Preventing Sexual Transmission of HIV

Myron S. Cohen
University of North Carolina School of Medicine, Chapel Hill

The risk of human immunodeficiency virus (HIV) transmission during sexual activity is dependent on the infectivity of the HIV-positive individual and the susceptibility of the uninfected partner. HIV is most often transmitted during periods of high HIV load, but factors such as the type of sexual activity and the innate and genetic defenses of the uninfected partner exert a strong influence on the risk of transmission. Certain factors, such as coinfection with other sexually transmitted diseases or the presence of genital lesions in either sexual partner, amplify the risk of transmission that is predicted on the basis of sexual contact alone. In the absence of more-reliable options, such as a vaccine, factors that define HIV infectivity and susceptibility and factors that amplify the risk of HIV transmission, may serve as critical targets for containment of the HIV epidemic

HIV infection is best characterized as a sexually transmitted disease (STD). In the United States, ~75% of HIV-infected individuals acquired the virus through sexual activity [1]. It is estimated that, in other areas of the world, >90% of new infections among adults are acquired via sexual activity [2]. Effective methods to prevent sexual transmission of HIV are critical to the effort to defeat the worldwide epidemic. Although injection drug use continues to be an important source of transmission in the United States (it ranks second, after sexual activity), other avenues of acquiring infection, including vertical transmission from mother to child and use of HIV-contaminated blood products, are of diminishing importance.

In the United States, male-male sex is the avenue of HIV transmission in ~60% of new cases. Heterosexual contact, although accounting for only ~17.5% of new infections, is the mode of HIV transmission in 80% of new cases in women [3]. From 2000 through 2003, the estimated number of HIV/AIDS cases increased by 5% among males and decreased by 2% among females. In 2003, a total of 72% of all HIV/AIDS cases were diagnosed in men or adolescent boys [3]. The difference in the HIV infection rate between men and women in the United States, which has persisted since the start of the epidemic, may be best understood in the context of the efficiency of different routes of HIV transmission, particularly the relative rates of transmission via vaginal and anal intercourse.

FACTORS AFFECTING INFECTIVITY AND SUSCEPTIBILITY

Many estimates of the risk of infection per sexual act have been low and inconsistent with the observed prevalence of HIV infection. In an earlier review of the risk of transmission per sexual contact, my colleagues and I estimated 1 case of HIV transmission for every 10–1600 sexual encounters between men and 1 case of transmission in 200–2000 sexual encounters between an infected male and an uninfected female; the risk of transmission between an infected female and an uninfected male was 1 in 700–3000 sexual encounters [4]. However, because coital frequency averages ~10 contacts per month among individuals <25 years of age (and decreases among older individuals) [5], HIV transmission should be a relatively uncommon occurrence, particularly among heterosexual persons.

More-sophisticated methods of estimating risk have been generated from improvements in identifying fac-

Presented in part: Opportunities for Improving HIV Diagnosis, Prevention & Access to Care in the U.S., Washington, D.C., 29–30 November 2006.

Reprints or correspondence: Dr. Myron S. Cohen, University of North Carolina School of Medicine, CB #7030, 130 Mason Farm Rd., 4123 Bioinformatics Bldg., Chapel Hill, NC 27599-7030 (mscohen@med.unc.edu).

Clinical Infectious Diseases 2007; 45:S287–92

1058-4838/2007/4512S4-0015$15.00
DOI: 10.1086/522552

tors that affect the risk of infection. In calculating the risk of horizontal spread of HIV within a population, the key factors include the efficiency of transmission during any specific sexual encounter *(b)*, the duration of infectiousness *(D)*, and the number of partners exposed *(C)*. On the basis of the equation Ro = *bDC*, the epidemic will be sustained if the rate of infection, Ro, is >1.

At the level of individuals, factors that influence infectivity and susceptibility complicate efforts to estimate the risk of HIV transmission per exposure. Two of the most fundamental variables include the inoculum size, which is typically the product of the genital viral burden, and the presence of resistance, which may be inherited or acquired [6]. However, a number of important additional variables modify these risks. For example, lesions from a genital infection may facilitate transfer of HIV by impairing natural barriers to infection, thereby amplifying any baseline risk predicted by a factor such as HIV load [7].

There is a strong correlation between the HIV load and the risk of HIV transmission. In a study of heterosexual persons, the risk of infection more than tripled when the HIV load in blood increased from 2.6–3.5 $\log_{10}$ HIV RNA copies/mL to 3.6–4.0 $\log_{10}$ HIV RNA copies/mL [8]. The risk almost doubled again when the blood HIV load increased from 3.6–4.0 $\log_{10}$ HIV RNA copies/mL to >4.7 $\log_{10}$ HIV RNA copies/mL. Conversely, transmission was rare among individuals who had an HIV load of <1500 HIV RNA copies/mL.

The stage of infection is also an important variable for infectivity, largely because of the accelerated rate of viral shedding during the acute stage. Viral loads in all fluids and tissues, including blood and genital secretions, peak ~4 weeks after infection [9]. The risk of sexual transmission of HIV during this stage is 30–300 times the risk during the postacute phase of infection, when antibodies and cytotoxic T cell lymphocytes directed against HIV appear (figure 1) [10]. Because of the increased risk of transmission, patients with acute HIV infection are believed to make a highly disproportionate contribution to the incidence of HIV infection [11], a contention supported by modeling estimates [12]. The increased transmissibility of HIV during the acute period is a likely explanation of why new infections commonly occur in clusters [13]. The risk of sexual transmission again begins to increase at late stages of infection, when AIDS-induced immune dysfunction permits viral loads in genital secretions to increase.

Relative differences in the virulence of HIV strains or in HIV subtype dynamics may also affect the risk of sexual transmission. Differences in the transmissibility of subtype B, the dominant strain of HIV in the United States, and subtype C, which is a major source of infection in sub-Saharan Africa, may explain some of the geographic differences in the growth of the epidemic, as well as the risk of transmission through heterosexual contact [14].

There is also evidence of racial differences in susceptibility that may explain discordant patterns of transmission. In a genotyping study to test for the presence of an inactive CCR5 allele associated with HIV resistance, the allele was most common in white persons and less common in people of color [15].

AMPLIFICATION FACTORS: A KEY TO THE EPIDEMIC

All variables associated with the relative risk of HIV transmission, such as the genital HIV burden of the infected partner at the time of sexual contact, can amplify the risk of transmission (figure 1). The type of sexual activity is among the most important of these variables. Although the risk of transmitting HIV via saliva appears to be very low [16], a study involving a cohort of heterosexual couples estimated that, for women, the odds of HIV transmission during receptive anal

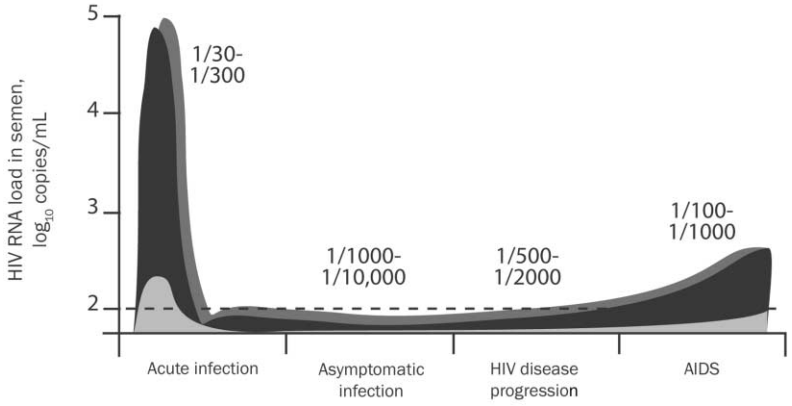

Figure 1. Probability of male-to-female HIV transmission per coital act, as a function of HIV disease stage. Viral loads peak ~4 weeks after infection onset. *Dark grey,* expected distribution of viral burden in semen among men over time; *dashed line,* potential threshold for HIV transmission; *light grey,* theoretical effect of a biological intervention designed to reduce viral excretion. Adapted from [10].

intercourse were ~10 times the odds of transmission during vaginal sex [17]. This increased risk, which is likely to explain some of the disparity between infection rates among gay men versus those among women in the United States, may be a product of several biological differences, particularly the fact that the density of cells receptive to HIV attachment is higher in the anal canal than in the vaginal canal. However, anal intercourse is also practiced by heterosexual couples, complicating efforts to interpret gender-based differences on the basis of epidemiologic data.

The presence of coexisting STDs is also an important amplification factor. Although the presence of any lesions or ulcers in the genital tract, including those caused by STDs, increases the opportunity for contact with infected blood, those due to urethritis, gonorrhea, and cytomegalovirus infection have been associated with increased frequency of HIV detection in semen specimens [18–20]. STDs and inflammation increase HIV shedding in the female genital tract [21], but difficulties in specimen collection may explain why increased HIV loads have been less consistently demonstrated in the genital tract of HIV-infected women [22, 23]. A higher rate of seroconversion in males after contact with women who had a concurrent genital ulcer disease has been reported [24]. Bacterial vaginosis, a very common infection in women, has also been identified as a risk factor for HIV transmission [17].

One of the most common STDs is infection with herpes simplex virus type 2 (HSV-2), which as recently as 1994 had a seroprevalence of 22% among individuals aged >12 years in the United States [25]. HSV-2 interacts with HIV and has been associated with an increased risk of HIV transmission [26, 27]. Prevention practices specifically directed at HIV-infected patients with HSV-2 infection are problematic because of the high proportion of such individuals who are unaware of their positive HIV serostatus [28]. Antiviral prophylaxis directed against HSV-2 may be a viable strategy to reduce the risk of HIV acquisition in high-risk populations. Clinical trials to test these hypotheses are under way.

Systemic coinfection may be another amplification factor, particularly in developing countries where the incidence of chronic contagious disease is high. Malaria in particular has been associated with an HIV load sufficiently large enough to increase the risk of HIV transmission [29], and the relationship between HIV load and other diseases, such as tuberculosis, may be similar. An increased HIV load in patients with systemic infection would likely involve stimulation of the inflammatory response that increases T cell activity, which, in turn, would lead to increased HIV replication. An example of this process is the increased HIV load observed after tetanus toxoid vaccination [30].

Several specific host factors may also amplify the risk of HIV transmission. In women, cervical ectopy, a condition that renders cervical tissues more friable, was found to increase the risk of HIV transmission by 2–3 times [31]. In men, the presence of foreskin has been associated with increased risk of HIV acquisition [17, 32], leading to several trials to test circumcision as a prophylactic strategy. In one of the completed trials conducted in South Africa, the risk of HIV transmission among circumcised men was 60% lower than that among uncircumcised men (relative risk, 0.40; 95% CI, 0.24–0.68; $P < .001$) [33]. Similar trials were stopped because a similar degree of benefit was observed [34]. In addition, there is evidence that HIV in circumcised men is less contagious.

Any factor that increases the opportunity for HIV to reach receptive immune cells may amplify the risk of HIV transmission. For example, hormonal contraceptives have been implicated in several studies, because of their association with thinning of the vaginal epithelia and increased ectopy of the cervix [35, 36]. Spermicides, which do not have a clear anti-HIV effect [37], have been associated with irritation that may increase the risk of infection [38]. The presence of blood during sexual intercourse, including blood associated with menstruation, has been associated with an increased risk of HIV transmission, particularly from females to males [17, 39].

Understanding the principles of HIV infectivity and susceptibility provide an opportunity to identify strategies to reduce the risk of transmission. The factors so far identified are unlikely to be a complete list, and the absolute risk of transmission may be greatly influenced by interactions between the variables themselves. However, the incremental contribution of interventions that address some or most of the known risk factors for HIV transmission may play an important cumulative role in slowing the epidemic.

PREVENTION STRATEGIES

Effective strategies to prevent sexual transmission of HIV are easy to define but difficult to implement. Abstinence and well-defined safe-sex practices, particularly condom use, could reduce the HIV epidemic if they are widely used [40]. The challenge is to implement strategies that are practical and realistic. Although efforts to improve safe-sex practices deserve to remain a cornerstone of infection control, other initiatives are appropriate to fill gaps anticipated by the difficulties in ensuring universal compliance with safe-sex practices and the limitations in dictating human behavior.

Safe sex is defined by practices that limit contact between bodily fluids of sexual partners, particularly blood and semen. When used consistently, male condoms, commonly used barriers to reduce the exchange of fluids, offer a degree of protection comparable to their ability to prevent pregnancy [41]. Variability in correct use relative to consistent use may explain the wide CIs in the estimated rates of protection afforded by this practice. Although all individuals at risk should be en-

couraged to use condoms to reduce the risk of HIV infection, it should also be emphasized that correct use has not been demonstrated to provide complete protection from HIV and that a substantial proportion of persons who consistently use condoms during sex do not use condoms correctly [42].

Antiretroviral therapy has been associated with reductions in infectivity [43]. These reductions are likely a product of the suppression of HIV RNA in the genital tract [44, 45]. In observational studies of HIV-serodiscordant couples, the rate of seroconversion among couples receiving antiviral therapy was 80% less than the rate among couples who received counseling on safe sex but no antiretroviral therapy [46, 47]. One important limitation of antiretroviral therapy as an infection-control strategy is that the peak period of infectivity occurs during the acute stage of infection, which typically precedes treatment. However, prophylaxis for patients at risk for infection, treatment during acute infection, and postexposure prophylaxis are all potential strategies to circumvent this limitation.

Several studies have been initiated to evaluate antiretroviral therapies as prophylaxis against HIV infection. In one study, the prophylactic efficacy of the nucleoside reverse-transcriptase inhibitor tenofovir was tested in 936 women at high risk for HIV infection [48]. During the follow-up period, 2 women who received tenofovir seroconverted, compared with 6 women who received placebo, but the difference was not statistically significant ($P = .24$). There were no serious adverse effects associated with tenofovir use, but the risk of adverse effects and of generating drug-resistant HIV strains will be important factors to consider as these trials advance. Moreover, extended follow-up periods will be required, to confirm that the reduced risk of HIV infection can be sustained over prolonged periods.

Prevention strategies targeted at individuals with acute HIV infection are dependent on the ability of health care professionals and the infected individuals themselves to rapidly recognize characteristic symptoms, which include those similar to mononucleosis, fever, pharyngitis, adenopathy, rash, and aseptic meningitis [49], and to seek prompt medical attention. The inability of infected individuals or clinicians to recognize the signs of acute HIV infection continues to pose a formidable hurdle even for testing of timely antiretroviral treatment in clinical trials. Even if more-effective methods become available to identify patients during the early stages of infection, it will be necessary to demonstrate that any protection against HIV transmission is not counterbalanced by unacceptable risks, including an increased rate of drug resistance.

Postexposure HIV prophylaxis is recommended by the Centers for Disease Control and Prevention on the basis of its presumed efficacy in reducing the risk of acquiring HIV [50]. Although these recommendations are largely based on findings from animal models rather than on findings of clinical trials, these steps, which include initiating antiretroviral therapy $\leqslant$72 h after exposure, are prudent and reasonable, given the limited risk for adverse consequences and the large potential for benefit. Individuals exposed to HIV should continue to receive therapy for at least 28 days after the exposure event.

Because the risk of sexual transmission of HIV is particularly high when the infected partner is unaware of their infection, vaccines represent the most secure strategy for HIV control. The importance of vaccine is recognized by the National Institute of Allergy and Infectious Diseases (NIAID), which established the Center for HIV/AIDS Vaccine Immunology (available at: http://www.chavi.org). Although prodigious efforts at vaccine development have been ongoing for >15 years, yielding several clinical trials, results have consistently been disappointing. Creation of a vaccine for preventing HIV infection may be $\geqslant$10 years away, but several vaccines with the potential to modify the course of disease and the risk of transmission are in the late stages of development and field testing. A summary of the progress of vaccines currently under study can be found on the NIAID HIV Vaccination Trials Network Web site [51].

The deployment and impact of many strategies to control the spread of HIV will likely differ according to population-specific risk factors. For example, the reduction in the rate of HIV transmission among circumcised men in South Africa has limited relevance in the United States, where 77% of men are circumcised [52]. Similarly, the potential off-label role of antimalarial treatments for control of HIV has no apparent relevance in areas of the world where antimalarial agents are not commonly used. Variability in the prevalence of individual STDs, such as those that impair immune defenses versus those that facilitate infection by creating genital lesions, might also affect the types of infection-control strategies to emphasize in a specific target group.

It is also important to recognize the distance between the identification of a risk factor for HIV transmission and the development of a viable infection-control strategy that targets the risk factor. For example, independent of the formidable potential costs of a population-wide circumcision strategy, the efficacy of this strategy will be dependent on cooperation from the target population. From the standpoint of public health, the risks of circumcision, such as procedure-related infection, must be weighed against the relative protection it offers against HIV infection. As with any HIV prophylaxis strategy, it is also important to consider that false security arising from use of a partially effective risk-reduction strategy may, because of an increase in the frequency of unsafe sexual practices, result in a paradoxical increase in HIV transmission.

Other strategies now in development to change sex practices include female condoms with improved designs that render them more affordable and easier to use, topically applied viricidal agents that inhibit the risk of HIV transmission, and more aggressive dissemination of more detailed information

about infection control. For example, in areas of high risk it may be possible to substantially reduce HIV transmission rates by recommending that individuals delay sexual intercourse or use condoms consistently for the first 3 months of a new partnership, when the period of high infectiousness in a recently infected partner is greatest. The hurdle for such strategies, already implicit in safe-sex recommendations, is to generate a level of concern sufficiently high enough to ensure their rigorous implementation by individuals at risk.

CONCLUSION

The progress in identifying the variables that underlie HIV transmission is producing new opportunities for infection control. In the absence of a highly effective vaccine, implementation of multiple risk-reduction strategies will likely be required in an effort to halt the HIV epidemic. Safe-sex strategies are fundamental to current efforts to reduce HIV transmission, but these efforts may continue to have only a limited impact on infection rates, because of the complex and unpredictable factors associated with human sexual behavior. By recognizing the amplification factors as well as the fixed variables of infectivity and susceptibility, strategies oriented to both the individual and to a general population can be developed for infection control. Although additional progress in infection control is anticipated, meaningful immediate progress toward control of the HIV epidemic depends on the willingness of public health authorities, clinicians, and individuals at risk to embrace the range of strategies that are known to protect against HIV transmission.

Acknowledgments

I thank Ted Bosworth for his assistance in preparing this manuscript.

The "Opportunities for Improving HIV Diagnosis, Prevention & Access to Care in the U.S." conference was sponsored by the American Academy of HIV Medicine, amfAR, the Centers for Disease Control and Prevention, the Forum for Collaborative HIV Research, the HIV Medicine Association of the Infectious Diseases Society of America, and the National Institute of Allergy and Infectious Diseases. Funding for the conference was supplied through an unrestricted educational grant from Gilead Sciences, amfAR, GlaxoSmithKline, Pfizer, Abbott Virology, OraSure Technologies, Roche Diagnostics, and Trinity Biotech.

Supplement sponsorship. This article was published as part of a supplement entitled "Opportunities for Improving the Diagnosis of, Prevention of, and Access to Treatment for HIV Infection in the United States," sponsored by the American Academy of HIV Medicine, amfAR, the Centers for Disease Control and Prevention, the Forum for Collaborative HIV Research, the HIV Medicine Association of the Infectious Diseases Society of America, and the National Institute of Allergy and Infectious Diseases.

Potential conflicts of interest. M.S.C.: no conflicts.

References

1. Centers for Disease Control and Prevention (CDC). HIV/AIDS surveillance report, 2004. Rev. ed., Vol. 16. Atlanta, GA: US Department of Health and Human Services, CDC, **2006**. Available at: http://www.cdc.gov/hiv/topics/surveillance/resources/reports/2004report/default.htm. Accessed 8 March 2007.
2. Gouws E, White PJ, Stover J, Brown T. Short term estimates of adult HIV incidence by mode of transmission: Kenya and Thailand as examples. Sex Transm Infect **2006**; 82(Suppl 3):iii51–5.
3. Centers for Disease Control and Prevention (CDC). HIV/AIDS surveillance report, 2003. Rev. ed., Vol. 15. Atlanta, GA: US Department of Health and Human Services, CDC, **2006**. Available at: http://www.cdc.gov/hiv/topics/surveillance/resources/reports/2003report/default.htm. Accessed 8 March 2007.
4. Royce RA, Sena A, Cates W Jr, Cohen MS. Sexual transmission of HIV. N Engl J Med **1997**; 336:1072–8.
5. Rao KV, Demaris A. Coital frequency among married and cohabiting couples in the United States. J Biosoc Sci **1995**; 27:135–50.
6. Galvin SR, Cohen MS. The role of sexually transmitted diseases in HIV transmission. Nat Rev Microbiol **2004**; 2:33–42.
7. Wasserheit JN. Epidemiological synergy: interrelationships between human immunodeficiency virus infection and other sexually transmitted diseases. Sex Transm Dis **1992**; 19:61–77.
8. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. N Engl J Med **2000**; 342:921–9.
9. Pilcher CD, Tien HC, Eron JJ Jr, et al. Brief but efficient: acute HIV infection and the sexual transmission of HIV. J Infect Dis **2004**; 189: 1785–92.
10. Cohen MS, Pilcher CD. Amplified HIV transmission and new approaches to HIV prevention. J Infect Dis **2005**; 191:1391–3.
11. Wawer MJ, Gray RH, Sewankambo D, et al. Rate of HIV transmission per coital act by stage of HIV-1 infection in Rakai, Uganda. J Infect Dis **2005**; 191:1403–9.
12. Ahlgren DJ, Gorny MK, Stein AC. Model-based optimization of infectivity parameters: a study of the early epidemic in San Francisco. J Acquir Immune Defic Syndr **1990**; 3:631–43.
13. Jacquez JA, Koopman JS, Simon CP, Longini IM Jr. Role of the primary infection in epidemics of HIV infection in gay cohorts. J Acquir Immune Defic Syndr **1994**; 7:1169–84.
14. Walker PR, Pybus OG, Rambaut A, Holmes EC. Comparative population dynamics of HIV-1 subtypes B and C: subtype-specific differences in patterns of epidemic growth. Infect Genet Evol **2005**; 5: 199–208.
15. Zimmerman PA, Buckler-White A, Alkhatib G, et al. Inherited resistance to HIV-1 conferred by an inactivating mutation in CC chemokine receptor 5: studies in populations with contrasting clinical phenotypes, defined racial background, and quantified risk. Mol Med **1997**; 3:23–36.
16. Cohen MS, Shugars DC, Fiscus SA. Limits on oral transmission of HIV-1. Lancet **2000**; 356:272.
17. Seidlin M, Vogler M, Lee E, Lee YS, Dubin N. Heterosexual transmission of HIV in a cohort of couples in New York City. AIDS **1993**; 7:1247–54.
18. Cohen MS, Hoffman IF, Royce RA, et al. Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. Lancet **1997**; 349:1868–73.
19. Krieger JN, Coombs RW, Collier AC, Ross SO, Speck C, Corey L. Seminal shedding of human immunodeficiency virus type 1 and human cytomegalovirus: evidence for different immunologic controls. J Infect Dis **1995**; 171:1018–22.
20. Dyer JR, Eron JJ, Hoffman IF, et al. Association of CD4 cell depletion and elevated blood and seminal plasma human immunodeficiency virus type 1 (HIV-1) RNA concentrations with genital ulcer disease in HIV-1–infected men in Malawi. J Infect Dis **1998**; 177:224–7.
21. Spinillo A, Zara F, Gardella B, Preti E, Mainini R, Maserati R. The effect of vaginal candidiasis on the shedding of human immunodeficiency virus in cervicovaginal secretions. Am J Obstet Gynecol **2005**; 192:774–9.
22. Henin Y, Mandelbrot L, Henrion R, Pradinaud R, Coulaud JP, Montagnier L. Virus excretion in the cervicovaginal secretions of pregnant and nonpregnant HIV-infected women. J Acquir Immune Defic Syndr **1993**; 6:72–5.
23. Kreiss J, Willerford DM, Hensel M, et al. Association between cervical

inflammation and cervical shedding of human immunodeficiency virus DNA. J Infect Dis **1994**; 170:1597–601.
24. Cameron DW, Simonsen JN, D'Costa LJ, et al. Female to male transmission of human immunodeficiency virus type 1: risk factors for seroconversion in men. Lancet **1989**; 2:403–7.
25. Fleming DT, McQuillan GM, Johnson RE, et al. Herpes simplex virus type 2 in the United States, 1976 to 1994. N Engl J Med **1997**; 337: 1105–11.
26. Legoff J, Bouhlal H, Lecerf M, et al. HSV-2– and HIV-1–permissive cell lines co-infected by HSV-2 and HIV-1 co-replicate HSV-2 and HIV-1 without production of HSV-2/HIV-1 pseudotype particles. Virol J **2007**; 4:2.
27. Reynolds SJ, Risbud AR, Shepherd ME, et al. Recent herpes simplex virus type 2 infection and the risk of human immunodeficiency virus type 1 acquisition in India. J Infect Dis **2003**; 187:1513–21.
28. Andreoletti L, Piednoir E, Legoff J, et al. High seroprevalence of herpes simplex virus type 2 infection in French human immunodeficiency virus type 1–infected outpatients. J Clin Microbiol **2005**; 43:4215–7.
29. Kublin JG, Patnaik P, Jere CS, et al. Effect of *Plasmodium falciparum* malaria on concentration of HIV-1–RNA in the blood of adults in rural Malawi: a prospective cohort study. Lancet **2005**; 365:233–40.
30. Stanley SK, Ostrowski MA, Justement JS, et al. Effect of immunization with a common recall antigen on viral expression in patients infected with human immunodeficiency virus type 1. N Engl J Med **1996**; 334: 1222–30.
31. Nicolosi A, Correa Leite ML, Musicco M, Arici C, Gavazzeni G, Lazzarin A. The efficiency of male-to-female and female-to-male sexual transmission of the human immunodeficiency virus: a study of 730 stable couples. Italian Study Group on HIV Heterosexual Transmission. Epidemiology **1994**; 5:570–5.
32. Hunter DJ. AIDS in sub-Saharan Africa: the epidemiology of heterosexual transmission and the prospects for prevention. Epidemiology **1993**; 4:63–72.
33. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. PLoS Med **2005**; 2:e298.
34. Roehr B. Dramatic drop in HIV infections halts circumcision trials. BMJ **2007**; 334:11.
35. Critchlow CW, Wolner-Hanssen P, Eschenbach DA, et al. Determinants of cervical ectopia and of cervicitis: age, oral contraception, specific cervical infection, smoking, and douching. Am J Obstet Gynecol **1995**; 173:534–43.
36. Marx PA, Spira AI, Gettie A, et al. Progesterone implants enhance SIV vaginal transmission and early virus load. Nat Med **1996**; 2:1084–9.
37. Feldblum PJ, Morrison CS, Roddy RE, Cates W Jr. The effectiveness of barrier methods of contraception in preventing the spread of HIV. AIDS **1995**; 9(Suppl A):S85–93.
38. Van Damme L, Ramjee G, Alary M, et al. Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomised controlled trial. Lancet **2002**; 360:971–7.
39. Comparison of female to male and male to female transmission of HIV in 563 stable couples. European Study Group on Heterosexual Transmission of HIV. BMJ **1992**; 304:809–13.
40. Cohen MS, Dallabetta G, Laga M, Holmes KK. A new deal in HIV prevention: lessons from the global approach. Ann Intern Med **1994**; 120:340–1.
41. Davis KR, Weller SC. The effectiveness of condoms in reducing heterosexual transmission of HIV. Fam Plann Perspect **1999**; 31:272–9.
42. Warner L, Clay-Warner J, Boles J, Williamson J. Assessing condom use practices: implications for evaluating method and user effectiveness. Sex Transm Dis **1998**; 25:273–7.
43. Musicco M, Lazzarin A, Nicolosi A, et al. Antiretroviral treatment of men infected with human immunodeficiency virus type 1 reduces the incidence of heterosexual transmission. Italian Study Group on HIV Heterosexual Transmission. Arch Intern Med **1994**; 154:1971–6.
44. Vernazza PL, Troiani L, Flepp MJ, et al. Potent antiretroviral treatment of HIV-infection results in suppression of the seminal shedding of HIV. The Swiss HIV Cohort Study. AIDS **2000**; 14:117–21.
45. Cu-Uvin S, Caliendo AM, Reinert S, et al. Effect of highly active antiretroviral therapy on cervicovaginal HIV-1 RNA. AIDS **2000**; 14: 415–21.
46. Kayitenkore K, Bekan B, Rufagari J, et al. The impact of ART on HIV transmission among HIV serodiscordant couples [abstract MOKC101]. In: Program and abstracts the XVIth International AIDS Conference (Toronto, Canada). **2006**.
47. Bunnell R, Ekwaru JP, Solberg P, et al. Changes in sexual behavior and risk of HIV transmission after antiretroviral therapy and prevention interventions in rural Uganda. AIDS **2006**; 20:85–92.
48. Peterson L, Taylor D, Roddy R, et al. Tenofovir disoproxil fumarate (TDF) for prevention of HIV infection in women: a phase 2, double-blind, randomized, placebo-controlled trial. PLoS Clin Trials **2007**; 2: e27.
49. Schacker T, Collier AC, Hughes J, Shea T, Corey L. Clinical and epidemiologic features of primary HIV infection. Ann Intern Med **1996**; 125:257–64.
50. Smith DK, Grohskopf LA, Black RJ, et al. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States: recommendations from the U.S. Department of Health and Human Services. MMWR Recomm Rep **2005**; 54:1–20.
51. National Institute of Allergy and Infectious Diseases (NIAID). NIAID HIV Vaccine Trials Network (HVTN). February **2004**. Available at: http://www.niaid.nih.gov/factsheets/hvtn.htm. Accessed 8 March 2007.
52. Laumann EO, Masi CM, Zuckerman EW. Circumcision in the United States: prevalence, prophylactic effects, and sexual practice. JAMA **1997**; 277:1052–7.