Current Concepts

Sexual Transmission of HIV

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TRANSMISSION through sexual contact accounts for 75 to 85 percent of the nearly 28 million infections with the human immunodeficiency virus (HIV) that have occurred so far.[1] The probability of infection through sexual contact, although it varies greatly, appears to be lower than that of infection through other routes of exposure (Fig. 1). The variability observed among and within routes of HIV exposure depends partly on the viral dose and also on whether the virus is transmitted directly into the blood or onto a mucous membrane. In addition, these differences are influenced by a variety of host factors, including both factors common to all routes of exposure and those unique to sexual transmission.

HIV infectivity is the average probability of transmission to another person after that person is exposed to an infected host. Infectivity plus two other parameters — the duration of infectiousness and the average rate at which susceptible people change sexual partners — determines whether the epidemic grows or slows.[12] On a population level, all three corners of the classic epidemiologic triangle — host-related factors (susceptibility and infectiousness), environmental factors (the social, cultural, and political milieu), and agent factors (HIV type 1) determine HIV infectivity. Host-related and environmental factors can amplify the epidemic through their dual effect on infectivity and the rate of sexual-partner change. Although the entire triangle is key to understanding infectivity, our article focuses on the epidemiology and biology of the host-related factors that affect the sexual transmission of HIV.

HOST SUSCEPTIBILITY AND INFECTIOUSNESS

Host susceptibility depends on viral entry into cells through CD4 and chemokine surface receptors.[13,14] These cells include CD4 T lymphocytes, Langerhans' cells, and other macrophages. In macaques, virus appears in dendritic cells of the vaginal lamina propria soon after vaginal inoculation with simian immunodeficiency virus (SIV).[15] HIV-receptive cells have been found in the lamina propria of oral, cervicovaginal, foreskin, urethral, and rectal epithelia in other primate models.[16]

In women, the glandular epithelium harbors HIV in the zone of transformation between the columnar and squamous cells of the cervix.[17] Cervical swabs yield HIV DNA more readily than vaginal swabs (33 percent vs. 17 percent).[18] In men, HIV is detectable in seminal cells and seminal plasma. Although sperm cells do not express CD4 receptors and are unlikely to be a major source of infection, HIV DNA has been detected in some sperm cells and their precursors.[19]

Host factors affecting infectivity have been identified through both population-level studies of HIV transmission and direct measurement of virus in genital secretions (Table 1). These factors may operate through several interrelated mechanisms. Host susceptibility may be affected by factors linked to inflammation or immune activation that alter either the number of susceptible target cells or the receptivity of those cells. In addition, these same mechanisms may affect the production of virus within infected cells, thereby influencing the infectiousness of the host. For example, during immune activation after vaccination with tetanus toxoid, the blood concentration of virus increases 2- to 36-fold.[20] Other factors may induce microscopic erosions that provide the virus direct access to the bloodstream. Still others may act by facilitating the survival of HIV in the oral, genital, or rectal mucosa. The vaginal pH may affect the survival of HIV under some conditions.[21]

Host Genetics

Epidemiologic data suggest that occasionally hosts may lack susceptibility to HIV infection.[14,22] Some sex workers and homosexual men remain uninfected despite repeatedly having unprotected sexual intercourse with HIV-infected partners.[14,22-24] A mutation in the chemokine-receptor gene has been identified.[24] This mutation apparently varies greatly according to race, with 11 percent and 1.7 percent homozygosity among whites and blacks, respectively. People who are homozygous for the *CKR5* mutation appear to be resistant to infection. While heterozygosity for this mutation does not prevent infection, it may slow the progression of the disease. The effect of heterozygosity on HIV infectiousness is unknown.

Stage of Infection

A late stage of infection is a strong predictor of infectiousness according to both epidemiologic and biologic data. When the index partner has more advanced HIV infection — indicated by symptoms of

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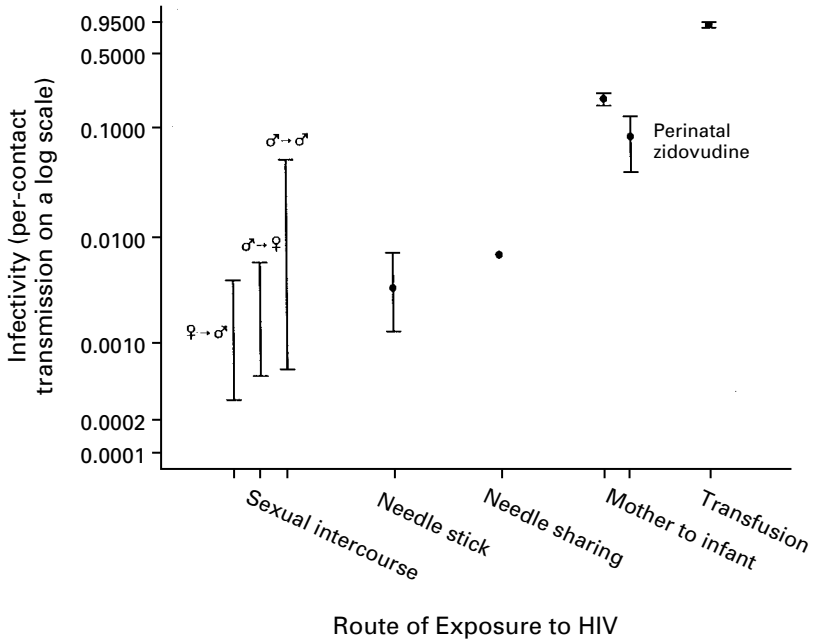

Figure 1. Per-Contact Probability of HIV Transmission.

The infectivity ranges for sexual contact are derived from a comprehensive review of the literature (lower and upper bounds are from modeling per-contact transmission in different study populations with different modeling techniques). Each infectivity estimate for the other routes of infection originates from one representative study. The routes of infection are as follows: sexual intercourse, with ♀→♂ indicating female-to-male transmission,[2,3] ♂→♀ indicating male-to-female transmission,[2,4] and ♂→♂ indicating male-to-male transmission[5,6]; needle stick[7]; needle sharing[8]; transmission from mother to infant with[9] and without[10] perinatal zidovudine treatment; and transfusion.[11]

HIV disease, a diagnosis of the acquired immunodeficiency syndrome (AIDS), CD4 counts below 200 cells per cubic millimeter, or p24 antigenemia — sexual partners are at a much higher risk of acquiring infection (relative-risk range, 6.1 to 17.6).[25-30]

Host infectiousness is likely to increase as a function of the concentration of virus in the genital tract. Higher viral loads in the blood have been associated with the transmission of HIV to sexual partners of people with transfusion-acquired infections.[31] Data on viral concentration in blood and semen generally support the epidemiologic inferences about the importance of the stage of infection in the transmission of HIV. Recent studies show that HIV is more readily detected, and in some cases is present in higher concentrations, in the blood[32,33] or semen[34,35] of men with low CD4 T-lymphocyte counts or more advanced HIV disease than in that of men with higher counts or less advanced disease. This correlation was not observed in some studies,[19,36-40] however, and two small studies of the stage of infection and concentrations of HIV in cervicovaginal fluids also found no relation.[41,42]

Primary infection (which occurs during the period between exposure to HIV and the appearance of HIV antibodies) may also be associated with increased infectiousness.[5,12,43,44] Across studies, blood viral titers in men at about the time of seroconversion[45-47] are higher than in men in later stages of infection.[32,33,45] Although the concentration of HIV in genital secretions during primary infection has not been determined, epidemiologic evidence supports a peak in the transmissibility of HIV soon after a person is infected. The probability of infection was greater when high-risk sexual behavior occurred early in the epidemic, presumably because of the large proportion of people with primary infection at that time.[48] The fact that the probability of female-to-male transmission per contact is higher in Thailand[3] (0.056) than in Europe[2] and the United States[49] (0.0003 to 0.0014) may reflect the more recent introduction of HIV to Asia. The Thai estimate is in the range reported for male-to-male infectivity in the early years of the U.S. epidemic.[6,43,50] Primary infection may account for a great part of the risk of transmission, according to modeling estimates.[5,43,44] The large contribution to the propagation of the epidemic may be attributed to the association of primary infection with two parameters that influence the spread of HIV — higher infectivity and a higher rate of sexual-partner change, especially among high-risk groups.[5,43,44]

TABLE 1. BIOLOGIC HOST-RELATED FACTORS AFFECTING SEXUAL TRANSMISSION OF HIV.*

BIOLOGIC FACTOR	HOST-RELATED INFECTIVITY FACTORS		
	HIV CONCENTRATION IN GENITAL SECRETIONS	INFECTIOUSNESS (TRANSMISSION)	SUSCEPTIBILITY (ACQUISITION)
Mutation of chemokine-receptor gene	?	?	↓↓↓
Late stage of HIV infection	↑↑	↑↑↑	Not applicable
Primary HIV infection	↑↑	↑↑	Not applicable
Antiretroviral therapy	↓	↓↓	↓?
Local infection (inflammation or ulcer of reproductive tract or rectal or oral mucosa)	↑↑	↑	↑↑
Presence of cervical ectopy	↑↑	↑?	↑↑
Presence of foreskin	?	↑↑	↑↑
Method of contraception			
Barrier	Not applicable	↓↓↓	↓↓↓
Hormonal contraceptives	↑↑	↕?	↕
Spermicidal agents	?	↓?	↕
Intrauterine devices	?	?	↑↑
Menstruation	?	↑↑	↑
Factors that lower cervicovaginal pH	↓?	↓?	↓?
Immune activation	↑?	↑	↑
Genital tract trauma	↑?	↑↑	↑↑
Pregnancy	↑↑	↑?	↑?

*The associations represented were statistically significant in at least one study. The degrees of positivity (↑ to ↑↑↑) and negativity (↓ to ↓↓↓) of the associations are indicated with arrows, with three arrows indicating a very strong association. The symbol ↕ denotes that there is evidence in support of both a positive and a negative association. A question mark indicates an unknown or hypothesized association that is not currently supported by data.

Antiretroviral Therapy

Antiretroviral therapy may affect infectivity. Decreases in concentrations of and detection of seminal HIV in men taking zidovudine or newer antiretroviral drugs have been observed in some[33,51] but not all[36,37,40,52] studies. Antiretroviral therapy apparently does not affect the detection of HIV in cervicovaginal specimens.[41,42] However, such therapy is associated with a 50 percent reduction in the sexual transmission of HIV.[53] The effect on susceptibility to infection of administering antiretroviral agents immediately after sexual exposure to HIV is unknown,[54] although administering zidovudine decreases the risk of infection after needle-stick injuries.[55] Arguments for antiretroviral prophylaxis after sexual exposure to HIV must be carefully weighed against the cost and toxicity of the drugs, as Katz and Gerberding point out elsewhere in this issue of the *Journal*.[54] Finally, antiretroviral drugs slow the progression of the disease and thus have an effect on the stage of infection.

Reproductive Tract Infections

The presence of reproductive tract infections is strongly associated with susceptibility to HIV, even after adjustment for sexual behavior.[56] The prevalence of genital ulcer disease (chancroid, syphilis, or herpes) is associated with an increased relative risk of HIV infection, ranging from 1.5 to 7.0 in both men[3,57] and women.[25,26,58,59] Gonorrhea and chlamydia and trichomonas infection are associated with a relative increase of 60 to 340 percent in the prevalence of HIV infection in men[3,25,59] and women.[26,59-61] Bacterial vaginosis has also been shown to be associated with HIV infection.[61] In women, genital ulcer disease may have a potentiating effect on the incidence of HIV infection.[62]

Measurement of HIV in genital secretions indicates that HIV infectiousness may be greater in the presence of concurrent reproductive tract infections. For men the data are consistent. Seminal leukocytosis,[35] urethritis,[63-65] gonorrhea,[63,64] and cytomegalovirus infection[37] are associated with increased detection of HIV in semen. Treatment of urethritis diminishes the detection of HIV in the urethra[63] and the concentration of HIV in semen.[64] For women the data are scarce and inconsistent. A twofold increase in HIV detection associated with sexually transmitted diseases or with purulent cervical secretions has been ob-

served in two studies of women,[18,42] but no association was noted in another.[66] In the negative study, however, cervical inflammation correlated with HIV detection. One study of HIV transmission demonstrated that men were more likely to seroconvert after sexual contact with women who had concurrent genital ulcer disease.[67] These findings suggest that genital ulcers cause an increase in infectiousness.

Cervical Ectopy

Cervical ectopy (replacement around the cervical os of normal multilayered cervical squamous cells with glandular, single-layered columnar cells that are typically found inside the os) often leaves cervical tissues more friable. Cervical ectopy has been identified as a risk factor for the acquisition of HIV infection (relative risks ranging from 1.7 to 5.0) in some[62,68] but not all[69] of the studies of this association. HIV is five times as likely to be detected in women with ectopy as in those without.[18]

Male Circumcision

Male circumcision consistently shows a protective effect against HIV infection.[70] This may be due to the abundance of Langerhans' cells in the foreskin or to a receptive environment for HIV in the sulcus between the foreskin and glans. The prevalence of HIV infection is 1.7 to 8.2 times as high in men with foreskins as in circumcised men, and the incidence of infection is 8 times as high. A greater proportion of the sex partners of uncircumcised men than of circumcised men are infected with HIV, which suggests that the presence of the foreskin may also increase infectiousness.[28,71]

Contraception

The choice of contraceptive method affects the likelihood of HIV transmission.[72,73] Condoms, used consistently, protect both sexes against HIV.[25,27,29,53,74] Spermicides containing nonoxynol 9 protect against bacterial infections of the reproductive tract, but their effect against HIV is uncertain.[72,73] Furthermore, these compounds may cause vaginal irritation.[72,73] One study found that the use of intrauterine devices carried an increased risk of HIV infection (odds ratio, 3.0),[26] but another did not.[69] Conflicting results have also been reported for hormonal contraceptives. Some investigators report an increased relative risk (range, 2.0 to 4.5),[72,75-77] possibly due to increased cervical ectopy[69-78] or thinning of the vaginal epithelia.[79] Others report a protective effect (relative risk, 0.6)[26,68] or no effect.[62-69] In HIV-seropositive women, cervical HIV shedding strongly correlated with the use of oral contraceptives in one study[18] but not in another.[66]

Menstruation and Pregnancy

Sex during menstruation may increase women's risk of acquiring HIV infection (odds ratio, 1.5),[26] as may bleeding during sexual intercourse (odds ratio, 4.9).[28] Men who have sex with HIV-infected women during menstruation are 3.4 times as likely to have HIV infection as those who do not,[27] even though intermittent secretion of HIV occurs throughout the menstrual cycle.[66,80] During pregnancy, infected women are two to three times as likely to have HIV detected in genital secretions.[18,42,66]

ENVIRONMENT

The HIV epidemic, like any other, occurs within a complex social environment.[81] Social norms that affect infectivity include specific sexual practices (e.g., anal-receptive intercourse),[82] patterns of sexual partnering, contraceptive choices, and the use of substances that lower sexual inhibitions. Environmental factors also affect the average rate of sex-partner change, which may affect the growth of the epidemic dramatically. Such factors include the presence of unregulated commercial-sex facilities, "crack" cocaine houses, and bathhouses, as well as social norms that affect the average number and concurrency of sex partnerships.[44,83,84] Geographic differences in the length of time the epidemic has been present in a community lead to differences in both the local prevalence of HIV infection and the number of people with AIDS. The former affects the probability of exposure to infection; the latter has an effect on awareness of the epidemic, which in turn influences both individuals' behavior and the social response. Exposure to risky environmental factors indicates a social vulnerability that largely parallels the maldistribution of social and economic resources — a macroscopic force shaping the epidemic.[85]

BIOLOGIC AGENT

The properties of HIV itself may also influence transmission. HIV subtypes have distinct geographic distributions, with A, C, D, and E predominant in sub-Saharan Africa and Asia and B predominant in the United States, the Caribbean, South America, and Western Europe.[86] Subtype E, the most common subtype in Thailand, is reported to have a greater tropism for Langerhans' cells than subtype B.[87] This tropism may contribute to the rapid epidemic spread of HIV through Thailand and the high per-contact transmission rate observed there.[3] High concentrations of HIV in semen specimens from sub-Saharan Africa may reflect differences among HIV clades in the ability to replicate in vivo.[65]

There appear to be phenotypic differences between isolates in blood and those in semen. Non–syncytia-inducing viral isolates that are macrophage-tropic are found early in HIV disease and may be better adapted to spreading than lymphocytotropic organisms.[88] Particular viral-envelope genetic sequences are required for vaginal transmission of

chimeric simian–human immunodeficiency viruses.[89] Genotypic differences in the viral envelope in blood as compared with genital specimens have been reported in women.[90] In addition, other phenotypic differences between HIV harvested from blood plasma and that harvested from genital secretions may affect the efficiency of transmission.[88] Antiretroviral-drug resistance, for example, appears in cell-free and cell-associated virus in the blood and semen at different times.[91]

THE FUTURE: PREVENTING SEXUALLY TRANSMITTED HIV INFECTION

Strategies for preventing the sexual transmission of HIV have focused on three main areas: encouraging the use of condoms, treating sexually transmitted diseases, and reducing the amount of unsafe sexual behavior (by promoting sexual abstinence or decreased numbers of partners).[92] The combination of these strategies involves intervention at all three corners of the epidemiologic triangle for the infectivity parameter as well as for the contact-rate parameter of the epidemic. Several population-level interventions have helped reduce the sexual spread of HIV. For example, Thailand's 100 percent condom policy has had a profound effect on the prevalence of sexually transmitted diseases, including HIV.[93] (Under this policy, the government aggressively promotes the use of condoms through the media, distributes free condoms to sex workers, and sanctions commercial-sex establishments where condoms are not used consistently.) In Tanzania, communities that managed sexually transmitted diseases aggressively reduced their incidence of HIV infection by 42 percent.[94] In addition, periodic mass therapy for sexually transmitted diseases, currently under evaluation in Uganda, shows promise.[95] These strategies have succeeded in moderating the growth of the epidemic in selected populations.

Future interventions based on an increased understanding of host-related factors will complement the above approaches to help curtail the growth of the epidemic. First, the development of an HIV vaccine is crucial, not only to provide people with primary protection from infection, but also to reduce the concentration of HIV in genital secretions or to render the virus less contagious in newly infected hosts. However, the introduction of vaccines that were less than 100 percent effective could intensify the epidemic if risky sexual behavior increased as a result of the perception that vaccination conferred protection from infection.[96]

Second, topical microbicidal agents that can be safely employed and controlled by women must be developed to reduce both the susceptibility and the infectiousness of hosts. At least three trials of nonoxynol 9 formulations to prevent the acquisition of HIV are in progress.[72] In addition, the effects of routine vaginal douching need to be more thoroughly investigated.

Third, messages on safer sexual behavior could be refocused. Recent studies show that the number of sex partners is not as important as their concurrency to the propagation of the epidemic.[84] Hence, if people in newly formed partnerships delay the onset of sexual intercourse or use condoms consistently for the first three months, unprotected sex in overlapping partnerships will be reduced in the period of high infectiousness during primary infection.

These interventions may have the greatest impact on the epidemic if they are directed at people in the early stages of HIV infection. Early detection of infections will require new approaches. Clients and clinicians alike will need to recognize the symptoms and signs of primary HIV disease — a mononucleosis-like illness with fever, pharyngitis, adenopathy, rash, and aseptic meningitis.[46,97] Available viral-amplification techniques that can detect primary infection before seroconversion should be evaluated for their preventive potential. In addition, kits to test for HIV at home will provide people the option of learning their serologic status earlier in infection and will also reach people who might not otherwise seek testing.

Once early infection is identified, coordination with health departments is essential to interrupt ongoing transmission within sexual networks. Breaking the chain of transmission during the period of primary and early infection is potentially the most effective intervention. Furthermore, the early detection of infection affords an opportunity for antiretroviral therapy to reduce the viral burden, which may both improve the prognosis[32] and reduce infectiousness.

Finally, as with other sexually transmitted diseases, preventing the sexual transmission of HIV will require more than a single approach. A combination of preventive strategies will be needed that is based on an understanding of the complex interrelations driving the epidemic of sexual transmission. Now is the time to develop, integrate, and implement public health policies that build on the past 15 years of work on these interrelations. With a combined approach, using our knowledge of the epidemiology of the spread of HIV, the biology of the virus, and the sociology of the affected sectors of society, we can work toward substantially reducing the sexual transmission of HIV.

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CORRECTION

Sexual Transmission of HIV

Sexual Transmission of HIV . On page 1073, in Figure 1, the infectivity ranges for female-to-male and male-to-female transmission are incorrect. The corrected figure appears below. We regret the error.

Figure 1. Per-Contact Probability of HIV Transmission.

The infectivity ranges for sexual contact are derived from a comprehensive review of the literature (lower and upper bounds are from modeling per-contact transmission in different study populations with different modeling techniques). Each infectivity estimate for the other routes of infection originates from one representative study. The routes of infection are as follows: sexual intercourse, with indicating female-to-male transmission,[2,3] indicating male-to-female transmission,[2,4] and indicating male-to-male transmission[5,6]; needle stick[7]; needle sharing[8]; transmission from mother to infant with[9] and without[10] perinatal zidovudine treatment; and transfusion.[11]