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Cervical Shedding of HIV-1 RNA Among Women With Low Levels of Viremia While Receiving Highly Active Antiretroviral Therapy

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Abstract

Background—Among women with low or undetectable quantities of HIV-1 RNA in plasma, factors associated with genital HIV-1 RNA shedding, including choice of treatment regimen, are poorly characterized.

Methods—We measured HIV-1 RNA in cervical swab specimens obtained from participants in the Women's Interagency HIV Study who had concurrent plasma viral RNA levels <500 copies/mL, and we assessed factors associated with genital HIV shedding. The study was powered to determine the relative effects of antiretroviral protease inhibitors (PIs) versus nonnucleoside reverse transcriptase inhibitors (NNRTIs) on viral RNA shedding.

Results—Overall, 44 (15%) of 290 women had detectable HIV-1 RNA in cervical specimens. In the final multivariate model, shedding was independently associated with NNRTI (vs. PI) use (odds ratio [OR], 95% confidence interval [CI]: 2.24, 1.13 to 4.45) and illicit drug use (OR, 95% CI: 2.41, 0.96 to 5.69).

Conclusions—This is the largest study to define risks for genital HIV-1 RNA shedding in women with low/undetectable plasma virus. Shedding in this population was common, and NNRTI-based highly active antiretroviral therapy (HAART) (vs. PI-based HAART) was associated with genital HIV shedding. Further study is required to determine the impact of these findings on transmission of HIV from mother to child or to sexual partners.

Keywords

compartmentalization; genital; HIV; nonnucleoside reverse transcriptase inhibitor; protease inhibitor; undetectable; viral replication; women

As we and others have demonstrated, HIV-1 viral replication in plasma and female genital secretions is not equivalent.¹ In our previous study, 158 (64%) of 247 women had detectable viral RNA in cervical secretions at a single time and plasma HIV-1 RNA was the most important determinant of cervical HIV-1 shedding.¹ Of the 83 women with low or undetectable plasma viral RNA (<500 copies/mL), however, 27 (33%) had detectable cervical viral RNA.

Although the risk of HIV transmission to sexual partners² or to a woman's newborn infant³ is proportional to the plasma viral RNA level, vertical transmission from mother to fetus has been documented even with undetectable plasma virus.⁴ The risk, albeit low, of transmission in this setting may be related to the discordance between plasma and cervical viral replication. Therefore, it is critical in the current highly active antiretroviral therapy (HAART) era to understand factors that have an impact on cervical shedding of HIV-1 RNA in women with low or undetectable plasma HIV-1 RNA better and whether the frequency of cervical shedding differs by type of anti-retroviral therapy (ART) and/or other treatment-related factors.

To identify factors associated with cervical HIV-1 RNA shedding in women with low and undetectable plasma HIV-1 RNA better, we investigated a larger cohort than in our previous study.¹ In particular, because of differences between non-nucleoside reverse transcriptase inhibitor (NNRTI) and protease inhibitor (PI) penetration into semen,⁵ this study was designed to test the hypothesis that among treated HIV-infected women with a plasma viral load of <500 copies/mL (and therefore presumed good adherence), the percentage with cervical HIV-1 RNA shedding would differ between those taking NNRTI-containing HAART versus PI-containing HAART.

METHODS

Study Population

The Women's Interagency HIV Study (WIHS) has been previously described.⁶ Briefly, the WIHS is an ongoing cohort study conducted at 6 clinical sites across the United States (Bronx, NY; Brooklyn, NY; Washington, DC; Los Angeles and San Francisco Bay areas, CA; and Chicago, IL). The original WIHS cohort included a total of 2056 HIV-positive women enrolled from October 1, 1994, through November 15, 1995. An expansion cohort included 737 HIV-positive women enrolled from October 1, 2001, through September 30, 2002. The cross-sectional study reported here used data collected between April 1, 2000, and March 31, 2003 from 290 women from both cohorts. All HAART users with a cervical swab specimen available for HIV-1 RNA quantification with a concurrent plasma HIV-1 RNA level <500 copies/mL were eligible. A plasma viral RNA level of <50 copies/mL was defined in the standard fashion as "undetectable," and a plasma viral RNA level from 50 to 500 copies/mL was defined as "low." The upper threshold of 500 copies/mL was chosen to

model the effect on cervical HIV-1 RNA shedding of a low level of plasma viral replication, or “blips,” above the lower limit of the standard plasma assay (400 copies/mL).

We classified HAART users in 2 groups: those who reported use of a PI-containing regimen ($n = 179$), defined by the use of at least 3 drugs comprising ≥ 2 nucleoside analogue reverse transcriptase inhibitors (NRTIs) with ≥ 1 PIs and no history of NNRTI use, including therapy to prevent mother-to-child transmission, and those who reported use of an NNRTI-containing regimen ($n = 111$), defined by the use of ≥ 2 NRTIs with at least 1 NNRTI and no history of PI use.

Data Collection

We investigated a broad range of demographic and clinical characteristics as potential predictors of shedding. For this report, at each semiannual WIHS study visit, participants were queried about sexual activity since the last visit; the time of their last menses; use of tampons, intravaginal medications, or douches; illicit drug, cigarette, and hormonal contraceptive use; and symptoms associated with genital tract infections. Interval and current use of antiretroviral drugs was obtained by standardized self-report, assisted by use of photographic depictions of these drugs, labeled with brand, generic, and abbreviated names. Blood specimen testing included a complete blood cell count with lymphocyte subsets and plasma HIV-1 RNA level; cervical tract assessment included a vaginal swab for a pH and potassium hydroxide preparation (including an amine odor test and microscopy), visual inspection for blood, a saline preparation for microscopy (including the presence of red blood cells, *Trichomonas vaginalis*, and bacterial vaginosis by the Amstel definition), and 2 endocervical swabs for HIV-1 RNA quantification, followed by cervical cytology. All laboratories participate in the National Institute of Allergy and Infectious Diseases (NIAID) Division of Acquired Immune Deficiency Syndrome (DAIDS) Flow Cytometry Quality Assessment and Viral Quality Assurance (VQA) Programs. Testing at study visits for herpes, syphilis, gonorrhea, and *Chlamydia* infections was only performed if the history or physical examination was suggestive.

Cervical Swab Collection and Analysis

Cervical HIV-1 RNA shedding was measured using a Puritan (Guilford, ME) sterile Dacron polyester tip applicator 25-806-1PD swab as previously described.^{7,9} HIV-1 RNA quantification was done in our laboratory (University of Southern California, Los Angeles, CA) using isothermal nucleic acid sequence-based amplification (NucliSens; bio-Merieux, Durham, NC, USA; lower limit of 25 copies/mL with 1-mL input) and 0.50 mL of the guanidine buffer in which each swab had been stored.⁷ This specimen collection approach reflects considerable prior research to determine the most sensitive method.^{1,8-14} Cervical HIV-1 RNA was reported in copies per milliliter of swab buffer.

Statistical Methods

The outcome of interest was the detection of cervical HIV-1 RNA shedding, defined as ≥ 50 copies/mL in the cervical swab specimen. Logistic regression models with the logit link under a binomial distribution were used for univariate and multivariate analyses according to a stepwise modeling procedure.¹⁵ For forward selection at each step, involving each factor of interest, we used a likelihood ratio test (LRT) to 2 models: a reduced model with all factors identified from previous steps but without the factor of interest and a full model with all previously identified factors plus the factor of interest. For the initial step, the reduced model was an intercept-only model. We selected the factor that most significantly reduced the log likelihood provided that the P value for the LRT was < 0.10 . We also required that the P value for the Wald statistic for the given factor be < 0.10 . We used an

alpha level of 0.15 for removal. The final model included only factors with Wald P values <0.05 . All analyses were conducted using SAS (v9; SAS Institute, Cary, NC).

RESULTS

Cervical swab, history, and examination data were available from 290 women on HAART at the swab visit. We observed cervical HIV-1 RNA shedding in 44 (15%) women overall: 23 (13%) of the 179 PI users and 21 (19%) of the 111 NNRTI users. Among the 44 shedders, 6 (14%) were “high shedders” with >1000 copies/mL. Table 1 shows the distribution of shedders by drug and period of enrollment. Table 2 shows comparisons between nonshedders, and shedders. Shedders were more likely to have had more than 1 male sex partner in the previous 6 months, to have used crack cocaine or injected drugs, to have smoked tobacco, and to have 50 to 500 plasma HIV-1 RNA copies/mL at the swab collection visit. Shedders were also more likely to have a history of seropositivity for syphilis, but there was no association between shedding and a clinical assessment of genital tract inflammation or active infection with syphilis, herpes, gonorrhea, *Chlamydia*, or *Trichomonas*. There were no significant differences in reported rates of at least 95% adherence between women in the PI-naïve NNRTI group or the NNRTI-naïve PI group ($P = 0.60$).

Original recruits were older ($P < 0.0001$), had a higher prevalence of hepatitis C virus (HCV; $P < 0.0001$), initiated HAART earlier ($P < 0.0001$), were more likely to use PIs ($P < 0.0001$), were more likely to have been exposed to mono- or dual-drug ART before HAART initiation ($P < 0.0001$), and were more likely to have had clinical AIDS within 1 year of the swab visit ($P = 0.03$) compared with the expansion recruits (data not shown). None of these factors were independently associated in the multivariate analysis with shedding, except for PI use.

Table 2 also shows the results of the stepwise multivariate analysis procedure. Adjusting for enrollment period, injection drug use, and NNRTI use were independently associated with shedding.

Six women (14% of all shedders and 2% of all women in the cohort) had cervical viral RNA levels >1000 copies/mL. This small sample, although interesting in the magnitude of shedding, lacks power to exclude differences from the whole cohort confidently. All 6 women were enrolled in the mid-1990s: 3 in the NNRTI group and 3 in the PI group. This was not a statistically significantly different distribution with respect to treatment than among shedders as a whole. As shown in Table 2, there were trends but no statistically significant differences between those with >1000 cervical RNA copies/mL and all shedders.

DISCUSSION

This study demonstrated that in a large cohort of treated HIV-infected women with low or undetectable plasma viral RNA, 15% were nonetheless shedding viral RNA from the cervix and that NNRTI use (vs. PI use) correlated with cervical viral RNA shedding. We have previously shown that the presence of genital HIV-1 RNA correlates with shedding of culturable infectious HIV.¹ Therefore, the current data suggest that in the HAART era, women with low or undetectable plasma virus may still be at risk, albeit low, for transmitting HIV to their sexual partners or infants; indeed, this has already been reported for vertical transmission.¹⁶ Our finding that genital viral RNA shedding was related to the choice of anti-retroviral regimen implies that future assessments of the effects of novel antiretroviral agents or combinations of agents could include genital viral replication in addition to plasma replication, especially because divergence between plasma and genital

HIV quasispecies has been demonstrated.^{17–19} The number of shedders is lower in this cohort than previously reported,^{1,20,21} most likely because all participants in our cohort were treated with HAART that effectively reduced plasma viral replication. Potential treatment-related confounders, such as adherence and length of therapy before the swab visit, were not significant predictors of cervical RNA shedding in the univariate or multivariate analysis.

Recent data suggest that the penetration of antiretrovirals into cervicovaginal secretions is drug specific, with nevirapine, zidovudine, lamivudine, and emtricitabine demonstrating greater penetration than efavirenz or PIs.^{22,23} Our study was not powered to detect differences in cervical HIV-1 RNA shedding related to specific drugs, and we did not measure concentrations of antiretrovirals in the genital tract; however, a trend toward increased shedding among women in this cohort treated with efavirenz (see Table 1) is consistent with the pharmacokinetic data. In contrast, our finding of decreased cervical HIV-1 viral RNA in women treated with PIs is unexpected, given the reportedly decreased PI penetration into female genital secretions,^{22,23} and indicates that studies are required to measure drug concentrations and HIV-1 RNA simultaneously in the female genital tract. This pharmacokinetic-pharmacodynamic relation is the subject of a planned future investigation.

Although there were significant differences between early and expansion recruits, none of these factors were independently associated with shedding in univariate or multivariate analysis; therefore, it is likely that period of enrollment was a surrogate for a combination of these exposures and/or unmeasured cofactors, such as archived antiretroviral resistance, because these women had been relatively heavily mono- or dual-ART exposed before receiving HAART. Although the WIHS cohort is followed prospectively, this investigation was carried out retrospectively, and therefore limited our exploration of potential factors associated with cervical HIV-1 RNA shedding, such as plasma and genital antiretroviral drug concentrations. Furthermore, this was a cross-sectional study; therefore, we do not yet understand any treatment-related differences in cervical HIV-1 RNA shedding that may exist over time. We did not measure genital antiretroviral resistance in the 6 women with >1000 cervical copies/mL, and this is an important addition to future explorations of the class- or drug-specific relations between genital tract drug concentrations and effect on viral RNA shedding.

In summary, we have demonstrated that 44 (15%) of a cohort of 290 women on HAART with plasma HIV-1 RNA levels <500 copies/mL were shedding cervical HIV-1 RNA at a single time point. The risk of cervical HIV-1 RNA shedding was independently increased by use of NNRTI-based HAART versus PI-based HAART. The common occurrence of cervical viral RNA shedding in this cohort has implications for counseling women about the possibility of HIV transmission to infants or sexual partners or the spread of resistant virus from the sanctuary of the genital tract, even when plasma viral replication is effectively suppressed. The finding of more frequent cervical viral RNA shedding among women treated with an NNRTI-based antiretroviral regimen deserves further prospective investigation.

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TABLE 1

Cervical HIV-1 RNA Shedding by Drug and Period of Enrollment

	Early Recruits		Late Recruits		All Recruits [*]	
	Shedders n (%) [†]	Nonshedders n (%)	Shedders n (%)	Nonshedders n (%)	Shedders n (%)	Nonshedders n (%)
PI						
Amprenavir	0 (0)	1 (100)	0 (0)	1 (100)	0 (0)	2 (100)
Indinavir	6 (16)	32 (84)	0 (0)	1 (100)	6 (15)	33 (85)
Lopinavir	2 (33)	4 (67)	0 (0)	4 (100)	2 (20)	8 (80)
Nelfinavir	11 (16)	58 (84)	0 (0)	16 (100)	11 (13)	74 (87)
Ritonavir	2 (100)	0 (0)	—	—	2 (100)	0 (0)
Saquinavir	2 (13)	13 (87)	—	—	2 (13)	13 (87)
Multiple [‡]	0 (0)	23 (100)	0 (0)	3 (100)	0 (0)	26 (100)
NNRTI [§]						
Efavirenz	6 (30)	14 (70)	2 (18)	9 (82)	8 (26)	23 (74)
Nevirapine	11 (24)	35 (76)	1 (3)	29 (97)	12 (16)	64 (84)

^{*} There were no statistically significant differences between shedders and nonshedders by individual drug.

[†] All percentages are row.

[‡] At the study visit, multiple PI users were taking more than 1 PI concurrently, including low-dose ritonavir boosting.

[§] Two early recruits used delavirdine alone (1 shedder), and 1 early recruit and 1 late recruit used nevirapine and efavirenz (both nonshedders).

TABLE 2
Participant Characteristics by ART Group and Shedding Status

	Shedders n = 44 (15%)	Nonshedders n = 246 (85%)	Multivariate OR*, P ≤ 0.05
HAART group			
PI (NNRTI naive)	23 (52%)	156 (63%)	
NNRTI (PI naive)	21 (48%)	90 (37%)	2.24 (1.13 to 4.45)
95% to 100% adherent 6 months before swab visit	36 (82%)	196 (80%)	
First HAART use ≤6 months before swab visit	9 (20%)	36 (15%)	
Mono- or dual-ART experienced at HAART initiation	29 (66%)	151 (61%)	
Mean age ± SD [†]	42 ± 8	39 ± 8	
Race/ethnicity			
African American	26 (59%)	118 (48%)	
Latina/Hispanic	10 (23%)	75 (30%)	
White/other	8 (18%)	53 (22%)	
HCV antibody positive at swab visit	24 (55%)	99 (40%)	
IDU, crack, or cocaine use	9 (20%)	21 (9%)	2.41 (0.96 to 5.69)
Smokers	30 (68%)	120 (49%)	
>10 lifetime male sex partners	23 (52%)	112 (46%)	
>1 male sex partner in previous 6 months	8 (18%)	21 (9%)	
Intercourse in previous 48 hours	4 (9%)	35 (14%)	
Hormonal contraceptive use in previous 6 months	4 (9%)	26 (11%)	
Genital tract infections			
<i>Candida</i> at swab visit	5 (11%)	23 (9%)	
Bacterial vaginosis at swab visit	7 (16%)	52 (21%)	
<i>Trichomonas</i> at swab visit	2 (5%)	9 (4%)	
Positive syphilis blood test ever before swab visit	9 (20%)	23 (9%)	
Herpes at WIHS baseline (among those with result)	34 (94%)	154 (91%)	
HPV ever	37 (84%)	182 (74%)	
HPV ≤1 year before swab (among those with result)	18 (46%)	113 (50%)	
Potential swab contaminants			
Use of tampons, douche, or vaginal medications in previous 48 hours	1 (2%)	11 (4%)	
Blood	5 (11%)	36 (15%)	
Clinical AIDS			
Ever	17 (39%)	98 (40%)	
≤1 year of swab	8 (18%)	32 (13%)	
Mean CD4 cells ± SD [†]			
Concurrent	538 ± 295	501 ± 247	
Post-HAART nadir	381 ± 234	344 ± 214	
Mean CD4 percent ± SD [†]			
Concurrent	28 ± 12	27 ± 10	

	Shedders n = 44 (15%)	Nonshedders n = 246 (85%)	Multivariate OR*, P ≤ 0.05
Post-HAART nadir	23 ± 10	22 ± 10	
Concurrent plasma HIV-1 RNA			
Mean (log ₁₀) [†] ± SD [‡]	1.68 ± 0.39	1.60 ± 0.38	
>50 copies/mL	17 (39%)	60 (24%)	
HIV-1 RNA before swab			
Mean peak (log ₁₀) [†] ± SD [‡]	2.52 ± 1.12	2.75 ± 1.16	
Ever >500 copies/mL	16 (36%)	102 (41%)	

Bold indicates $P < 0.10$ in univariate analysis.

* Odds ratio (95% profile likelihood confidence interval, adjusted for enrollment period).

[†] Set to one half of the limit of detection = 25 copies/mL for undetectable values.

[‡] Standard deviation.

HPV indicates human papillomavirus infection; IDU, injection drug use.