

Association between Bacterial Vaginosis and Expression of Human Immunodeficiency Virus Type 1 RNA in the Female Genital Tract

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We assessed the effect of lower genital tract infections on human immunodeficiency virus type 1 (HIV-1) RNA shedding in the female genital tract. Bacterial vaginosis was significantly associated with HIV-1 RNA expression in the female genital tract of HIV-infected women.

Both ulcerative sexually transmitted infections (syphilis, chancroid, and herpes) and nonulcerative sexually transmitted infections (gonorrhea and chlamydia) have been associated with higher rates of transmission and acquisition of HIV [1]. Conditions associated with cervical inflammation and genital ulcers have been associated with HIV shedding in the genital tract. The association between other nonulcerative lower genital tract infections (bacterial vaginosis, candidiasis, and trichomoniasis) and genital tract HIV shedding is less well defined. The presence of lower genital tract infections such as bacterial vaginosis may increase HIV type 1 (HIV-1) viral shedding in the genital tract.

We assessed the effect of lower genital tract infections on HIV-1 RNA levels in the genital tract for 108 HIV-infected women from the Rhode Island site of the HIV Epidemiologic Research Study. We obtained a total of 136 paired plasma and cervico-

vaginal lavage (CVL) specimens; for several women we obtained multiple samples. CVL was done by instilling 10 cc of sterile saline solution into the vaginal and cervical areas and aspirating after a few seconds. We determined HIV-1 RNA levels using the NucliSens assay (NASBA) to analyze unfractionated CVL specimens. The lower limit of detection was 400 copies/mL.

Lower genital tract infections were diagnosed on the basis of the following criteria: for bacterial vaginosis, Amsel's criteria [2]; for trichomoniasis, positive culture results; and for *Candida* vaginitis, a culture positive for *Candida* species with abnormal discharge and either pruritus, erythema, or edema of the vagina or vulva. A previous study showed very low rates of gonorrhea and chlamydia [3]; therefore, tests for these infections were not routinely done.

Highly active antiretroviral therapy (HAART) was defined as treatment with ≥ 2 nucleoside reverse-transcriptase inhibitors (NRTIs) and ≥ 1 protease inhibitors or a nonnucleoside reverse-transcriptase inhibitor. Monotherapy or dual therapy with NRTIs was classified as non-HAART.

The median age of the women in our sample was 34 years; 56% were white, 25% were African American, and 17% were Hispanic. Fifty-one percent had a history of injection drug use. CD4 cell counts in this group were as follows: <200 cells/mm³, 21% of patients; 200–500 cells/mm³, 47%; and >500 cells/mm³, 32%. Thirty percent of patients were not receiving antiretroviral therapy, 25% were receiving non-HAART treatment, and 45% were receiving HAART therapy. *Candida* vaginitis was the most prevalent infection, affecting 13% of patients; 11% of the patients had bacterial vaginosis, and only 4% had trichomoniasis. The CVL virus load was <400 copies/mL for all women with a plasma virus load <400 copies/mL.

To calculate the effect of bacterial vaginosis and *Candida* vaginitis on virus load in the genital tract, we determined the crude proportion of occasions on which women had CVL specimens with HIV-1 RNA levels >400 copies/mL and had plasma virus load >400 copies/mL, and we compared this value with the women's genital tract infection status. We also stratified our comparisons according to whether antiretroviral therapy was received. Comparisons were made using Fisher's exact test.

We used data for 108 women for whom data on genital tract infection status was available for ≤ 3 study visits each. Of the 108 women in the sample, 82 women contributed data that was obtained at 1 visit only, 24 contributed data from 2 visits, and 2 contributed data from 3 visits, for a total of 136 observations. Data on plasma virus load, CVL status, presence of trichomoniasis, and presence of *Candida* vaginitis were avail-

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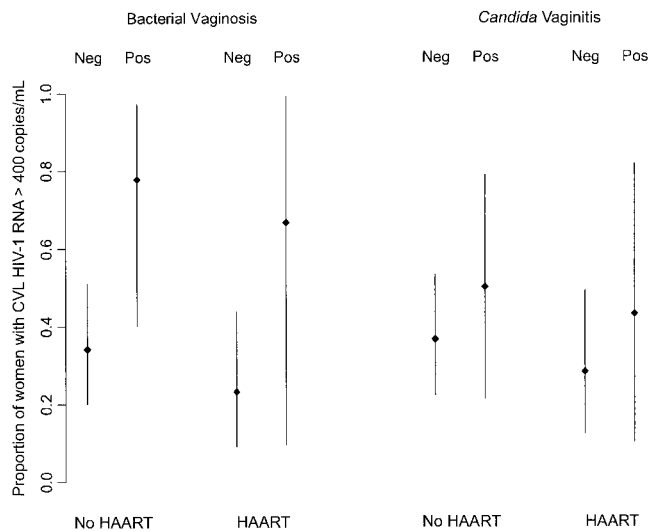


Figure 1. Proportion of women with plasma HIV type 1 (HIV-1) RNA level >400 copies/mL from whom cervicovaginal lavage (CVL) samples were obtained that had an HIV-1 RNA level >400 copies/mL, stratified by genital tract infection status and receipt of highly active antiretroviral therapy (HAART). Vertical bars represent 95% CIs for the estimated proportions. Neg, negative results of tests for infection; Pos, positive results of tests for infection.

able for all 136 observations. For 9 observations, information on the presence of bacterial vaginosis was missing; for 8, the CD4 cell count was missing; for 7, information on whether there was “any genital tract infection” was missing; and for 1, information on HAART status was missing. Because the percentage of observations with missing data was small, we used all available data for each analysis.

Among women who were receiving either no therapy or non-HAART therapy, HIV-1 RNA was detectable in CVL samples on 14 (34%) of 41 occasions when bacterial vaginosis was not

present, compared with 7 (78%) of 9 occasions when bacterial vaginosis was present ($P = .025$). Among women who were receiving HAART therapy, the corresponding proportions were 6 (23%) of 26 occasions and 2 (67%) of 3 occasions, respectively ($P = .176$; figure 1).

Among women who were receiving either no therapy or non-HAART therapy, HIV-1 RNA was detectable in CVL samples on 15 (36%) of 41 occasions when *Candida* vaginitis was not present, compared with 6 (50%) of 12 when it was present ($P = .507$). For women receiving HAART, the proportions were 7 (28%) of 25 occasions and 3 (43%) of 7 occasions, respectively ($P = .648$; figure 1).

To investigate our primary hypothesis about associations between lower genital tract infections and HIV-1 RNA levels in the genital tract, we used logistic regression to compare the odds of having viral expression in the genital tract with and without a lower genital tract infection, adjusting for plasma virus load, receipt of antiretroviral therapy, and CD4 cell count. Because some women were assessed on multiple occasions, we used generalized estimating equations with robust SEs to account for within-subject correlation [4]. We found that having any lower genital tract infection was significantly associated with increased odds of virus expression (adjusted OR, 3.7; 95% CI, 1.4–10.0), as was bacterial vaginosis (adjusted OR, 5.9; 95% CI, 1.4–25.0). We found no corresponding effect for *Candida* vaginitis (adjusted OR, 1.0; 95% CI 0.3–3.0; table 1).

Bacterial vaginosis is a common gynecologic infection that has been associated with pelvic inflammatory disease, premature delivery, and postabortion infection. Several studies have shown that bacterial vaginosis is associated with increased acquisition of HIV [5, 6]. In a study of pregnant women in Malawi, increasing prevalence of HIV was significantly associated with increasing severity of disturbance of vaginal flora

Table 1. ORs and associated 95% CIs, calculated by logistic regression, for 3 models of infection, showing the association between expression of HIV type 1 RNA (>400 copies/mL) in cervicovaginal lavage samples and different genital tract infections, adjusting for receipt of highly active antiretroviral therapy (HAART), CD4 cell count, and plasma virus load.

Variable	OR (95% CI), by model of infection		
	Model I: any GTI (104 individuals; 124 observations)	Model II: BV (105 individuals; 123 observations)	Model III: CV (104 individuals; 125 observations)
Any GTI	3.7 (1.4–10.1)	—	—
BV	—	5.9 (1.4–25.0)	—
CV	—	—	1.0 (0.3–3.0)
Receiving HAART (yes/no)	0.3 (0.1–1.2)	0.3 (0.1–1.3)	0.3 (0.1–1.4)
CD4 count <200 cells/mm ³ (yes/no)	3.4 (0.8–14.3)	2.8 (0.7–10.5)	2.5 (0.7–9.2)
Plasma virus load ^a	6.6 (2.5–17.3)	6.8 (2.6–17.5)	6.4 (2.7–15.4)

NOTE. BV, bacterial vaginosis; CV, *Candida* vaginitis; GTI, genital tract infection.

^a Plasma virus loads were coded as follows: 0, <400 copies/mL; 1, 400–9,999 copies/mL; 2, ≥10,000 copies/mL.

[7]. In that study, the OR for the association of bacterial vaginosis with prevalent HIV infection was 3.0 (95% CI, 2.4–3.8).

The findings in our study indicate that bacterial vaginosis is associated with increased expression of HIV-1 RNA levels in the female genital tract. Studies have also shown that bacterial vaginosis-associated microflora activates HIV expression in the female genital tract and may thus increase genital tract virus load, potentially contributing to HIV transmission [7, 8]. Our study is limited by the small sample size of women with genital tract infections other than bacterial vaginosis. Bacterial vaginosis may be a surrogate marker for other nonspecific inflammatory states, or even some behavioral or clinical factors that might put women at risk for greater HIV RNA expression in the genital tract. Further studies are required to determine whether control of bacterial vaginosis may reduce HIV virus load in the genital tract and thus reduce HIV sexual transmission.

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