two different tests (Hybrid Capture 2 or VIA) was combined with immediate cryotherapy of screening-positive women (screen-and-treat) and the two different testing groups were compared with a control group in which evaluation or treatment was delayed for 6 months. The endpoints were very robust ones: CIN2+ or CIN3+ detected by colposcopy and biopsies at month 6 and, in a subset of study women, month 12, 24, and 36. Screen-and-treat using HPV testing was demonstrated to be as feasible, safe, and efficacious in HIV-infected women as it was in HIV-uninfected women. As expected, HPV test specificity was lower, but sensitivity and positive and negative predictive values were not compromised by the presence of HIV infection. The number of CIN2+ prevented per 100 women screened was actually greater among HIV-infected women (11.9) than among HIV-uninfected (3.1) women. Screen-and-treat based on VIA was substantially less beneficial than that based on HPV testing, mainly on account of the low sensitivity of visual methods even in skilled hands. On the negative side, after cryotherapy, HIV-infected women continued to have many more HPV infections [18] and CIN1 (i.e., the histological manifestation of HPV infection) [17] than HIV-uninfected women.

The findings on HPV testing reported by Kuhn *et al*. [17] may also be indirectly relevant to HIV-infected women outside sub-Saharan Africa, regardless of whether screen-and-treat is used. High HPV prevalence and the consequent loss of specificity for CIN2+ may not be a good enough reason to forgo using the best screening test (i.e., HPV testing) if the positive predictive value for CIN2+ is not lowered [17]. In fact, HPV-positive women who are also HIV-infected have been shown to have a similar [17], or even higher [19], probability of developing CIN2+ than HIV-uninfected women.

A larger percentage of screening-positive findings and of subsequent lesion work-up or treatment may be an unavoidable price to pay to prevent cervical cancer in HIV-infected women. However, a few important issues need more research, most notably the short-term influence of cryotherapy and other cervical treatments on the probability of transmitting HIV to a male partner, and the best management of HPV-positive women who are also infected with HIV. The way to distinguish many transient HPV infections from long-duration cancer-inducing infections, however, is currently the most important priority to improve HPV test-based screening regardless of HIV status [20].

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