as in genital inflammatory states such as urethritis and epididymitis, conditions closely associated with other STIs. The virus has also been demonstrated in cervical smears and vaginal fluid. There is an elevated risk of HIV transmission associated with unprotected receptive anal intercourse (URAI) among both men and women compared to the risk associated with receptive vaginal intercourse. Although data are limited, the per-act risk for HIV transmission via URAI has been estimated to be ~1.4% (Table 226-3). The risk of HIV acquisition associated with URAI is probably higher than that seen in penile-vaginal intercourse because only a thin, fragile rectal mucosal membrane separates the deposited semen from potentially susceptible cells in and beneath the mucosa, and micro-trauma of the mucosal membrane may be associated with anal intercourse. Anal douching and sexual practices that traumatize the rectal mucosa also increase the likelihood of infection. It is likely that anal intercourse provides at least two modalities of infection: (1) direct inoculation into blood in cases of traumatic tears in the mucosa; and (2) infection of susceptible target cells, such as Langerhans cells, in the mucosal layer in the absence of trauma. Insertive anal intercourse also confers an increased risk of HIV acquisition compared to insertive vaginal intercourse. Although the vaginal mucosa is several layers thicker than the rectal mucosa and less likely to be traumatized during intercourse, the virus can be transmitted to either partner through vaginal intercourse. As noted in Table 226-3, male-to-female HIV transmission is usually more efficient than female-to-male transmission. The differences in reported transmission rates between men and women may be due in part to the prolonged exposure to infected seminal fluid of the vaginal and cervical mucosa, as well as the endometrium (when semen enters through the cervical os). By comparison, the penis and urethral orifice are exposed relatively briefly to infected vaginal fluid. Among various cofactors examined in studies of heterosexual HIV transmission, the presence of other STIs has been strongly associated with HIV transmission. In this regard, there is a close association between genital ulcerations and transmission, owing to both susceptibility to infection and infectivity. Infections with microorganisms such as *Treponema pallidum* **(Chap. 206)**, *Haemophilus ducreyi* **(Chap. 182)**, and herpes simplex virus (HSV; **Chap. 216**) are important causes of genital ulcerations linked to transmission of HIV. In addition, pathogens responsible for non-ulcerative inflammatory STIs such as those caused by *Chlamydia trachomatis* **(Chap. 213)**, *Neisseria gonorrhoeae* **(Chap. 181)**, and *Trichomonas vaginalis* **(Chap. 254)** also are associated with an increased risk of transmission of HIV infection. Bacterial vaginosis, an infection related to sexual behavior, but not strictly an STI, also may be linked to an increased risk of transmission of HIV infection. Several studies suggest that treating other STIs and genital tract syndromes may help prevent transmission of HIV. This effect is most prominent in populations in which the prevalence of HIV infection is relatively low. It is noteworthy that this principle may not apply to the treatment of HSV infections since it has been shown that even following anti-HSV therapy with resulting healing of HSV-related genital ulcers, HIV acquisition is not reduced. Biopsy studies revealed the likely explanation is that HIV receptor–positive inflammatory cells persisted in the genital tissue despite the healing of ulcers, and so HIV-susceptible targets remained at the site.

The quantity of HIV-1 in plasma is a primary determinant of the risk of HIV-1 transmission. In a cohort of heterosexual couples in Uganda discordant for HIV infection and not receiving antiretroviral therapy, the mean serum HIV RNA level was significantly higher among HIV-infected subjects whose partners seroconverted than among those whose partners did not seroconvert. In fact, transmission was rare when the infected partner had a plasma level of <1700 copies of HIV RNA per milliliter, even when genital ulcer disease was present **(Fig. 226-7)**. The rate of HIV transmission per coital act was highest during the early stage of HIV infection when plasma HIV RNA levels were high and in advanced disease as the viral set point increased.

Antiretroviral therapy dramatically reduces plasma viremia in most HIV-infected individuals (see "Treatment," below) and is associated with a reduction in risk of transmission. In a large study of serodiscordant couples, earlier treatment of the HIV-infected partner with antiretroviral therapy rather than treatment delayed until the CD4+ T cells count fell below 250 cells per μL was associated with a 96% reduction in HIV transmission to the uninfected partner. This approach has been widely referred to as *treatment as prevention* or TasP. Several studies also have suggested a beneficial effect of antiretroviral treatment at the community level.

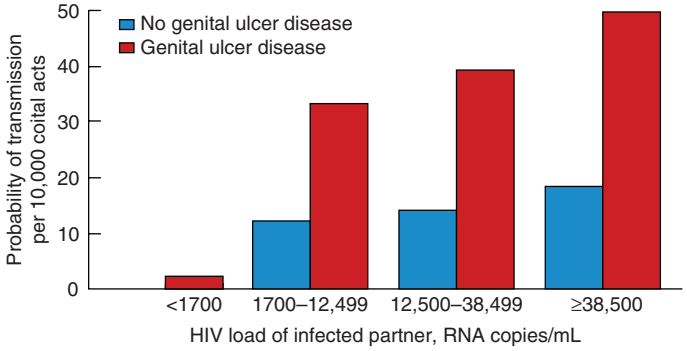

FIGURE 226-7 Probability of HIV transmission per coital act among monogamous, heterosexual, HIV-serodiscordant couples in Uganda. *(From RH Gray et al: Lancet 357:1149, 2001.)*

A number of studies including large, randomized, controlled trials clearly have indicated that male *circumcision* is associated with a lower risk of acquisition of HIV infection for heterosexual men. Studies are conflicting as to whether circumcision protects against HIV acquisition among men who have sex with men, but data suggest that circumcision is protective in those men who have sex with men who are insertive only. The benefit of circumcision may be due to increased susceptibility of uncircumcised men to ulcerative STIs, as well as to other factors such as microtrauma to the foreskin and glans penis. In addition, the highly vascularized inner foreskin tissue contains a high density of Langerhans cells as well as increased numbers of CD4+ T cells, macrophages, and other cellular targets for HIV. Finally, the moist environment under the foreskin may promote the presence or persistence of microbial flora that, via inflammatory changes, may lead to even higher concentrations of target cells for HIV in the foreskin. In addition, randomized trials have demonstrated that male circumcision also reduces hepatitis C virus (HCV) type 2, human papillomavirus virus (HPV), and genital ulcer disease in men as well as HPV, genital ulcer disease, bacterial vaginosis, and *Trichomonas vaginalis* infections among female partners of circumcised men. Thus, there may be an added benefit of diminution of risk for HIV acquisition to the female sexual partners of circumcised men.

In some studies the use of oral contraceptives was associated with an increase in incidence of HIV infection over and above that which might be expected by not using a condom for birth control. This phenomenon may be due to drug-induced changes in the cervical mucosa, rendering it more vulnerable to penetration by the virus. Adolescent girls might also be more susceptible to infection upon exposure due to the properties of an immature genital tract with increased cervical ectopy or exposed columnar epithelium.

Oral sex is a much less efficient mode of transmission of HIV than is anal intercourse or vaginal intercourse (Table 226-3). A number of studies have reported that the incidence of transmission of infection by oral sex among couples discordant for HIV was extremely low. However, there have been well-documented reports of HIV transmission that likely resulted from fellatio or cunnilingus. Therefore, the assumption that oral sex is completely safe is not warranted.

The association of alcohol consumption and illicit drug use with unsafe sexual behavior, both homosexual and heterosexual, leads to an increased risk of sexual transmission of HIV. Methamphetamine and other so-called club drugs (e.g., ecstasy, ketamine, and gamma hydroxybutyrate), sometimes taken in conjunction with PDE-5 inhibitors such as sildenafil (Viagra), tadalafil (Cialis), or vardenafil (Levitra), have been associated with risky sexual practices and increased risk of HIV infection, particularly among men who have sex with men.