A Comparison of Genital HIV-1 Shedding and Sexual Risk Behavior Among Kenyan Women Based on Eligibility for Initiation of HAART According to WHO Guidelines

R. Scott McClelland, MD, MPH,*†§ Jared M. Baeten, MD, PhD,† Barbra A. Richardson, PhD,‡||
Ludo Lavreys, MD, PhD,†§ Sandra Emery, BS,¶ Kishorchandra Mandaliya, MBChB,§
Jeckoniah O. Ndinya-Achola, MBChB, MSc,§ and Julie Overbaugh, PhD||¶

Background: Guidelines for initiating antiretrovirals are based on markers of advanced disease and are not directly linked to markers of HIV-1 transmission such as viral shedding.

Methods: We evaluated genital HIV-1 shedding and risk behavior among 650 antiretroviral-naive women stratified by WHO criteria for initiating antiretrovirals based on CD4 count and symptoms.

Results: Genital HIV-1 concentrations increased in stepwise fashion with declining CD4 counts and the presence of symptoms. Compared with the reference group (asymptomatic with CD4 >350 cells/µL), those with advanced immunosuppression (CD4 <200 cells/µL) had significantly higher cervical HIV-1 RNA concentrations (2.4 log₁₀ copies/swab vs. 3.8 log₁₀ copies/swab, P < 0.001). However, women with CD4 counts <200 cells/µL were also less likely than the reference group to report intercourse during the past week (58% vs. 26%, P < 0.001).

Conclusions: Antiretroviral guidelines focusing on individuals with the most advanced immunosuppression will target those with the highest genital HIV-1 concentrations. However, individuals with less advanced immunosuppression also have high levels of genital HIV-1 and may be more sexually active. The effect of increased antiretroviral availability on the spread of HIV-1 might be enhanced by extending treatment, in addition to other risk reduction services, to those with less advanced disease.

Key Words: HIV-1, shedding, infectivity, antiretroviral therapy, Africa

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participants at the University of Washington and the University of Nairobi approved the protocol.

Participants completed a standardized interview covering demographic characteristics, sexual behavior, and medical history. A physical examination including pelvic speculum examination was performed. Polyester (Dacron; Invista, Wichita, KS) swabs were used to collect cervical and vaginal secretions for HIV-1 detection and quantitation. A dry swab and a swab in freezing medium (70% RPMI [Roswell Park Memorial Institute], 20% fetal calf serum, 10% dimethyl sulfoxide with added penicillin, streptomycin, and amphotericin B) were collected from each site. Vaginal secretions were sampled by rotating a swab 3 full turns against the lateral vaginal wall. After collection of swabs for HIV-1 detection, additional vaginal swabs were collected from the posterior fornix for vaginal Gram stain and saline wet preparation. Cervical secretions were sampled by inserting a swab 1 cm into the cervical os and rotating it 2 full turns. An additional cervical swab was collected for Gram stain and culture for Neisseria gonorrhoeae. A blood sample was collected for CD4 lymphocyte count and plasma HIV-1 RNA quantitation. Samples were stored on ice for up to 4 hours, then transferred to −70°C (dry swabs and plasma) or liquid nitrogen (swabs in freezing medium).

**Serology and Microbiology**

HIV-1 serostatus was determined using enzyme-linked immunosorbent assay (ELISA; Detect HIV 1/2, BioChem Immunosystems, Montreal, Canada), and confirmed with a 2nd ELISA (Recombigen, Cambridge Biotech, Worcester, MA). CD4 counts were determined using a semiautomated system (ZymuSure CD4/CD8 Cell Monitoring Kit, Bartels, Issaquah, WA) with a lower limit of 25 cells/μL. Vaginal Gram-stained secretions were evaluated for bacterial vaginosis.

Vaginal saline and potassium hydroxide wet mounts were examined for the presence of trichomonads, yeast, and sperm. The number of polymorphonuclear leukocytes in 3 nonadjacent high-power fields on microscopy of cervical Gram stains was quantified, and the presence of sperm was recorded. Culture for N. gonorrhoeae was performed on modified Thayer–Martin media.

**Assays for Plasma, Cervical, and Vaginal HIV-1 RNA and DNA**

Quantitation of HIV-1 RNA (a marker for expressed virus) was performed using transcription-mediated amplification (Gen-Probe, San Diego, CA). The lower limit of the assay is 3 copies/reaction, corresponding to 12 copies/mL for plasma and 15 copies/swab for genital swabs for the volumes tested in this study. Measurements that were below the limits for quantitation were assigned a value of half of the quantitation limit. Detection of HIV-1 DNA (a marker for infected cells) was performed using nested polymerase chain reaction amplification of the gag gene.

**Data Analysis**

We stratified participants according to WHO criteria for initiating antiretroviral therapy based on CD4 count and the presence of symptoms. The group of women who had CD4 counts >350 cells/μL and no symptoms of HIV-1 disease (reference group) was compared with the other strata of women.

Statistical analyses were performed using SPSS 11.0 (SPSS, Chicago, IL). Univariate comparisons were made using χ² tests and Fisher’s exact tests for binary data and independent-samples t-tests for continuous data. Multivariate comparisons were performed using logistic or linear regression. The multivariate models included known and suspected confounding factors related to HIV-1 shedding and sexual behavior that were identified a priori for these analyses. Multivariate models of cervical HIV-1 shedding were adjusted for the presence of blood on the swab (a marker for trauma during the examination), use of depot medroxyprogesterone acetate (DMPA), week of the menstrual cycle, and presence of N. gonorrhoeae by culture. Multivariate models of vaginal HIV-1 shedding were adjusted for the presence of blood on the swab, use of DMPA, week of the menstrual cycle, the presence of bacterial vaginosis by Gram stain criteria, and the presence of yeast and motile trichomonads on vaginal wet mount. Because identification of sperm in the cervical or vaginal secretions could indicate that the HIV-1 identified was from the male partner rather than from the woman participating in the study, we performed HIV-1 shedding analyses both excluding and including women who had sperm identified in genital samples. The results did not differ significantly, so we have reported only the analyses including these women. Multivariate models for the sexual behavior outcomes were adjusted for age, educational level, marital status, and history of transactional sex.

**RESULTS**

Characteristics of the 650 Kenyan women enrolled in this study are presented in Table 1, stratified by WHO criteria for initiation of antiretroviral therapy. Overall, the women had an average age of 29 years and approximately half were currently married. Only 6% reported a history of transactional sex. Although women with symptomatic genital tract infections were excluded, asymptomatic conditions, especially vaginal infections, were common. A total of 424 women (65%) had symptomatic HIV-1 infection based on the presence of ≥1 of the following: fever >1 month, cough >1 month, diarrhea >1 month, reported weight loss >5 kg, or clinical examination findings of oral candidiasis or oral hairy leukoplakia.

**Genital HIV-1 Shedding in Women Stratified by WHO Criteria for Initiating Antiretroviral Therapy**

Participants were stratified according to WHO criteria for initiating antiretroviral therapy utilizing both CD4 count and presence of symptoms. Cervical and vaginal HIV-1 shedding were compared between the reference group of asymptomatic women with CD4 counts >350 cells/μL and the other strata of women (Table 2). Progressive stepwise increases in genital HIV-1 shedding were observed among
TABLE 1. Baseline Characteristics of 650 HIV-1–Seropositive Kenyan Women, Mean (±SD) or Number (%)

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<td>No Symptoms*</td>
<td>Symptomatic*</td>
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<td></td>
<td>(n = 104)</td>
<td>(n = 90)</td>
<td>(n = 75)</td>
<td>(n = 102)</td>
<td>(n = 279)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>25 (±5)</td>
<td>28 (±7)</td>
<td>28 (±7)</td>
<td>29 (±6)</td>
<td>31 (±6)</td>
</tr>
<tr>
<td>Education (y)</td>
<td>7 (±3)</td>
<td>7 (±3)</td>
<td>7 (±4)</td>
<td>6 (±4)</td>
<td>6 (±4)</td>
</tr>
<tr>
<td>Currently married</td>
<td>72 (69%)</td>
<td>51 (57%)</td>
<td>42 (56%)</td>
<td>49 (48%)</td>
<td>129 (46%)</td>
</tr>
<tr>
<td>History of transactional sex†</td>
<td>1 (1%)</td>
<td>3 (3%)</td>
<td>7 (9%)</td>
<td>6 (6%)</td>
<td>23 (8%)</td>
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<tr>
<td>Obstetric/Gynecologic</td>
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<td>Pregnancies</td>
<td>2 (±2)</td>
<td>2 (±2)</td>
<td>3 (±2)</td>
<td>3 (±2)</td>
<td>3 (±2)</td>
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<tr>
<td>Using DMPA for contraception</td>
<td>35 (34%)</td>
<td>23 (26%)</td>
<td>16 (21%)</td>
<td>12 (12%)</td>
<td>26 (9%)</td>
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<tr>
<td>Trichomonas vaginalis</td>
<td>7 (7%)</td>
<td>12 (13%)</td>
<td>6 (8%)</td>
<td>9 (9%)</td>
<td>39 (14%)</td>
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<tr>
<td>Vulvovaginal candidiasis</td>
<td>16 (15%)</td>
<td>15 (17%)</td>
<td>17 (23%)</td>
<td>12 (12%)</td>
<td>56 (20%)</td>
</tr>
<tr>
<td>Bacterial vaginosis</td>
<td>51 (49%)</td>
<td>40 (44%)</td>
<td>32 (43%)</td>
<td>52 (51%)</td>
<td>128 (46%)</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>2 (2%)</td>
<td>2 (1%)‡</td>
</tr>
<tr>
<td>Vaginal friability§</td>
<td>3 (3%)</td>
<td>4 (4%)</td>
<td>2 (3%)</td>
<td>1 (1%)</td>
<td>14 (5%)</td>
</tr>
<tr>
<td>Cervical friability§</td>
<td>36 (35%)</td>
<td>42 (47%)</td>
<td>27 (36%)</td>
<td>48 (47%)</td>
<td>134 (48%)‡</td>
</tr>
<tr>
<td>Sperm on vaginal wet mount</td>
<td>0 (0%)</td>
<td>4 (4%)</td>
<td>2 (3%)</td>
<td>3 (3%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Sperm on cervical Gram stain</td>
<td>12 (12%)</td>
<td>14 (16%)</td>
<td>5 (7%)</td>
<td>2 (2%)</td>
<td>6 (2%)‡</td>
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<tr>
<td>HIV-1 Disease Markers</td>
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<tr>
<td>CD4 lymphocytes/μL</td>
<td>536 (±158)</td>
<td>524 (±159)</td>
<td>270 (±39)</td>
<td>266 (±46)</td>
<td>102 (±56)</td>
</tr>
<tr>
<td>Plasma HIV-1 RNA (log_{10} copies/mL)</td>
<td>4.7 (±1.0)</td>
<td>4.8 (±0.8)</td>
<td>5.2 (±0.6)</td>
<td>5.4 (±0.8)</td>
<td>5.8 (±0.6)</td>
</tr>
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</table>

*Symptoms included ≥1 of: fever >1 month, diarrhea >1 month, cough >1 month, weight loss >5 kg, oral thrush, and oral hairy leukoplakia.
†Reported history of exchanging money or goods for sex.
‡One patient had undergone a hysterectomy, so n = 649 for CD4 counts >350 cells/μL and no symptoms.
§Friability was defined as the presence of any visible blood on the swabs collected for detection of HIV-1 infected cells or RNA. Only trace blood (minimal discoloration) was noted on vaginal swabs. Among 287 women with any blood on cervical swabs, 157 (55%) had only trace blood.

women with increasing levels of immunosuppression and symptomatic disease. Significantly higher genital HIV-1 concentrations were observed among women with more advanced HIV-1 disease in comparison with the reference group. However, even the group of asymptomatic women with CD4 counts >350 cells/μL had substantial concentrations of HIV-1 RNA and frequent detection of HIV-1–infected cells in genital mucosal secretions. The findings for both cervical and vaginal HIV-1 shedding were similar after adjustment for potential confounding factors (Table 3).

TABLE 2. Univariate Analysis of Genital HIV-1 Shedding by WHO Criteria for Initiating Antiretroviral Therapy

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<tbody>
<tr>
<td></td>
<td>No Symptoms*</td>
<td>Symptomatic*</td>
<td>No Symptoms*</td>
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<td></td>
<td>(n = 104)</td>
<td>(n = 90)</td>
<td>(n = 75)</td>
<td>(n = 102)</td>
<td>(n = 279)</td>
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<tr>
<td>Cervical HIV-1</td>
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<tr>
<td>Log_{10} RNA copies/swab, mean (±SD)</td>
<td>2.39 (±1.15)</td>
<td>2.57 (±1.27)</td>
<td>3.09 (±1.08)</td>
<td>3.37 (±1.01)</td>
<td>3.79 (±0.91)†</td>
</tr>
<tr>
<td>RNA detected, n (%)</td>
<td>82 (79%)</td>
<td>73 (81%)</td>
<td>68 (91%)</td>
<td>95 (93%)</td>
<td>273 (98%)†</td>
</tr>
<tr>
<td>DNA detected, n (%)</td>
<td>47 (45%)</td>
<td>40 (44%)</td>
<td>43 (57%)</td>
<td>60 (59%)</td>
<td>187 (67%)†</td>
</tr>
<tr>
<td>Vaginal HIV-1</td>
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<tr>
<td>Log_{10} RNA copies/swab, mean (±SD)</td>
<td>2.21 (±1.23)</td>
<td>2.45 (±1.31)</td>
<td>2.70 (±1.48)</td>
<td>3.12 (±1.37)</td>
<td>3.63 (±1.21)†</td>
</tr>
<tr>
<td>RNA detected, n (%)</td>
<td>71 (68%)</td>
<td>67 (74%)</td>
<td>56 (75%)</td>
<td>84 (82%)</td>
<td>258 (93%)</td>
</tr>
<tr>
<td>DNA detected, n (%)</td>
<td>11 (11%)</td>
<td>8 (9%)</td>
<td>15 (20%)</td>
<td>26 (26%)</td>
<td>87 (31%)</td>
</tr>
</tbody>
</table>

*Symptoms included ≥1 of: fever >1 month, diarrhea >1 month, cough >1 month, weight loss >5 kg, oral thrush, and oral hairy leukoplakia.
†Reported history of exchanging money or goods for sex.
‡One patient had undergone a hysterectomy, so n = 649 for CD4 counts >350 cells/μL and no symptoms.
Ref indicates reference group; P values represent comparisons with the reference group (CD4 >350 cells/μL and no symptoms).
Multivariate models of vaginal HIV-1 shedding were adjusted for the presence of blood on the swab, use of DMPA, week of the menstrual cycle, the presence of yeast and motile trichomonads on vaginal wet mount.

### TABLE 3. Multivariate* Analysis of Genital HIV-1 Shedding by WHO Criteria for Initiating Antiretroviral Therapy

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<td></td>
<td>No Symptoms†</td>
<td>Symptomatic†</td>
<td>No Symptoms†</td>
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<tr>
<td>Cervical HIV-1</td>
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<tr>
<td>Mean difference in log₁₀ HIV-1 RNA copies/swab</td>
<td>Reference group</td>
<td>0.13 (0.16–0.41)</td>
<td>0.70 (0.40–1.00)</td>
<td>0.95 (0.67–1.23)</td>
<td>1.36 (1.13–1.60)†</td>
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<tr>
<td>RNA detected aOR (95% CI)</td>
<td>1</td>
<td>1.2 (0.6–2.5)</td>
<td>2.9 (1.1–7.3)</td>
<td>4.2 (1.7–10.7)</td>
<td>16.9 (6.0–47.9)‡</td>
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<tr>
<td>DNA detected aOR (95% CI)</td>
<td>1</td>
<td>0.9 (0.5–1.6)</td>
<td>1.6 (0.9–3.0)</td>
<td>1.7 (0.9–3.0)</td>
<td>2.3 (1.4–3.8)‡</td>
</tr>
<tr>
<td>Vaginal HIV-1</td>
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</tr>
<tr>
<td>Mean difference in log₁₀ HIV-1 RNA copies/swab</td>
<td>Reference group</td>
<td>0.22 (0.15–0.58)</td>
<td>0.44 (0.06–0.82)</td>
<td>0.93 (0.57–1.29)</td>
<td>1.36 (1.06–1.66)</td>
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<tr>
<td>RNA detected aOR (95% CI)</td>
<td>1</td>
<td>1.4 (0.7–2.6)</td>
<td>1.3 (0.7–2.7)</td>
<td>2.4 (1.2–4.7)</td>
<td>5.7 (3.0–10.8)</td>
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<tr>
<td>DNA detected aOR (95% CI)</td>
<td>1</td>
<td>0.8 (0.3–2.2)</td>
<td>2.0 (0.8–4.7)</td>
<td>3.1 (1.4–7.0)</td>
<td>4.1 (2.0–8.3)</td>
</tr>
</tbody>
</table>

- Mean difference in log₁₀ HIV-1 RNA copies/swab
- RNA detected aOR (95% CI)
- DNA detected aOR (95% CI)

*Multivariate models of cervical HIV-1 shedding were adjusted for the presence of blood on the swab, use of DMPA, week of the menstrual cycle, and the presence of yeast and motile trichomonads on vaginal wet mount.
†Symptoms included: fever >1 month, diarrhea >1 month, cough >1 month, weight loss >5 kg, oral thrush, and oral hairy leukoplakia.
‡n = 278 for cervical HIV-1 shedding because 1 woman had undergone hysterectomy.

### Table 4. Univariate and Multivariate Analysis of Sexual Risk Behavior by WHO Criteria for Initiating Antiretroviral Therapy

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<tr>
<td></td>
<td>No Symptoms*</td>
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<tr>
<td>Intercourse during past week</td>
<td>60 (58%)</td>
<td>42 (47%)</td>
<td>39 (52%)</td>
<td>36 (35%)</td>
<td>72 (26%)</td>
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<tr>
<td>OR (95% CI)</td>
<td>1</td>
<td>0.6 (0.4–1.1)</td>
<td>0.8 (0.4–1.4)</td>
<td>0.4 (0.2–0.7)</td>
<td>0.3 (0.2–0.4)</td>
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<tr>
<td>Adjusted‡ OR (95% CI)</td>
<td>1</td>
<td>0.8 (0.4–1.5)</td>
<td>1.0 (0.5–1.9)</td>
<td>0.5 (0.3–1.0)</td>
<td>0.3 (0.2–0.6)</td>
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<tr>
<td>Condom with last intercourse</td>
<td>6 (6%)</td>
<td>9 (10%)</td>
<td>11 (15%)</td>
<td>7 (7%)</td>
<td>37 (13%)</td>
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<tr>
<td>OR (95% CI)</td>
<td>1</td>
<td>1.8 (0.6–5.3)</td>
<td>2.8 (1.0–8.0)</td>
<td>1.2 (0.4–3.7)</td>
<td>2.5 (1.0–6.1)</td>
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<tr>
<td>Adjusted‡ OR (95% CI)</td>
<td>1</td>
<td>1.7 (0.5–5.2)</td>
<td>2.2 (0.7–6.8)</td>
<td>1.0 (0.3–3.1)</td>
<td>1.9 (0.7–5.1)</td>
</tr>
</tbody>
</table>

- Mean difference in log₁₀ HIV-1 RNA copies/swab
- RNA detected aOR (95% CI)
- DNA detected aOR (95% CI)

*Multivariate models were adjusted for age, educational level, marital status, and history of transactional sex.

Sexual Risk Behavior in Women Stratified by WHO Criteria for Initiating Antiretroviral Therapy

To test the hypothesis that sexual activity might be less frequent among women with more advanced HIV-1 infection, we compared the history of reported intercourse in the past week among the 650 women after stratifying by WHO criteria for initiating antiretrovirals (Table 4). Among 104 women with CD4 >350 cells/μL and no symptoms, 60 (58%) reported a history of intercourse during the previous week. The prevalence of reported intercourse during the previous week was significantly lower among symptomatic women with CD4 counts between 200–350 cells/μL (35%) and among women with CD4 counts <200 cells/μL (26%). The findings were similar after adjustment for potential confounding factors. Condom use was low in all groups but was

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generally higher among women with more advanced infection compared with asymptomatic women with CD4 counts >350 cells/μL. However, these differences were not statistically significant after adjustment for confounding factors.

**DISCUSSION**

Although the most important factor in deciding when to initiate antiretroviral therapy is the potential risk vs. benefit to the individual patient, additional consideration of the public health implications of treatment guidelines is important because it may help to maximize the benefit for communities in which antiretrovirals are being introduced. In this cohort of Kenyan women, the highest levels of genital HIV-1 shedding were observed among those who would qualify for initiation of antiretroviral therapy based on WHO guidelines. However, substantial levels of HIV-1 shedding were observed even among asymptomatic women with CD4 counts >350 cells/μL, and these women were more sexually active compared with those with more advanced infection.

Our results agree with previous studies demonstrating broad correlations between plasma HIV-1, CD4 count, and genital viral shedding, while also providing novel findings related to HIV-1 transmission risk markers in women. The analysis focused not on viral load, which is unavailable in many resource-limited countries, but on a combination of laboratory and clinical criteria that guide decisions about initiation of antiretroviral therapy. We simultaneously evaluated markers for infectivity and sexual risk, both of which contribute to the overall risk of HIV-1 transmission.

There are limitations to this study. Cross-sectional data are useful for identifying key associations but cannot definitively establish causality. For example, although women with CD4 counts <200 cells/μL had the lowest reported sexual frequency, this finding does not prove that HIV-1 progression resulted in decreased sexual activity. Likewise, it is uncertain whether sexual frequency would increase with immune recovery as a result of antiretroviral therapy. Despite this limitation, the data presented here are valuable and timely because they simultaneously quantify differences in markers of infectivity and sexual risk based on criteria that are used to identify patients for initiation of antiretroviral therapy. Thus, these results highlight critical questions for further study as antiretroviral programs are expanded.

Antiretrovirals may prove to be an important tool for decreasing the sexually transmitted epidemic of HIV-1 infection in resource-limited settings. The ultimate effect of expanding antiretroviral access on global HIV-1 epidemiology will depend at least in part on the policies that are in place as antiretroviral programs are brought to scale. Understanding the risk of HIV-1 transmission among individuals who would vs. those who would not qualify for treatment under current WHO guidelines is an important step. This study has identified women with early or intermediate stages of HIV-1 infection as an important target population for interventions to reduce the risk of sexual transmission. Potential strategies include risk reduction counseling, condom promotion and negotiation, screening and treatment of sexually transmitted infections, and earlier initiation of antiretroviral therapy. Additional research to determine the efficacy of these different approaches for reducing HIV-1 transmission will be essential even as efforts continue to make antiretroviral therapy more widely available.

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