Injectable Contraceptive Use and Genital Ulcer Disease during the Early Phase of HIV-1 Infection Increase Plasma Virus Load in Women

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We examined the association between host factors present near the time of human immunodeficiency virus type 1 (HIV-1) acquisition and subsequent virus loads, in a prospective cohort study of women in Mombasa, Kenya. Women were prospectively followed monthly before HIV-1 infection. One hundred sixty-six women who became infected with HIV-1 were followed for a median of 34 months, and 991 plasma samples collected ≥4 months after infection were tested for HIV-1 RNA. The median virus set point at 4 months after infection was 4.46 log10 copies/mL, and the average virus load increase during subsequent follow-up was 0.0094 log10 copies/mL/month. In a multivariate analysis that controlled for sexual behavior, the use of the injectable contraceptive depot medroxyprogesterone acetate (DMPA) at the time of HIV-1 infection was associated with a higher virus set point, and the presence of genital ulcer disease (GUD) during the early phase of HIV-1 infection was associated with greater change in virus load during follow-up. These findings suggest that, in women, the use of DMPA and the presence of GUD during the early phase of HIV-1 infection may influence the natural course of infection.

Primary HIV-1 infection is characterized by rapid replication of HIV-1, as evidenced by high levels of plasma viral RNA. HIV-1 RNA can be detected in plasma as early as 2 weeks after infection [1], and, during the acute phase of infection, concentrations can exceed 7 log10 RNA copies/mL [2]. Virus loads then decrease dramatically, often by >2 log10 copies/mL, as HIV-1-specific immunity develops [3]. By 3–4 months after infection, a balance between viral replication and host control results in a steady-state plasma virus level [4]. The infection point at which steady-state virus levels are established has been called the “virus set point,” and this phase is followed by a slow but steady increase of virus load during the asymptomatic phase of HIV-1 infection [4–6]. Higher virus set point has been shown to be a strong predictor of HIV-1 disease progression, AIDS, and death [7–9].

Although there have been many studies that have shown a relationship between virus loads and clinical outcome, it is largely unknown whether factors present during the early phase of infection may influence steady-state levels of viral replication. Thus, the degree to which the course of HIV-1 disease is determined at the time that infection occurs is unclear. Certainly, the virus that establishes the infection is a major determinant of disease, perhaps, in part, reflecting differences in the antigenicity of different virus variants. This is most clearly illustrated in studies of the simian immunodeficiency virus (SIV)mac model, in which it has been shown that the properties of the infecting virus have a dramatic effect on virus set point and pathogenesis [10]. There is also evidence that host genetics may influence disease progression, the most notable example being individuals with a deletion in the gene coding for the viral coreceptor CCR5 [11, 12].
have been no previous studies that have examined whether there are modifiable host factors present at the time of HIV-1 acquisition or during the early phase of infection that affect subsequent steady-state virus replication, although there is evidence that virus-host interactions within the first 4–6 months of infection affect the course of disease [3, 4]. There is a suggestion from one early study of the Multicenter AIDS Cohort Study (MACS) that the presence of sexually transmitted diseases (STDs) before seroconversion and sexual behavior before and after seroconversion may be determinants for faster progression to AIDS [13]. In the SIVmac model, treatment with progesterone after seroconversion may be determinants for faster progression (STDs) before seroconversion and sexual behavior before and after seroconversion may be determinants for faster progression to AIDS [13]. In the SIVmac model, treatment with progesterone before SIV infection has been linked with increased virus loads during the early phase of infection [14], but it is unknown whether there is a similar relationship between the use of hormonal contraceptives at the time of HIV-1 infection and increased virus load in women. Such modifiable host characteristics are of particular interest because intervention strategies directed at these factors before or soon after infection could potentially delay disease progression. Moreover, insight into virus-host interactions during the early phase of HIV-1 infection might provide a better understanding of the mechanisms governing HIV-1 pathogenesis.

There have been several studies of change in virus load over time, the majority using cohorts of homosexual men, including cross-sectional studies at various phases of infection [15, 16], as well as longitudinal analyses from the time of documented seroconversion [17, 18]. There have also been studies of change in virus load over time in HIV-1–infected injection drug users [19], hemophiliacs [20], and women [21]. However, most of these studies have been of North American and European cohorts, and, in most of these, the date of infection of the individuals was unknown. There have been few studies of African cohorts, and these have included small numbers of individuals enrolled at variable times after HIV-1 infection [22, 23]. Moreover, some studies have found differences in virus load between men and women during the course of infection, suggesting that sex-specific factors play a role in HIV-1 disease progression [24]. Thus, for the populations most affected by HIV-1 disease (most notably African women), there is a paucity of data on the natural history of HIV-1 infection from patients with known infection dates. Information on the temporal pattern of HIV-1 loads in African populations, including African women, will be important as programs to increase access to antiretroviral treatment for persons with HIV-1 infection in Africa gain momentum.

In 1993, we initiated an open, prospective cohort study of HIV-1–seronegative female commercial sex workers attending a municipal clinic in Mombasa. Women were invited to participate in the prospective cohort study, as described elsewhere [25]. At study enrollment, and at monthly intervals thereafter, women were interviewed by use of standardized questionnaires regarding recent sexual behavior and contraceptive practices. A physical examination was performed, including pelvic examination and STD screening. Clinical diagnoses were made for vaginal discharge (other than normal physiologic secretions), cervical mucopus (purulent discharge from the endocervix), and GUD (a breach of the normal genital epithelium). A blood sample was obtained for HIV-1 serologic testing. Women who seroconverted to HIV-1 during follow-up were asked to continue their monthly clinic visits, and blood samples were obtained quarterly. At each visit, study participants received individual risk-reduction counseling, confidential HIV-1 counseling, condoms, and general outpatient medical care. None of the women in the cohort reported using antiretroviral therapy at any time during follow-up. Informed consent was obtained from all participants. The present study was approved by the ethical review committees of the University of Nairobi, the University of Washington, and the Fred Hutchinson Cancer Research Center.

**Laboratory methods.** HIV-1 serologic testing was performed by use of an ELISA (Detect-HIV; Biochem Immuno-Sysm), and positive results were confirmed by use of a second ELISA (Recombigen; Cambridge Biotech). Diagnoses of *Trichomonas vaginalis* and vaginal candidiasis were made by wet mount. Endocervical secretions were collected for culture of *Neisseria gonorrhoeae* on modified Thayer-Martin media and for antigen detection of *Chlamydia trachomatis* (Microtrak; Syva). *Chlamydia* testing was discontinued in April 1999 because of the low incidence in the cohort. Bacterial vaginosis was defined as a Nugent score of ≥7 on Gram’s stain [26]. Cervicitis was defined as an average of >30 polymorphonuclear cells in 3 oil-immersion fields [27]. Syphilis serologic testing was performed by rapid plasma reagin (RPR; Becton Dickinson) and *Treponema pallidum* hemagglutination assay (TPHA; Biotech Laboratories). Genital ulcers were cultured on activated charcoal media for detection of *Haemophilus ducreyi*. Cases of GUD in patients who were negative for both *H. ducreyi* and *T. pallidum* were presumed to be due to herpes simplex virus (HSV)–2.

At all visits at which a blood sample was obtained, a plasma

**SUBJECTS, MATERIALS, AND METHODS**

**Study population and clinic procedures.** HIV-1–seronegative female commercial sex workers attending a municipal clinic in Mombasa were invited to participate in the prospective cohort study, as described elsewhere [25]. At study enrollment, and at monthly intervals thereafter, women were interviewed by use of standardized questionnaires regarding recent sexual behavior and contraceptive practices. A physical examination was performed, including pelvic examination and STD screening. Clinical diagnoses were made for vaginal discharge (other than normal physiologic secretions), cervical mucopus (purulent discharge from the endocervix), and GUD (a breach of the normal genital epithelium). A blood sample was obtained for HIV-1 serologic testing. Women who seroconverted to HIV-1 during follow-up were asked to continue their monthly clinic visits, and blood samples were obtained quarterly. At each visit, study participants received individual risk-reduction counseling, confidential HIV-1 counseling, condoms, and general outpatient medical care. None of the women in the cohort reported using antiretroviral therapy at any time during follow-up. Informed consent was obtained from all participants. The present study was approved by the ethical review committees of the University of Nairobi, the University of Washington, and the Fred Hutchinson Cancer Research Center.

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sample was frozen either at −70°C or in liquid nitrogen and was archived for future testing. Plasma samples from all visits after HIV-1 seroconversion, as well as from the 2 clinic visits before seroconversion, were shipped either on dry ice or in liquid nitrogen to Seattle for determination of HIV-1 virus load. Plasma HIV-1 RNA was quantified by use of the Gen-Probe HIV-1 virus load assay. This assay has been demonstrated to accurately and reproducibly quantify plasma HIV-1 from HIV-1 subtypes found in this population [28]. We used a lower cutoff level (100 copies of HIV-1 RNA) to define detection of virus in plasma [29].

**Date of HIV-1 infection.** For women with HIV-1 detected in plasma samples collected before HIV-1 seroconversion, we estimated that HIV-1 infection occurred 17 days before the first sample was found to be positive for HIV-1 RNA. This estimate was derived from detailed studies of blood donors and is based on the midpoint of the average time from HIV-1 infection to development of plasma viremia and to development of detectable HIV-1 antibodies [30]. For women who had no plasma viremia detected before HIV-1 seroconversion or for whom no preseroconversion samples were available for RNA testing, we estimated that HIV-1 infection occurred at the midpoint between the last clinic visit at which the woman was HIV-1 seronegative and the first clinic visit at which the woman was HIV-1 seropositive; we excluded women from the analysis who had >1 year between these 2 visits, unless they were found to have a positive HIV-1 load before seroconversion, because we could not estimate the date of HIV-1 infection with sufficient precision.

**Hormonal contraception, STDs, and sexual behavior at the time of HIV-1 infection.** We used self-reported data on use of hormonal contraception and on recent sexual behavior that were collected monthly, as well as clinical examination and laboratory data on STDs that were collected at a clinic visit near the estimated time of infection. We estimated that the effect of oral or injectable hormonal contraception would persist for 70 days after discontinuation of use, on the basis of the length of time that fertility is diminished after discontinuation of both forms of hormonal contraceptives [31, 32]. Thus, we defined a participant as having been exposed to hormonal contraception at the time of HIV-1 infection if her estimated date of infection occurred within 70 days of a clinic visit at which hormonal contraception was reported. Women for whom there was an interval of >70 days between the last visit while uninfected and the estimated date of infection were defined as having been exposed to hormonal contraception if they reported use of the same hormonal contraceptive method at the last visit while uninfected and at the first visit after infection. If the contraceptive methods reported at these 2 visits flanking the date of infection differed, we considered the method of contraception at the time of HIV-1 infection to be undefined. This definition was used in previous reports of this cohort [25, 33]. The injectable contraceptive contained 150 mg of depot medroxyprogesterone acetate (DMPA)/mL, and the recommended frequency of administration to maintain its optimal contraceptive effect is once every 3 months. For oral contraceptives, the majority of women used low-dose pills (0.03 mg of ethinylestradiol and 0.15 mg of levonorgestrel), but some women, especially earlier in the study, used higher-dose pills (0.05 mg of ethinyl estradiol and 0.25 mg of levonorgestrel or 0.5 mg of norgestrel) [25].

We estimated that the effect of STDs would persist for 15 days after treatment [25]. Because women were seen at intervals of ≥1 month, only a relatively small proportion of women had a clinic visit within 15 days of their estimated date of HIV infection. Thus, we defined a participant as having been exposed to an STD if it was present at the time of HIV acquisition or at the subsequent visit. The latter cases may include STDs present at the time of acquisition, as well as STDs acquired at the time of HIV-1 infection or soon after. To define sexual-behavior exposures at the time of HIV-1 infection, we calculated mean sexual frequency, number of sexual partners, and frequency of condom use during the 6 months preceding HIV-1 infection, to better reflect average behavior.

**Data analysis.** SPSS (version 10.0; SPSS) and S-PLUS 2000 (MathSoft) were used for data analysis. Samples collected after the estimated date of HIV-1 infection that were found to have a virus load <100 copies/mL were defined as having a virus load of 50 copies/mL (only 13 of 991 samples from 8 women had a virus load <100 copies/mL). Linear mixed-effect models were used to model HIV-1 virus load over time after virus set point and to determine virus set point, defined as occurring at 4 months after the date of HIV-1 infection. The choice of 4 months was based on findings from Kaufmann et al. [3] and Schacker et al. [4] and on a graphical examination of our own data, which showed an increase of virus load in a generally linear fashion 4 months after infection (data not shown). Variables were defined as changing virus set point if they changed the intercept of a linear mixed-effect model that included all samples from >4 months after infection. Variables having a statistically significant interaction with time from the estimated date of infection were defined as changing the slope of the mixed-effects model, which was expressed as the average increase or decrease of the number of copies of plasma HIV-1 RNA per mL per month.

**RESULTS**

**Study population.** Between February 1993 and August 2001, 1350 HIV-1–seronegative female commercial sex workers were enrolled in the cohort, of whom 228 acquired HIV-1 during study follow-up. Of these, 161 met the study criteria of having
a known date of infection and having virus load measurements available from >4 months after infection. The median time from infection to the first visit at which the woman was HIV-1 seropositive was 59 days (interquartile range [IQR], 42–103 days). Of these 161 women, 70 had plasma viremia detected before seroconversion. The 161 women were followed for a median of 34 months (IQR, 16–56 months) after HIV-1 infection. We collected 991 samples from ≥4 months after infection, with a median of 4 samples (IQR, 2–9 samples) from each woman. The median time between obtaining samples was 72 days (IQR, 35–150 days). Baseline demographic and behavioral characteristics are summarized in table 1.

**Virus load during the course of disease.** For the 70 women in whom HIV-1 RNA was detected in plasma samples before seroconversion, the maximum virus load was 7.76 log_{10} copies/mL, and the median virus load before seroconversion was 4.84 log_{10} copies/mL (IQR, 2.36–6.30 log_{10} copies/mL). These results most likely include data from throughout the window of primary infection, including some measurements that were near the peak in viral replication.

The virus load measurements from ≥4 months after infection for 161 women were entered in a linear mixed-effects model. Using this model, the estimated set point was 4.46 log_{10} copies/mL (95% confidence interval [CI], 4.32–4.60 log_{10} copies/mL), and the average change in virus load over time was an increase of 0.0094 log_{10} copies/mL/month (95% CI, 0.0057–0.0130 log_{10} copies/mL/month).

**Determinants of virus load at set point and during subsequent course of disease.** Table 2 shows the univariate analysis of covariates of virus set point and change in virus load over time during subsequent disease progression. For each variable present at time of HIV-1 infection, the additional effect, positive or negative, on the virus set point or change in virus load over time is shown. The use of the injectable contraceptive DMPA at the estimated time of HIV-1 acquisition was associated with a significantly increased virus set point (+0.29 log_{10} copies/mL), compared with women who used no contraceptive method at the time of infection (P = .04). Figure 1A depicts this difference in set point, as well as average virus load per quarter, for women using DMPA or no contraceptive method at the time of infection. The model demonstrates that DMPA use at the time of infection was associated with a persistently higher virus load, a difference that was established at set point. DMPA use at the time of infection was not associated with significantly different change in virus load over time during subsequent disease progression (−0.0021 log_{10} copies/mL/month; 95% CI, −0.0110 to +0.0067 log_{10} copies/mL/month; P = .6). The use of oral contraceptives at the time of infection was not associated with virus set point or change in virus load over time, compared with no contraceptive method.

Since women tend to use contraceptive methods for extended periods of time, we analyzed additional linear models, to confirm that the association between DMPA use and virus loads was specific to use at the time of HIV-1 acquisition rather than a result of DMPA use during subsequent HIV-1 infection. In one model, we adjusted for DMPA use during follow-up as a time-dependent variable. In this model, only DMPA use at the time of infection, and not during subsequent follow-up, was associated with higher virus set point. Neither DMPA use at the time of infection nor DMPA use during follow-up was associated with change in virus load over time. In a second model, we compared 4 women who used DMPA only at the time of infection and never thereafter with 88 women who used no contraceptive method either at the time of infection or during subsequent follow-up. In this model, DMPA use at the time of infection remained associated with higher virus set point (+0.65 log_{10} copies/mL; 95% CI, −0.18 to +1.48 log_{10} copies/mL; P = .12), although the small number of women in this cohort who used DMPA only at the time of infection limited statistical significance.

There was a trend toward a higher virus set point (+0.47 log_{10} copies/mL; P = .09) and a statistically significantly increased change in plasma virus load over time during disease progression (+0.0286 log_{10} copies/mL/month; P = .001) among those women who presented with a genital ulcer near the time of infection, compared with those women who presented without one. When both virus set point and change in virus load over time were considered in a single model, a statistically significant effect remained only on change over time. Figure 1B depicts this modelled difference in change in virus load over time, as well as the observed average virus load per quarter, for women with and without GUD near the time of infection. All 8 women with GUD were diagnosed at their first visit after HIV-1 infection, which occurred at a median of 21 days after infection (IQR, 17–54 days). Only 1 had evidence of syphilis (32-fold in RPR titer and positive TPHA result), none had a positive culture for *H. ducreyi*, and the remaining 7 had ul-

### Table 1. Demographic and behavioral characteristics at time of HIV-1 acquisition in 161 African women.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>28 (25–34)</td>
</tr>
<tr>
<td>Education, years</td>
<td>7 (6.5–9.0)</td>
</tr>
<tr>
<td>Time in cohort before HIV-1 infection, months</td>
<td>8.3 (2.2–21.1)</td>
</tr>
<tr>
<td>Age at first sexual contact, years</td>
<td>17 (15–18)</td>
</tr>
<tr>
<td>Years of prostitution</td>
<td>3 (2–6)</td>
</tr>
<tr>
<td>No. of sex partners per weeka</td>
<td>1 (0.7–1.3)</td>
</tr>
<tr>
<td>No. of sex acts per weeka</td>
<td>1.5 (1.0–2.0)</td>
</tr>
<tr>
<td>Frequency of condom use, %a</td>
<td>83 (11–100)</td>
</tr>
</tbody>
</table>

**NOTE.** IQR, interquartile range.

* Average values per week for each woman, for the 6 months preceding HIV-1 infection.
cerations clinically consistent with genital herpes. In a separate model, we found that the occurrence of GUD episodes during subsequent follow-up did not change the relationship between GUD near the time of infection and virus set point or change in virus load over time.

In univariate analysis, several variables for sexual behavior near the time of HIV-1 infection were associated with higher virus set point or change in virus load over time. Women reporting consistent condom use had significantly increased change in viral load over time (+0.0072 log$_{10}$ copies/mL/month; 95% CI, 0 to +0.0144 log$_{10}$ copies/mL/month; $P = .05$), compared with women reporting <100% condom use. A trend for a higher virus set point was seen among women who had $>2$ sexual contacts/week (virus set point, +0.28 copies/mL; $P = .06$) and $>1$ sex partner/week (virus set point, +0.25 copies/mL; $P = .07$), near the time of infection, compared with women who had $\leq 2$ sexual contacts/week and $= 1$ sexual partner/week, respectively.

To investigate the independent effects of DMPA use, GUD, and sexual behavior, a multivariate model was constructed. DMPA use at the time of infection remained significantly associated with an increased virus set point (+0.33 log$_{10}$ copies/mL; 95% CI, +0.04 to +0.62 log$_{10}$ copies/mL; $P = .03$). The presence of GUD at the time of HIV-1 infection remained significantly associated with an increased change in virus load over time (+0.0285 copies/mL/month; 95% CI, +0.0109 to +0.0460 log$_{10}$ copies/mL/month; $P = .002$) but was not associated with a significant change in virus set point. In the multivariate model, none of variables for sexual behavior remained associated with either virus set point or change in virus load over time. Further adjustment for additional variables—including age, education, and parity—had no effect on the findings on DMPA use and GUD.

**DISCUSSION**

In the present study, which is the first prospective study of plasma HIV-1 RNA in African women from the time of HIV-1 infection, we have found a median virus set point of 4.46 log$_{10}$ HIV-1 RNA copies/mL (95% CI, 4.32–4.60 log$_{10}$ copies/mL), followed by an increase in plasma virus load of 0.0094 log$_{10}$ copies/mL/month (95% CI, 0.0057–0.0130 log$_{10}$ copies/mL/month) during subsequent follow-up. The virus set point was similar to those reported from the MACS in the United States [17] and from a cohort study of men and women in India [34]. There have also been studies of plasma HIV-1 RNA loads in African cohorts, although these included only small numbers of women. In a cross-sectional analysis of 19 seroincident and 9 seroprevalent cases of HIV-1 in Guinea-Bissau, virus set point was 4.85 log$_{10}$ copies/mL [35], and, in a cohort study in Côte d’Ivoire, the median virus load at 10 months after serocon-
Figure 1. Plasma virus load (log_{10} copies per milliliter) vs. time since HIV-1 infection, demonstrating increased virus set point for women who used depot medroxyprogesterone acetate (DMPA) at time of infection (A) and increased change in virus load over time for women who presented with genital ulcer disease (GUD) during the early phase of HIV-1 infection (B). Solid lines depict linear mixed-effects models; dotted lines depict observed data, as average virus load per quarter. A, Squares represent women using DMPA and triangles represent women using no contraceptive method at the time of HIV-1 acquisition. B, Squares represent women with GUD and triangles represent women without GUD near the time of HIV-1 acquisition.
version in 104 patients, who were predominantly men, was 4.6 log₁₀ copies/mL [36]. On the other hand, the increase in change in virus load over time in the Mombasa women was higher than that reported in the MACS cohort of US men (0.0024 log₁₀ copies/mL/month) [17] and was closer to that reported in the cohort in India (0.014 log₁₀ copies/mL/month) [34]. The higher increase in change in virus load over time in the present study is interesting in light of the suggestion that disease progression may be slightly faster in developing countries than in industrialized countries [34, 37].

Few studies have carefully followed HIV-1–infected individuals from before HIV-1 acquisition, and, thus, our cohort offers a unique opportunity to assess the influence of factors present at the time of HIV-1 infection on subsequent HIV-1 disease. We have found that DMPA use at the time of HIV-1 acquisition and the presence of a GUD during the early phase of infection were associated with higher levels of HIV-1 replication.

Women who used DMPA at the time of HIV-1 infection had a higher virus set point and, thus, a persistently higher virus load throughout follow-up, compared with women who did not use hormonal contraception. This effect was specific to DMPA use and was not seen in women who used oral contraceptive pills. This finding suggests that an interaction between DMPA use and virus-host dynamics may be established during the early phase of infection. DMPA has previously been shown to increase the risk of acquiring HIV-1 in women at high risk for HIV-1 who were intensively monitored for HIV-1 infection [25], but not in discordant couples who were monitored for HIV-1 infection on a less frequent basis [38]. It is difficult to know whether the inconsistent results reflect differences in study design or real differences in the importance of hormonal contraception in HIV-1 acquisition in particular risk groups. The exact mechanism by which DMPA could increase susceptibility and virus set point is unknown. Potential mechanisms that could increase susceptibility include physiological effects on the integrity of the vaginal epithelium [14], an effect on the cell-surface levels of CCR5 (which is a key molecule for HIV-1 entry) [39, 40], or a direct effect on virus expression via hormone response elements within the HIV-1 promoter [41]. In the Mombasa cohort, and oral contraceptive use at the time of HIV-1 infection have both been associated with the acquisition of multiple viral genotypes [42]. DMPA treatment in mice has been shown to increase the susceptibility to genital herpes infection, suggesting that changes in female hormones may affect susceptibility to other enveloped viruses [43]. Collectively, the findings suggest that progesterone levels not only affect initial susceptibility to HIV-1 infection but also affect early events in viral replication, such as virus dissemination or the ability of the host to contain virus during primary infection.

We have found that the presence of GUD during the early phase of HIV-1 infection is associated with a more rapid increase in plasma virus load during chronic HIV-1 disease. We considered the possibility that the effect of GUD on plasma virus load could also be due to more-frequent HSV reactivation throughout the course of HIV-1 infection. However, when we adjusted our analysis for genital ulcers that occurred later during the course of the disease, the association between change in virus load over time and GUD near the time of infection remained. GUD is an important cofactor for HIV-1 acquisition [44, 45] and has also been described as a clinical feature of acute HIV-1 illness [46] (e.g., as a reactivation of latent HSV because of immunosuppression during the initial rapid increase in virus load). This could also explain the data in the present study, because the majority of genital ulcers were clinically diagnosed as episodes of genital herpes, a common infection in our cohort, and among individuals with HIV-1 [47, 48]. Cell-culture studies have suggested that HSV up-regulates HIV-1 replication [49, 50], and studies of chronic HIV-1 infection have also shown a link between HSV infection and increased HIV replication [48, 51]. Our findings suggest that interactions between HSV and HIV-1 during acute infection may also affect the levels of HIV-1 replication, although it is unclear why this effect is manifest in changes in virus loads over time rather than initial virus set point.

In this cohort of female commercial sex workers in Mombasa, virus set point and change in virus load over time were comparable to those found in studies of HIV-1–infected individuals in India and the United States. Virus set point and increase in change in virus load during subsequent disease progression were independently associated with DMPA use and the presence of GUD, respectively, at the time of HIV-1 infection. Both cofactors have been associated with increased risk of HIV-1 acquisition, and the present results extend these findings to suggest that progression to HIV-1 disease is also influenced if these factors are present at or near the time of HIV-1 acquisition. Identification of modifiable risk factors for HIV-1 acquisition and disease progression such as these may help in the development of intervention strategies that delay HIV-1 disease progression.

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