Antiretroviral Drug Concentrations and HIV RNA in the Genital Tract of HIV-Infected Women Receiving Long-Term Highly Active Antiretroviral Therapy


1Miriam Hospital, 2Warren Alpert Medical School of Brown University, and 3Center for Statistical Science, Brown University, Providence, Rhode Island; 4Division of Pharmacology and Experimental Therapeutics, School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill; and 5Department of Pathology and Laboratory Medicine and Center for AIDS Research, Emory University School of Medicine, Atlanta, Georgia

Objective. Our objective was to determine antiretroviral drug concentrations and human immunodeficiency virus (HIV) RNA rebound in cervicovaginal fluid (CVF) in relation to blood plasma (BP) in women receiving suppressive highly active antiretroviral therapy (HAART).

Methods. Thirty-four HIV-infected women who had plasma HIV RNA levels ≤80 copies/mL for at least 6 months were enrolled. Sixty-eight paired CVF and BP drug concentrations and HIV RNA levels were determined before and 3–4 h after drug administration. For each woman and antiretroviral drug, the CVF:BP drug concentration ratios before and after drug administration were calculated. The nonparametric Wilcoxon rank sum test was used to determine if these ratios were different from 1.0.

Results. Lamivudine (administered to 20 patients) and tenofovir (administered to 16) had significantly higher concentrations in CVF than in BP before drug administration, with mean CVF:BP concentration ratios of 3.19 (95% confidence interval, 1.2–8.5) and 5.2 (95% confidence interval, 1.2–22.6), respectively. Efavirenz (administered to 13 patients) and lopinavir (administered to 6) had significantly lower concentrations in CVF, with mean CVF:BP concentration ratios of 0.01 (95% confidence interval, 0.00–0.03) and 0.03 (0.01–0.11), respectively. During the study visit (median time after enrollment, 6 months), BP and CVF detectable HIV RNA levels were observed in 7 patients (20.6%) and 1 patient (2.9%), respectively.

Conclusion. Despite lower CVF concentrations of key HAART components, such as efavirenz and lopinavir, virologic rebound was rare. The high concentrations of tenofovir and lamivudine in CVF may have implications for the prevention of sexual transmission during HAART and for pre-exposure or postexposure prophylaxis.
combination of drugs from at least 2 classes is designed to achieve maximum suppression of viral replication. Cell-free virus in the genital tract is thought to arise from both blood plasma (BP) transudation and independent local viral replication and evolution [9, 10, 12, 13]. Therefore, one would expect that penetration of all components of the treatment regimen into compartments such as the female genital tract at concentrations sufficient to inhibit viral replication would be necessary to prevent the emergence of drug-resistant variants during HAART. Previous studies have found lower concentrations of some PIs and the NNRTIs in CVF, compared with levels in BP [14, 15], but there are limited published data on the concentrations of NRTIs in CVF. Also, there are scarce data on the relationship between CVF drug concentrations and suppression of viral replication in this compartment. The objective of this study was to assess paired CVF and BP antiretroviral drug concentrations and to correlate local drug concentrations with HIV RNA rebound in patients receiving long-term suppressive HAART.

PATIENTS, MATERIALS, AND METHODS

Study population. Thirty-four HIV-infected women who had achieved plasma HIV RNA levels ≤80 copies/mL after receiving HAART for ≥6 months were prospectively enrolled from 5 September 2003 through 15 November 2005. These women were part of a longitudinal study designed to understand the relative dynamics of viral failure and viral replication in the female genital tract, to assess drug exposure and patterns of drug resistance in the female genital tract, and to evaluate cellular reservoirs of HIV in the female genital tract. During the study period, we enrolled 47 women who had achieved full HIV RNA suppression for ≥6 months (present study) and 9 women who had experienced failure of therapy and needed to switch regimens. All enrolled patients received HAART under standard medical care at the Immunology Center of The Miriam Hospital (Providence, Rhode Island). This study was reviewed and approved by the Lifespan Institutional Review Board, and written informed consent was obtained prior to enrollment.

Sample collection and handling. Enrolled subjects had a baseline evaluation that examined their demographic characteristics and medical, sexual, and reproductive histories. At enrollment, each patient had urine specimens tested for Neisseria gonorrhea and Chlamydia trachomatis. Pelvic examination and tests for genital tract infections were performed, and paired BP and CVF samples were obtained at all study visits (by Snostrips [Akorn] or Tear Flo [Hub Pharmaceuticals]). The study visit during which samples were obtained for measurement of drug concentrations and quantitative HIV RNA could be scheduled at any time within 12 months after enrollment, with a mean time to sampling of 5.5 months (median time to sampling, 6 months; range, 1–11 months). On the day of study sampling, patients reported to the clinic before their morning dose of medications. Paired CVF and blood samples were obtained prior to and 3–4 h after antiretroviral drug administration. The blood sample was obtained first, and then the CVF was collected within 5 min after blood sampling. CVF from the posterior fornix of the vagina was collected with a volumetric vaginal aspirator and transferred to a 1.2-mL cryovial and frozen at −70°C until shipment for testing. Approximately 10 mL of blood was collected in vacutainers containing EDTA and centrifuged at 1500 g for 10 min, and the plasma was aliquoted and stored at −70°C. All frozen samples were shipped on dry ice for testing.

Drug concentration determination. Drug concentrations in BP were measured using validated high-performance liquid chromatography with UV detection methods [16–18]. The lower limit of quantitation for plasma specimens was 10 ng/mL for emtricitabine, tenofovir, lamivudine, zidovudine, didanosine, abacavir, and stavudine and 25 ng/mL for fosamprenavir, efavirenz, lopinavir, atazanavir sulfate, ritonavir, and nelfinavir.

Concentrations in CVF were quantified using a validated high-performance liquid chromatography, tandem mass spectrometry method [19]. In brief, CVF concentrations were measured using a simultaneous assay for 17 antiretroviral drugs. Samples underwent solid-phase extraction using Bond Elut C-18 columns (Varian), as described elsewhere [18]. Cimetidine (in acetate buffer; pH 5.0) was used as internal standard and was applied directly to the conditioned column prior to CVF introduction. An Agilent 1100 binary pump (Agilent) and an HTC Pal thermostatated (6°C) autosampler (LEAP Technologies) connected to an Applied Biosystems API4000 triple quadrupole mass spectrometer and Turbospray ion source (Applied Biosystems) with an Aquasil C18 column (Thermo-Electron) was used for the analysis. Multiple reaction monitoring and positive-to-negative polarity switching were used: 3 analytes (stavudine, didanosine, and zidovudine) were monitored in negative mode, and the remaining analytes were monitored in positive mode. The lower limits of quantitation in CVF were 1 ng/mL for fosamprenavir, nevirapine, nelfinavir, and abacavir; 5 ng/mL for efavirenz, emtricitabine, and tenofovir; 10 ng/mL for lopinavir; 50 ng/mL for lamivudine, zidovudine, didanosine, and stavudine; and 75 ng/mL for ritonavir. Overall assay precision, expressed as coefficient of variation, was 2.0%–14.3%, and accuracy was 88%–113%. Recovery for the drugs studied ranged from 80% for ritonavir and lopinavir to 99% for lamivudine, didanosine, and abacavir. All analytical work was performed by the University of North Carolina Center for AIDS Research Clinical Pharmacology and Analytical Chemistry Core (Chapel Hill, North Carolina), which participates in quarterly national and international external proficiency testing [20, 21].
These results consistently demonstrate high levels of accuracy and precision for our antiretroviral assays.

**HIV RNA determination.** Nucleic acid sequence–based amplification (bioMerieux) was used to measure HIV RNA levels. All results are expressed as copies per mL, with a lower limit of detection of 80 copies/mL for BP and 3300 copies/mL for CVF collected by Sno-strips.

**Statistical analysis.** Antiretroviral drug concentrations in 2 pairs of genital tract and BP samples from each woman were examined. When the result was below the limit of detection, the concentration was set to 0 ng/mL. When the result was below the limit of quantitation but above the lower limit of quantitation, the concentration was set to 50% of the lower limit of quantitation.

For each compartment and time period, the mean and associated 95% CI of the concentrations of each drug were calculated. As expected, the concentrations showed a skewed distribution, attributable to some very high concentrations and a lower bound of zero. For each woman and antiretroviral drug, we calculated the ratio of drug concentration in the genital tract to drug concentration in the BP at each time period. Ratios >1 indicated that genital tract concentrations were greater than BP concentrations. The means and 95% CIs of the ratios were estimated using the Student’s t test.

The nonparametric Wilcoxon rank-sum test was used to determine whether the ratios were different from 1.0 (i.e., whether drug concentrations were different in the 2 biological compartments at either time period or whether concentrations were different in the genital tract after drug administration, compared with before administration). Statistical significance was determined at the α = 0.05 level.

**RESULTS**

**Patient characteristics.** During the study period, 47 women met the selection criteria and were enrolled. Of these women, 13 (28%) did not complete the study visit for sampling of drug concentrations and quantitative HIV RNA. Of these 13 patients, 3 withdrew from the study, 3 were lost to follow-up, 3 had scheduling conflicts, 2 moved out of state, 1 was incarcerated, and 1 died.

Of the 34 women who completed the study, the median age was 45 years (range, 32–62 years), 44% were black, 35% were non-Hispanic white, 15% were Hispanic, and 6% were of other ethnicities (table 1). Fifty-nine percent of the patients had CD4 cell counts of 200–499 cells/mm³, and 35% had counts ≥500 cells/mm³. Thirty-two (97%) of 33 patients were seropositive for herpes simplex virus 2 IgG, 8 (24%) of 34 had test results that were positive for bacterial vaginosis, and 5 (16%) had PCR results that were positive for herpes simplex virus 2 in CVF (table 1). Thirty patients (88%) received at least 2 NRTIs plus a PI or an NNRTI, 3 (9%) were given 3 or 4 NRTIs, and only 1 patient (3%) received a regimen that did not contain an NRTI. Ritonavir was given to boost other PIs in all but 1 patient. All except 3 patients received either lamivudine (n = 15) or tenofovir (n = 11) or both (n = 5) in their treatment regimen; 2 of the other 3 women received emtricitabine, and 1 was given a non–NRTI-based regimen.

**Antiretroviral drug concentrations in BP and CVF.** A total of 4 specimens were collected from each of the 34 women, who were taking a total of 13 different antiretroviral combinations. The number of women taking each drug ranged from 2 for nevirapine to 20 for lamivudine. Test results and 95% CIs associated with antiretrovirals with <5 samples were not considered to be reliable; they are included in the tables as preliminary information. Furthermore, 8 of 9 concentrations of zidovudine in the CVF were below the limit of quantitation (<50 ng/mL) before drug administration; 3 of the BP concentrations were below the limit of detection, 2 were below the limit of quantitation (<10 ng/mL), and 4 were <25 ng/mL. As a result, we could not compare CVF and BP concentrations of

| Table 1. Participant demographic data and clinical characteristics at baseline. |
|-----------------------------------|-----------|
| Characteristic                  | Patients  |
| Age, median years (range)       | 45 (32–62) |
| Race/ethnicity                  |           |
| Black                            | 15 (44)   |
| White/Non-Hispanic               | 12 (35)   |
| Hispanic                         | 5 (15)    |
| Other                            | 2 (6)     |
| CD4 cell count                   |           |
| <200 cells/mm³                   | 2 (6)     |
| 200–499 cells/mm³                | 20 (59)   |
| ≥500 cells/mm³                   | 12 (35)   |
| Hysterectomy                     | 8 (24)    |
| Test results positive for sexually transmitted infection | |
| Chlamydia                        | 0/24 (0)  |
| Syphilis                         | 0/23 (0)  |
| Gonorrhea                        | 0/23 (0)  |
| Trichomonas                      | 1 (3)     |
| Candida                          | 3 (9)     |
| Bacterial vaginosis              | 8 (24)    |
| Herpes simplex virus 2           |           |
| By IgG                           | 32/33 (97) |
| By PCR                           | 5/32 (16) |
| Antiretroviral therapy           |           |
| NRTI and PI                      | 17 (50)   |
| NRTI and NNRTI                   | 13 (38)   |
| 3 NRTIs                          | 3 (9)     |
| NNRTI and PI                     | 1 (3)     |

NOTE. Data are no. (%) of patients, unless otherwise indicated. NNRTIs, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.
concentrations in BP, with CVF:BP concentration ratios and NNRTIs had lower concentrations in CVF, compared with
and 0.03 (95% CI, 0.01–0.11), respectively. All of the other PIs mean CVF:BP concentration ratios of 0.01 (95% CI, 1.2–22.6) for teno-
fovir. On the other hand, efavirenz (administered to 13 patients)
and lopinavir (administered to 6) had significantly lower con-
centrations in CVF than in paired BP samples, with
mean CVF:BP concentration ratios of 3.19 (95% CI, 1.2–8.5) for lamivudine and 5.2 (95% CI, 1.2–22.6) for teno-
fovir. On the other hand, efavirenz (administered to 13 patients)
and lopinavir (administered to 6) had significantly lower con-
centrations in CVF samples than in paired BP samples, with
mean CVF:BP concentration ratios of 0.01 (95% CI, 0.0–0.03)
and 0.03 (95% CI, 0.01–0.11), respectively. All of the other PIs and NNRTIs had lower concentrations in CVF, compared with
concentrations in BP, with CVF:BP concentration ratios <1 but with statistically insignificant differences.

The mean concentrations of each drug in CVF and BP 3–4
h after administration are shown in table 3. Abacavir, efavirenz, ritonavir, and lopinavir had significantly lower concentrations in CVF than in BP 3–4 h after administration, with CVF:BP ratios significantly <1. The CVF:BP drug concentration ratios decreased for all of the drugs except efavirenz, lopinavir, nel-
finavir, and nevirapine after administration, indicating that
most drugs accumulated faster in BP than in CVF.

Virologic rebound in BP and CVF. There were 7 patients
who had detectable HIV RNA in BP at the time of sampling,
with viral loads of 100–1400 copies/mL. Of the 7 patients who
had low plasma viremia at the study visit, 3 had fully suppressed plasma viral loads on subsequent visits, 2 subsequently ex-
perienced failure of therapy because of treatment nonadherence,
and data was unavailable for 2 patients, because the study visit
was their last follow-up visit. Only 1 (3%) of the 34 patients
had a detectable HIV RNA level of 6000 copies/mL in the CVF
sample at the time of paired sampling; this patient also had an
HIV RNA level of 1400 copies/mL in the BP sample. At the
time of evaluation, the patient was receiving didanosine, la-
mivudine, and efavirenz and was noted to be nonadherent to
therapy. The didanosine concentration before administration
was below the limit of detection in both BP and CVF samples,
and efavirenz concentrations were low, compared with our ob-
served mean concentration for all patients, in BP (913.9 ng/
ml vs. 2087.8 ng/mL) and in CVF (6.9 ng/mL vs. 18.4 ng/mL).
However, the concentration of lamivudine in the patient’s BP
sample was higher than the observed mean concentration for
all of the patients (455.8 ng/mL vs. 123.7 ng/mL).

**DISCUSSION**

Maximum suppression of viral replication in the genital tract is believed to be essential to prevent evolution and trans-
mission of drug-resistant virus during HAART. The ability of
components of a triple-drug regimen to reach the genital tract in concentrations adequate to inhibit local viral replication
may be important to prevent the evolution of drug-resistant
variants of HIV in the genital tract during HAART, because
HIV replication has been shown to be compartmentalized at
this site [9, 10, 12, 13]. Also, it may be desirable that anti-
retroviral drugs given for pre- or post–sexual exposure pro-
phylaxis penetrate and accumulate in high concentrations in
the CVF, which is the likely site of exposure and initial in-
fecion. This study examined the concentrations of compo-
ents of HAART in the CVF of women who had achieved
excellent viral suppression in BP and sought to correlate local
drug concentrations with subsequent virologic rebound. In
general, the NRTIs demonstrated good penetration into the
CVF, with lamivudine and tenofovir achieving concentrations
in CVF of nearly 3–5 times their concentration in BP at the
end of the dosing interval. The excellent accumulation of these
agents in the CVF may be beneficial for the prevention of
HIV transmission during HAART and for pre- or post–sexual
exposure antiretroviral prophylaxis. On the other hand, se-
lective accumulation of NRTIs but not the PIs or NNRTIs in
the CVF may provide an environment for the selection of
drug-resistant variants in this compartment. Transmission of
antiretroviral drug–resistant HIV variants has been shown to
occur through sexual contact as well as from mother to child
[22–24]. However, it is not clear whether the drug-resistant
strains arose from the genital tract or systemically. Also, the
underlying mechanism for the protective effect of antiretro-
viral therapy against vertical transmission of HIV is not well
understood, because therapy that maximally suppressed viral
replication in BP demonstrated the best benefit in reducing
mother-to-child transmission of HIV, but zidovudine
monotherapy that did not have significant sustained ef-
ects on BP viral loads also reduced transmission

Our data also confirmed that the PIs and NNRTIs penetrate
poorly into CVF, as has been reported elsewhere [12, 13]. At
the end of the dosing interval, the concentrations of these clas-
ses of drugs in CVF was only 3%–33% of the concentrations
in the paired BP. Efavirenz and lopinavir, which were prescribed
to 19 (55.8%) of the 34 patients, achieved lower pre- and
post-dose concentrations in CVF, compared with BP. Despite
the lower concentrations of these agents in CVF, sustained sup-
pression of HIV RNA levels was observed in the genital tract
compartment. It is possible that there was a bias in our study,
because we enrolled only women who had achieved maximum
viral suppression in BP for at least 6 months, and the follow-
up period was relatively short (median duration, 6 months).
It was not possible for us to determine the relationship between CVF drug concentrations and viral rebound, because there was only 1 patient with HIV RNA rebound in the genital tract compartment. Other investigators have proposed that failure to fully suppress BP HIV RNA levels, rather than CVF drug concentrations, is the main determinant of genital tract viral shedding [25–29]. Alternatively, it is also possible that adequate drug concentration of the PIs and NNRTIs are achieved at the intracellular site of HIV replication, as demonstrated in studies that have examined intracellular pharmacokinetics [30–32].

We recognize that these data have limitations and should be interpreted with caution, especially for the drugs that were administered to 5 patients. Second, sampling for measurement of drug concentrations and viral loads was performed at only 1 time during the 12-month study period and at only 2 points

### Table 2. Steady state antiretroviral drug concentrations at the end of an 8–12-h dosing interval.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug class</th>
<th>No. of patients</th>
<th>Concentration in CVF, mean ng/mL (95% CI)</th>
<th>Concentration in BP, mean ng/mL (95% CI)</th>
<th>CVF:BP mean ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3TCa</td>
<td>NRTI</td>
<td>20</td>
<td>394.17 (134.7–1153.7)</td>
<td>123.74 (63.08–242.72)</td>
<td>3.19 (1.19–8.53)</td>
</tr>
<tr>
<td>TDFa</td>
<td>NRTI</td>
<td>16</td>
<td>84.03 (24.47–288.56)</td>
<td>16.3 (7.04–37.74)</td>
<td>5.15 (1.18–22.6)</td>
</tr>
<tr>
<td>ZDVa</td>
<td>NRTI</td>
<td>2</td>
<td>31.25 (18.68–52.25)</td>
<td>5.3 (1.85–15.19)</td>
<td>5.9 (2.11–16.52)</td>
</tr>
<tr>
<td>ABC</td>
<td>NRTI</td>
<td>8</td>
<td>28.17 (5.73–138.6)</td>
<td>48.26 (8.74–266.52)</td>
<td>0.58 (0.16–2.19)</td>
</tr>
<tr>
<td>ddI</td>
<td>NRTI</td>
<td>6</td>
<td>26.06 (23.42–29.01)</td>
<td>2.63 (0.22–31.45)</td>
<td>9.92 (0.81–121.63)</td>
</tr>
<tr>
<td>FTC</td>
<td>NRTI</td>
<td>4</td>
<td>250.51 (69.89–950.89)</td>
<td>167.14 (29.51–946.58)</td>
<td>1.5 (0.1–27.22)</td>
</tr>
<tr>
<td>EFVc</td>
<td>NNRTI</td>
<td>13</td>
<td>18.4 (6.95–48.73)</td>
<td>2087.81 (1483.43–2938.42)</td>
<td>0.01 (0–0.03)</td>
</tr>
<tr>
<td>NVP</td>
<td>NNRTI</td>
<td>2</td>
<td>272.02 (2.49–2973.16)</td>
<td>3499.78 (961.05–12744.92)</td>
<td>0.08 (0–2.33)</td>
</tr>
<tr>
<td>RTV</td>
<td>PI</td>
<td>11</td>
<td>58.73 (13.71–251.61)</td>
<td>72.71 (20.88–253.18)</td>
<td>0.81 (0.14–4.54)</td>
</tr>
<tr>
<td>LPVc</td>
<td>PI</td>
<td>6</td>
<td>74.64 (15.09–369.3)</td>
<td>2870.42 (1523.0–7391.19)</td>
<td>0.03 (0.01–0.11)</td>
</tr>
<tr>
<td>NFV</td>
<td>PI</td>
<td>4</td>
<td>113.7 (11.01–1173.87)</td>
<td>2363.78 (1523.0–3652.1)</td>
<td>0.05 (0.01–0.37)</td>
</tr>
<tr>
<td>ATV</td>
<td>PI</td>
<td>3</td>
<td>390.23 (81.94–1858.33)</td>
<td>1188.04 (585.2–2411.87)</td>
<td>0.33 (0.07–1.64)</td>
</tr>
<tr>
<td>FPV</td>
<td>PI</td>
<td>3</td>
<td>54.84 (2.21–1360.56)</td>
<td>1009.88 (125.76–8109.63)</td>
<td>0.05 (0–0.61)</td>
</tr>
</tbody>
</table>

**NOTE.** 3TC, lamivudine; ABC, abacavir; ATV, atazanavir sulfate; BP, blood plasma; CVF, cervicovaginal fluid; ddI, didanosine; EFV, efavirenz; EPV, fosamprenavir; FDC, emtricitabine; LPV, lopinavir; NVP, nevirapine; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; RTV, ritonavir; TDF, tenofovir; ZDV, zidovudine.

* Drugs that had significantly higher concentrations in CVF than in BP at the end of the dosing interval.

### Table 3. Steady state antiretroviral drug concentrations 3–4 h after administration.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug class</th>
<th>No. of patients</th>
<th>Concentration in CVF, mean ng/mL (95% CI)</th>
<th>Concentration in BP, mean ng/mL (95% CI)</th>
<th>CVF:BP mean ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3TCa</td>
<td>NRTI</td>
<td>20</td>
<td>782.9 (279.6–2192.6)</td>
<td>805.2 (351.8–1843.2)</td>
<td>0.97 (0.41–2.3)</td>
</tr>
<tr>
<td>TDFa</td>
<td>NRTI</td>
<td>16</td>
<td>67.4 (16.5–274.9)</td>
<td>90.0 (58.9–336.4)</td>
<td>0.75 (0.16–3.49)</td>
</tr>
<tr>
<td>ZDVa</td>
<td>NRTI</td>
<td>2</td>
<td>62.2 (23.7–162.9)</td>
<td>151.1 (67.9–336.4)</td>
<td>0.41 (0.12–1.43)</td>
</tr>
<tr>
<td>ABCa</td>
<td>NRTI</td>
<td>8</td>
<td>168.4 (82.5–343.7)</td>
<td>1596.1 (916.8–2778.8)</td>
<td>0.11 (0.04–0.28)</td>
</tr>
<tr>
<td>ddI</td>
<td>NRTI</td>
<td>6</td>
<td>39.2 (3.3–172.7)</td>
<td>34.3 (1.6–741.4)</td>
<td>1.14 (0.02–53.08)</td>
</tr>
<tr>
<td>FTC</td>
<td>NRTI</td>
<td>4</td>
<td>374.8 (1.4–7149.3)</td>
<td>823.0 (268.3–2524.8)</td>
<td>0.46 (0.29–2.05)</td>
</tr>
<tr>
<td>EPVa</td>
<td>NNRTI</td>
<td>13</td>
<td>29.8 (6.3–142.1)</td>
<td>3195.8 (2559.1–3991.0)</td>
<td>0.07 (0.01–0.71)</td>
</tr>
<tr>
<td>NVP</td>
<td>NNRTI</td>
<td>2</td>
<td>565.4 (364.8–876.2)</td>
<td>4334.8 (547.2–3340.8)</td>
<td>0.13 (0.01–1.6)</td>
</tr>
<tr>
<td>RTVa,b</td>
<td>PI</td>
<td>11</td>
<td>146.6 (44.4–483.6)</td>
<td>752.1 (471.2–1200.6)</td>
<td>0.19 (0.04–0.89)</td>
</tr>
<tr>
<td>LPVc</td>
<td>PI</td>
<td>6</td>
<td>215.1 (62.8–737.5)</td>
<td>6625.9 (4715.4–9310.4)</td>
<td>0.05 (0.01–0.2)</td>
</tr>
<tr>
<td>NFV</td>
<td>PI</td>
<td>4</td>
<td>162.4 (69.4–379.9)</td>
<td>2965.8 (1564.1–5623.4)</td>
<td>0.05 (0.01–0.37)</td>
</tr>
<tr>
<td>ATV</td>
<td>PI</td>
<td>3</td>
<td>724.9 (425.3–1235.7)</td>
<td>5068.1 (3660.3–7017.5)</td>
<td>0.14 (0.06–0.34)</td>
</tr>
<tr>
<td>FPV</td>
<td>PI</td>
<td>3</td>
<td>54.84 (2.21–1360.56)</td>
<td>1009.88 (125.76–8109.63)</td>
<td>0.05 (0–0.61)</td>
</tr>
</tbody>
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**NOTE.** 3TC, lamivudine; ABC, abacavir; ATV, atazanavir sulfate; BP, blood plasma; CVF, cervicovaginal fluid; ddI, didanosine; EFV, efavirenz; EPV, fosamprenavir; FDC, emtricitabine; LPV, lopinavir; NVP, nevirapine; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; RTV, ritonavir; TDF, tenofovir; ZDV, zidovudine.

* Drugs that had significantly lower CVF:BP drug concentrations 3–4 h after doing.

* Drugs that had significant increases in the genital tract concentrations after observed administration.
in the 8–24-h period of drug exposure during the dosing interval. Finally, we did not measure intracellular drug concentrations or the triphosphate form of the NRTIs, which are important for pharmacologic action. Notwithstanding these limitations, our data demonstrate that lamivudine and tenofovir accumulate well in the female genital tract and may have potential for use as part of combination therapy in reducing the sexual transmission of HIV. In addition, despite lower concentrations of the PIs and NNRTIs in the CVF, compared with concentrations in BP, we found no virologic rebound in the genital tracts of any of the patients who had undetectable viral loads in BP during a median follow-up period of ~6 months.

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