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Impact of loop electrosurgical excision procedure for cervical intraepithelial neoplasia on HIV-1 genital shedding: a prospective cohort study

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Abstract

Objective—We sought to examine the impact of the loop electrosurgical excision procedure (LEEP) on the rate and magnitude of HIV-1 genital shedding among women undergoing treatment for cervical intraepithelial neoplasia 2/3 (CIN2/3).

Design—Prospective cohort study.

Population—Women infected with HIV-1 undergoing LEEP for CIN2/3 in Kisumu, Kenya.

Methods—Participants underwent specimen collection for HIV-1 RNA prior to LEEP and at 1, 2, 4, 6, 10, and 14 weeks post-LEEP. HIV-1 viral load was measured in cervical and plasma specimens using commercial real-time polymerase chain reaction (PCR) assays, to a lower limit of detection of 40 copies per specimen.

Main outcome measures—Presence and magnitude of HIV-1 RNA (copies per specimen or cps) in post-LEEP specimens, compared with baseline.

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Disclosure of interests
The authors have no relevant conflicts of interest to declare.

Contribution to authorship
M.H. conceived and designed the study, and wrote the study protocol, institutional review board applications, training materials, and data collection forms. She oversaw all aspects of study activities and wrote the article. V.W. carried out the study-specific training, oversaw specimen collection, and assisted with writing the article. T.L. provided technical advice on the HIV viral load testing and validated a method of measurement of HIV levels from cervical fluid in anticipation of this study. She carried out specimen analysis and contributed to writing the article. H.L. oversaw all aspects of data analysis for this study. K.S.M., G.S., E.B., and C.C. contributed substantially to the study concept and data analysis plan. All authors offered critical revisions to the article and gave final approval for publication.

Details of ethics approval
The study activities described in this manuscript were approved by the ethics committees of the University of California, San Francisco (CHR# 10-00197, first approval 4/14/2010, current approval until 4/21/2013) and the Kenya Medical Research Institute (SSC# 1825, first approval 10 August 2010, current approval until 20 August 2013).

Results—Among women on highly active antiretroviral therapy (HAART), we found a statistically significant increase in cervical HIV-1 RNA concentration at week 2, with a mean increase of 0.43 $\log_{10}$ cps (95% CI 0.03–0.82) from baseline. Similarly, among women not receiving HAART, we found a statistically significant increase in HIV-1 shedding at week 2 (1.26 $\log_{10}$cps, 95% CI 0.79–1.74). No other statistically significant increase in concentration or detection of cervical HIV-1 RNA at any of the remaining study visits were noted.

Conclusions—In women infected with HIV undergoing LEEP, an increase in genital HIV shedding was observed at 2 but not at 4 weeks post-procedure. The current recommendation for women to abstain from vaginal intercourse for 4 weeks seems adequate to reduce the theoretical increased risk of HIV transmission following LEEP.

Keywords

Cervical dysplasia; genital shedding; HAART; HIV; Kenya

Introduction

As increasing numbers of individuals infected with HIV gain access to life-saving antiretroviral therapy, programme planners and healthcare professionals must turn their attention to the care of chronic and HIV-associated illnesses, including cervical cancer. The optimal treatment for cervical intraepithelial neoplasia (CIN) 2/3 should be effective, safe, and affordable. An additional consideration among HIV-infected women is the potential impact on HIV-1 genital shedding, which has been shown to be associated with an increased risk of HIV transmission.[1] Gains in efficacy against cervical dysplasia may be offset by the increased risk for transmission if a treatment method is associated with significantly greater duration and magnitude of HIV-1 genital shedding. This issue is especially critical in developing countries where healthcare resources remain limited, the majority of infected individuals are in relationships with partners who are HIV-negative or unknown, and women may not be able to negotiate the timing of intercourse or contraception.[2–4]

Inflammatory mediators, which may be increased in the cervix up to 4 months after treatment, are associated with increased levels of HIV-1 in cervicovaginal secretions.[5–8] Although little is known about how these findings relate to a cervix treated for CIN 2/3, the prolonged presence of inflammatory markers suggests the possibility of increased levels of HIV-1 in cervicovaginal secretions throughout that period. An exploratory study of 14 women not receiving highly active antiretroviral therapy (HAART) who were followed up to 10 weeks after undergoing cold-knife cone, loop electrosurgical excision procedure (LEEP), or cryotherapy showed significant increases of HIV-1 in their cervicovaginal secretions after treatment.[9] A more recent study showed no significant increase in HIV-1 shedding up to 4 weeks after treatment with cryotherapy in a cohort in which the majority of women were receiving HAART.[10] We sought to examine the impact of LEEP on clinically significant HIV-1 cervical shedding among women either on stable and effective HAART regimens, or not medically eligible for HAART.

Methods

Recruitment and enrollment

This prospective cohort study enrolled women infected with HIV who had undergone cervical cancer screening at Family AIDS Care and Education Services (FACES) clinics in the Kisumu East District of Kenya, had an abnormal colposcopy, and had a biopsy-confirmed diagnosis of CIN 2/3, and were scheduled to have LEEP performed in the clinic. To be eligible for cervical cancer screening, women had to be 23 years of age or older, and

not be currently pregnant. Additional eligibility criteria for the study included willingness to abstain from intercourse for 3 days prior to each study visit and absence of clinically or laboratory diagnosed vaginal or cervical infection with *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or *Trichomonas vaginalis*, or the presence of genital ulcers at the time of their diagnostic colposcopy and biopsy.

We evaluated two groups of women: women receiving HAART and women not eligible for HAART. We elected to look at the groups separately because we felt that the impact of HAART on HIV-1 shedding would introduce too much biological heterogeneity to be controlled for in the analysis. In order to look at the impact of HAART on the genital shedding of HIV-1, women who were on HAART must have been stable on the same regimen for at least 3 months, with greater than 90% self-reported adherence and no clinical or immunological evidence of treatment failure.[11] The HAART regimens were those available at FACES, in accordance with the Kenyan Ministry of Health Guidelines. First-line nucleoside reverse transcriptase (NRTI)-based regimens contained zidovudine or stavudine, plus lamivudine, plus a non-nucleoside reverse transcriptase inhibitor (NNRTI; either nevirapine or efavirenz). Second-line NRTI-based regimens included tenofovir, plus lamivudine and an NNRTI. Third-line protease inhibitor (PI)-based regimens contained lopinavir/ritonavir in combination with two other antiretrovirals. For the substudy of women not receiving HAART, women were eligible if their CD4+ count was greater than 350 cells/mL, they had no clinical indications for starting HAART, and they had not used HAART for the prevention of mother-to-child transmission within the previous 6 months. This study received approval from the ethical review committees at the Kenya Medical Research Institute and the University of California, San Francisco. All women signed informed consent prior to study enrollment.

Study visits and specimen collection

Women had study visits at enrollment (the date of their LEEP) and at 1, 2, 4, 6, 10, and 14 weeks after their procedure. At the enrollment visit, participants had blood drawn for a plasma viral load and a pelvic exam to confirm final study eligibility based on absence of clinically evident cervicitis, vaginitis, or genital ulcers. Baseline cervical specimen collection was performed prior to LEEP. All LEEPs were performed by one of two trained clinical officers.[12] Immediately before the procedure, the clinician performed a colposcopy, documented the lesion size, and chose the appropriate loop electrode size (1.0× 1.0, 1.5 × 1.0, or 2.0 × 1.5cm). LEEPs were performed in a single or double pass, using a ‘blend’ electrocautery setting at 46–50 W, followed by coagulation of the excisional bed with a ball electrode. After adequate haemostasis was achieved with cautery, ferric subsulfate solution was applied to the LEEP bed. No additional packing or haemostatic materials were used; participants were given instructions to call the study phone number or to return to clinic if they experienced any heavy bleeding, pain, fever, or foul-smelling discharge.

At each follow-up visit participants completed a questionnaire assessing recent sexual activity as well as any bleeding, pain, or abnormal discharge since the time of their procedure, and then underwent a speculum exam for the collection of cervical secretions for HIV-1 RNA.

Cervical and plasma viral load Measurements

Cervical fluid samples were collected immediately after speculum insertion by inserting three Tear Flo strips (Odyssey Medical, Bartlett, TN, USA) into the cervical os until approximately 20 mm of fluid was absorbed. Strips were withdrawn and cut at the 15-mm line, collecting approximately 12μL fluid per wick or 36μL per participant. Wicks were immediately immersed in 1.0 mL of Abbott lysis buffer solution and stored at −80 °C for up

to 4 months before being shipped on dry ice for testing at the ARI-UCSF Laboratory of Clinical Virology using the Abbott RealTime viral load assay (lower limit of detection, LLOD, 40 copies/specimen). The three wicks per participant were pooled and run as a single specimen. Cervical wick vaginal lavage (VL) results are presented as $\log_{10}$ number of copies per specimen (cps), with three wicks per participant. Blood samples for plasma viral load were shipped on dry ice to the KEMRI laboratory in Nairobi. HIV-1 RNA measurements were determined using the Abbot RealTime viral load assay with an LLOD of 40 copies/mL.

Statistical analysis

The primary outcomes for this study were presence and concentration of detectable HIV-1 virus in the cervix at each time point. We hypothesised that there would be an initial increase in the detection and concentration of HIV-1 cervical RNA, with a return to baseline by 4–6 weeks post-LEEP, when re-epithelialisation has taken place on the cervix. We felt that the presence of at least 3 $\log_{10}$ cps would represent a clinically significant level of virus in the genital tract.[1] Assumptions for sample size calculations were based on previous studies of variation in HIV-1 RNA levels within women,[13] and the prevalence of HIV-1 genital shedding among women on HAART.[14,15] We calculated that a sample size of 30 women on HAART would allow us to investigate the relationship between baseline and post-LEEP cervical viral load at each time point, and explore factors related to any observed change in viral load. The substudy of women not receiving HAART was planned as an exploratory analysis, so power calculations were not performed. Statistical analyses were performed independently by HAART status because of the anticipated clinical differences between the two groups.

Plasma and cervical viral load measurements were transformed into $\log_{10}$ values, with 1 added to 0 values before transforming undetectable values. The prevalence of viral detection at each time point was compared using chi-square tests with 95% confidence intervals. In order to look at within-participant change in viral load, we fitted a random-effects model. To check the robustness of our results, we also looked at generalised estimating equations (GEEs) with a binomial distribution and logit link to model viral detection, and a Gaussian distribution with an identity link to model $\log_{10}$ viral load, following LEEP. We specified a single-degree autoregressive correlation structure and robust standard errors. Time since LEEP was coded as a categorical variable to permit the assessment of change from baseline at each week. Because we were looking at viral load change within participants in the mixed-effects model, we did not control for baseline clinical or demographic characteristics. All statistical analysis was performed using STATA 11 (StataCorp, College Station, TX, USA).

Results

Among the 42 women in the study, 32 (76%) were receiving HAART and ten (24%) were not receiving HAART, as they were not clinically or immunologically eligible. As expected, the two groups had statistically significant differences in their average CD4+ count, WHO stage, and baseline plasma and cervical HIV-1 viral loads (Table 1). Participants returned for 97% (284/294) of their follow-up visits, and 99% (281/284) of their cervical specimens were available for RNA viral load measurements. Of the available specimens, 92% (258/281) yielded valid RNA viral load results, with the remaining specimens demonstrating target PCR inhibition, indicated by insufficient internal control amplification.

Among women on HAART, four (12%) had detectable cervical and nine (28%) had detectable plasma HIV-1 viral loads at baseline. Among the four participants with detectable baseline cervical HIV-1 RNA, the mean cervical viral load was 2.7 $\log_{10}$ cps (SD = 0.7). All four women had detectable plasma viral load (mean 3.9 $\log_{10}$ copies/mL, SD = 1.0). There

was no association between detectable baseline cervical HIV-1 RNA and CD4+ count, phase of menstrual cycle, or size of cervical lesion. Over the entire follow-up period, HIV-1 was detected in 32 of 201 (15%) cervical specimens from women on HAART. Eighteen (56%) women had undetectable cervical HIV-1 viral load at every study visit. The only time point that demonstrated a statistically significant increase in the odds of detectable HIV-1 in the cervical fluid compared with baseline was at week 2 (Figure 1). This association remained significant when controlling for detectable plasma viral load at baseline (adjusted OR 5.4, 95% CI 1.0–29.5). When we looked at the entire group of women on HAART, there was a significant increase of approximately four-fold in concentration of cervical viral load at 2 weeks compared with baseline (0.43 $\log_{10}$ cps, 95% CI 0.034–0.82). This mean concentration returned to baseline levels at 4 weeks post-LEEP (Figure 2; Table 2). There was no association between detection or concentration of HIV-1 in the cervix at week 2 and phase of the menstrual cycle. Results from the sensitivity analysis were similar (not shown).

Among the ten women not on HAART, 100% had detectable cervical and plasma HIV-1 levels at baseline. Throughout the follow-up period, 44 of 48 (92%) available cervical specimens from women not receiving HAART had detectable HIV-1 viral load. The mean baseline cervical viral load was 3.0 $\log_{10}$ cps and median plasma viral load was 4.5 $\log_{10}$ copies/mL (interquartile range, IQR = 4.3–5.1). In this group of women, similar to the HAART users, there was a statistically significant increase of over ten-fold in HIV-1 cervical viral load at week 2, controlling for baseline plasma viral load (1.26 $\log_{10}$ cps, 95% CI 0.79–1.74). This increase was not associated with any change in the menstrual phase.

Questionnaires for post-procedure symptoms and sexual activity were available for 239 follow-up visits. Overall, eight participants (19%) reported vaginal bleeding or spotting, all of them at or before 4 weeks post-procedure. Foul-smelling or vaginal discharge was reported at 32 (13%) visits. This was reported by 21/41 (51%) at week 1, 10/41 (24%) at week 2, and 1/39 (3%) at week 6. No women reported that symptoms interfered with her daily activities or caused her to seek medical attention or treatment, and there was no evidence of cervical infection during any of the follow-up examinations. There was no increase in the detection of cervical HIV-1 RNA during the visits in which participants reported bleeding or discharge ($P = 0.78$).

Two participants (5%) reported a resumption of intercourse prior to the 4-week recommended abstinence period post-procedure. Of the 30 women who resumed intercourse prior to the end of the study period, 23 (77%) stated that they used condoms. There were 16 visits (7%) in which women reported sexual activity within the 3 days immediately prior to the visit; in 14 of these cases, the women reported using a condom. There was no correlation with recent sexual activity and the detection of HIV-1 in the cervical fluid ($P = 0.65$).

Discussion

Main findings

Loop electrosurgical excision procedure (LEEP) treatment for CIN 2/3 was associated with minimal changes in the detection and magnitude of cervical HIV-1 viral load in women followed for up to 14 weeks post-procedure. The only significant increase in both the detection and the concentration of cervical virus was seen at 2 weeks post-procedure, with a return to baseline at 4–6 weeks post-procedure that was sustained throughout the follow-up. This finding was consistent in women receiving HAART or not, and is biologically plausible given the increase in inflammatory mediators related to healing that are present during this period.[16]

Strengths and weaknesses

This is the first study, to our knowledge, that looks at the impact of LEEP on HIV-1 cervical RNA viral load with a large enough sample size to detect a significant difference in detection and concentration between time points. When interpreting the findings of this study, we want to emphasise that cervicovaginal HIV-1 RNA levels are a proxy for potential HIV infectivity, and we are not commenting on actual HIV-transmission risk in this population. The strengths of this study include the length of the follow-up period, the high retention of participants in a clinical setting, and the precise measurements of cervical viral load to an LLOD of 40 cps. This study is limited by the small number of women in the group not receiving HAART, and by the measurement of clinical and demographic variables at just the baseline visit. Although the baseline characteristics are the most clinically relevant, and most would not have changed during the follow-up time, it would be interesting to look for a pattern in CD4+ count or serum viral load at various time points in relation to cervical HIV-1 shedding.

Interpretation

Our findings build on results from the two prior studies looking at HIV-1 shedding after treatment for CIN. The first study looked at a variety of treatment methods and showed increases in detectable shedding up to 10 weeks post-procedure.[9] That study included only 14 women, none of whom were on HAART, so differences in shedding for different time points or procedures were not evaluated. The next study focused on cryotherapy, and found that only women not on HAART demonstrated a pattern of increased detectable shedding 2 weeks after the procedure, although this was not statistically significant.[10] Similarly, we focused on a single treatment modality, looked separately at women receiving HAART or not, and saw a pattern of increased shedding at 2 weeks. Given that our sample size was similar to this study, one explanation for the fact that our results were statistically significant might be that LEEP has a greater impact on shedding than cryotherapy. This is biologically plausible, given a potentially increased area of ulceration and greater inflammatory response from an excisional procedure compared with an ablative procedure.

It is not clear why increased detection and concentration of viral shedding was not seen at 1 week post-LEEP. It is possible that an eschar forms on the LEEP bed early after the procedure, covering the raw area of the cervix and limiting the release of exudate. Although the study clinicians did not document seeing an eschar, the data collection forms did not specifically prompt assessment for this finding. Little is known about the inflammatory milieu of the post-LEEP cervix; future studies looking at the association between increased HIV-1 secretions of inflammatory cytokines and immune markers in the cervix would be useful in defining the mechanism behind the observed increased shedding at 2 weeks post-procedure.[16] Regardless, precautions to avoid sexual activity for a month to allow wound healing should be emphasised, as that window of time includes the period of maximal HIV-1 shedding, and hence covers the time of theoretical risk for infectivity in the immediate post-procedure period.

Although this study did not measure HIV infectivity directly, two recent studies have linked plasma and genital HIV viral load levels with HIV transmission, with a 2.2–2.9-fold increase in risk associated with each $\log_{10}$ increase in genital and plasma viral load, respectively.[1,17] In one study, the HIV-transmission rate among women with <3 $\log_{10}$ cps was 1.4/100 person years, compared with 6.2/100 person years, or a greater than four-fold increase, for women with >5 $\log_{10}$ cps.[1] The mean post-LEEP increases in cervical HIV-1 viral load in our study were 0.44 and 1.37 $\log_{10}$ cps for women receiving HAART or not, respectively. This relatively modest and temporary increase in cervical viral load suggests

that treatment for CIN 2/3 with LEEP would be unlikely to increase the risk of HIV infectivity, especially for women on HAART.

Overall, women experienced a very low rate of adverse events, and only 5% of women reported a return to sexual activity before the end of the recommended 4-week abstinence period. None of these women reported adverse events, and there was no association between sexual activity and the detection or the concentration of HIV-1 in cervical secretions. These data support findings from our previous study demonstrating the safety of LEEP in this population of women who are HIV-1 positive.[18] However, given that women are not always able to negotiate their sexual interactions, the finding that HIV-1 shedding after LEEP is elevated, although modestly, in the 2 weeks post-procedure should be taken into consideration in planning the timing of and counselling for the procedure.

Conclusion

Our findings demonstrate that the impact of LEEP on cervical HIV-1 RNA levels is modest, time limited, and may be moderated by HAART use. The current guidelines that recommend abstinence for 1 month after LEEP to allow wound healing appear to be adequate to protect against theoretical increased HIV infectivity in this population. Our current findings support the use of LEEP as a feasible, safe option for the treatment of CIN 2/3 in women who are positive for HIV in a low-resource setting.

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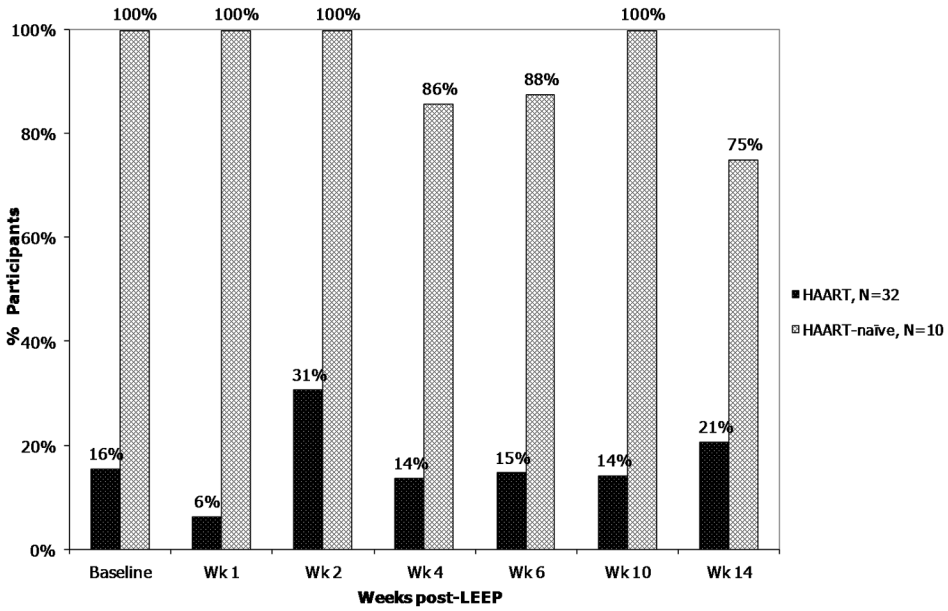

Figure 1.
Participants with detectable cervical HIV-1 RNA at each visit, by HAART status.

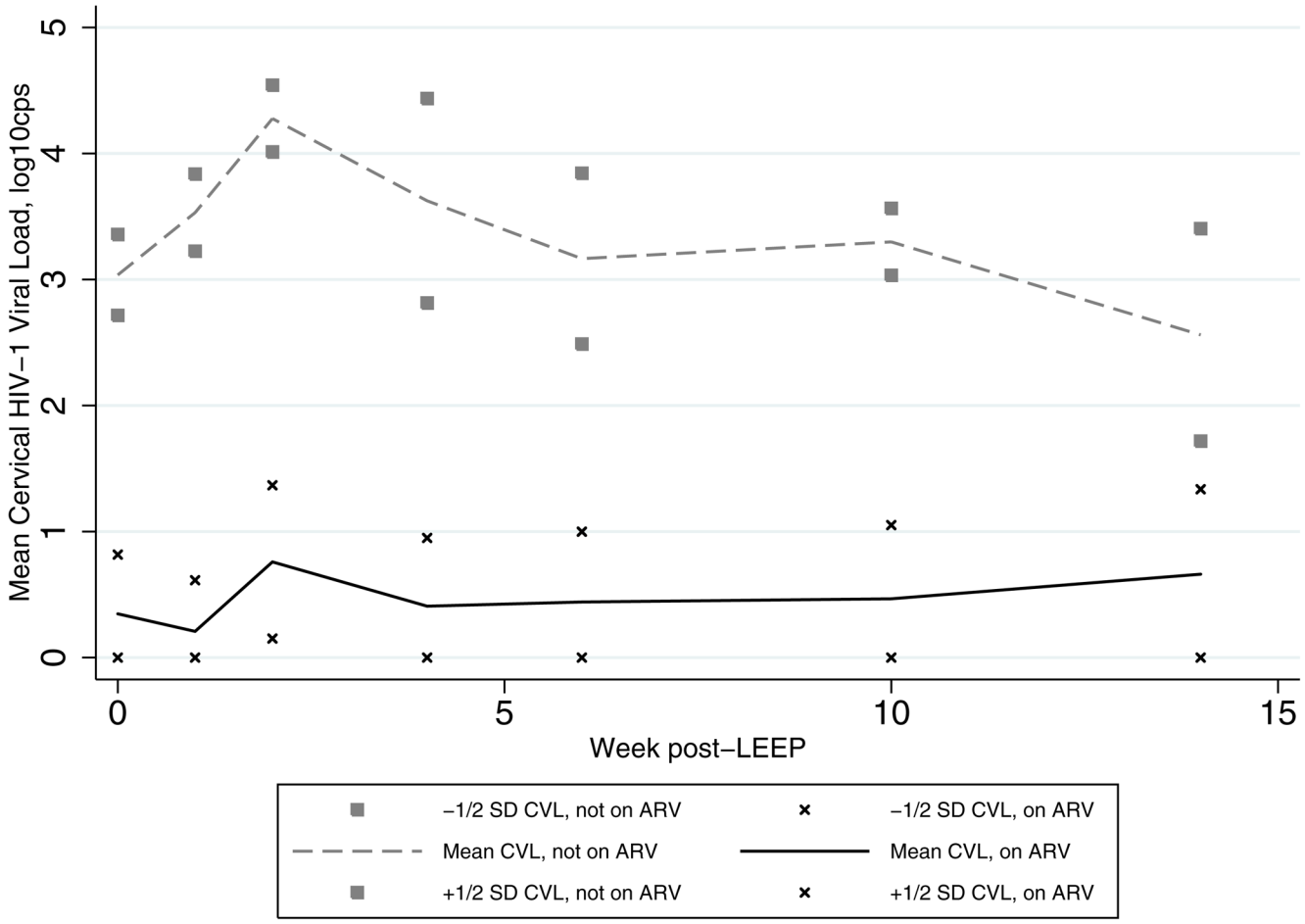

Figure 2.
Post-LEEP concentration of cervical HIV-1 RNA, by HAART status.

Table 1

Clinical and demographic characteristics of the study participants

Characteristic	On HAART (*n* = 32)	Not on HAART (*n* = 10)
Age, mean years (SD)	31.8 (5.7)	31.2 (6.2)
Marital status *n* (%)		
Married	7 (22%)	0 (0%)
Single	12 (38%)	9 (90%)
Widowed	10 (31%)	1 (10%)
Separated	3 (9%)	0 (0%)
Parity, mean (SD)	2.2 (1.6)	3.3 (2.5)
Using hormonal contraception, *n* (%)	8 (25%)	4 (40%)
Menstrual cycle phase, n (%)		
Follicular (days 1–14)	18 (56%)	3 (30%)
Luteal (days 15–35)	8 (25%)	4 (40%)
Amenorrhea (>35 days)	6 (19%)	3 (30%)
Lifetime number of partners, mean (SD)	5.0 (2.2)	4.9 (2.4)
Previous sexually transmitted infection *n* (%)	7 (22%)	3 (30%)
Current symptoms of vaginal discharge, odor or pruritis, *n* (%) *	13 (41%)	2 (20%)
Size of lesion > 2.5 cm, *n* (%)	2 (6%)	0 (0%)
CD4+ count, mean cells/dL (SD)	331 (257)	541 (144)
WHO stage *n* (%)		
1	8 (25%)	7 (70%)
2	9 (28%)	2 (20%)
3	13 (41%)	1 (10%)
4	2 (6%)	0 (0%)
Time since HIV diagnosis, months (SD)	34.0 (33.8)	26.1 (17.7)
Time on current HAART regimen in months (median, IQR)	8.5 (5.3–29.5)	n/a
Previous HAART regimen, *n* (%)	9 (28%)	n/a
HAART regimen, *n* (%)		
First-line NRTI	25 (78%)	n/a
Second-line NRTI	5 (16%)	n/a
Third-line PI	2 (6%)	n/a
Detectable plasma viral load, *n* (%)	9, 28%	10, 100%
Plasma viral load among women with detectable levels, mean $\log_{10}$ cps/ml (SD), *n* = 19	6.4 (2.9)	10.8 (1.5)
Detectable baseline cervical viral load, *n* (%)	4 (12%)	10 (100%)
Baseline cervical viral load among women with detectable levels, mean $\log_{10}$ cps/ml (SD), *n* = 13	6.2 (1.5)	7.0 (1.5)

* Women with evidence of genital ulcers, cervicitis, abnormal vaginal discharge, abnormal results on wet mount or laboratory-confirmed *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, or *Trichomonas vaginalis* were excluded from the study.

** First-line non-nucleoside reverse transcriptase inhibitors (NRTI), AZT/D4T + 3TC + NVP/EFV; second-line NRTI, TDF + 3TC + NVP/EFV; third-line protease inhibitor (PI): LPV/RTV + 3TC + NRTI.

Table 2

Change in cervical HIV-1 RNA concentration up to 14 weeks post-LEEP, by HAART status*

Women receiving HAART (*n* = 32)				
Visit week	**Mean change from baseline (log_{10} cps)**	**SE**	***P***	**95% CI**
1	−0.14	0.10	0.14	−0.33 to 0.05
2	**0.42**	0.20	0.03	0.03 to 0.82
4	0.07	0.14	0.61	−0.20 to 0.34
6	0.08	0.17	0.65	−0.25 to 0.41
10	0.12	0.15	0.44	−0.18 to 0.41
14	0.30	0.20	0.13	−0.09 to 0.69
Women not receiving HAART (*n* = 10)				
1	0.21	0.21	0.31	−0.20 to 0.62
2	**1.26**	0.24	<0.01	0.79 to 1.74
4	0.50	0.48	0.30	−0.44 to 1.44
6	0.15	0.41	0.71	−0.64 to 0.95
10	0.08	0.37	0.84	−0.64 to 0.80
14	−0.48	0.61	0.43	−1.68 to 0.72

*Means estimated with linear regression using random-effects model with robust standard error.