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Preventing Sexual Transmission of HIV — New Ideas from Sub-Saharan Africa

When human immunodeficiency virus type 1 (HIV-1) was identified as the cause of AIDS more than 15 years ago, it seemed possible that an end to the epidemic would follow. However, the control of communicable diseases requires far more than the identification of causative pathogens. It also requires an understanding of the ways in which a pathogen is spread; an understanding of the biologic, behavioral, and social requirements for transmission; the development of both biologic and behavioral approaches to prevention; the mobilization of social and political forces; and money. Perhaps no disease has highlighted the importance of these requirements more than HIV-1 infection, and the continuing pandemic can be viewed in terms of the limitations in these opportunities for control.

The spread of any microbial pathogen among humans depends on the infectiousness of the host (determined by the concentration of the pathogen and its potential for transmission) and the susceptibility of those exposed (determined by hereditary and acquired resistance to infection). In this issue of the *Journal*, Quinn and his colleagues demonstrate that the blood viral burden determines the efficiency of its sexual transmission.¹

Quinn et al. enrolled 15,127 persons in rural Uganda in a randomized, controlled trial designed to determine whether intermittent antibiotic treatment to reduce the prevalence of other sexually transmitted diseases would also reduce the rate of transmission of HIV-1. For reasons yet to be completely defined, this approach was not successful.² Quinn et al. were subsequently able to identify 415 couples in the study population in which one partner was initially HIV-1–positive and the other HIV-1–negative. Despite the provision of counseling and condoms as part of the study, 90 of the initially HIV-1–negative partners (21.7 percent) seroconverted during a follow-up period of up to 30 months. The rate of transmission from female to male partners did not differ significantly from the rate of transmission from

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male to female partners.

Using blood samples collected during the study, Quinn et al. showed that the HIV-1–positive subjects with the highest serum HIV-1 RNA levels were the most likely to infect their sexual partners: 36.7 percent of the instances of transmission occurred among couples in which the seropositive partners had serum HIV-1 RNA levels of 50,000 or more copies per milliliter. Conversely, none of the 51 HIV-1–positive subjects with serum HIV-1 RNA levels of less than 1500 copies per milliliter transmitted the virus to their sexual partners. Because the study subjects were not receiving antiretroviral therapy, the concentration of HIV-1 RNA in blood represents a balance between viral replication and host factors limiting replication.

Other factors associated with the transmission of the virus in these couples included genital discharge or dysuria and the presence of more advanced disease in the HIV-1–infected partner. Circumcision appeared to prevent infection among the men. These results support hypotheses concerning risk factors for transmission put forward by other investigators using different methods.^{3,4,5}

Programs aimed at preventing HIV-1 infection have focused primarily on uninfected people in high-risk populations. Results from this study in Uganda suggest that it may be equally important to identify HIV-1–infected persons in order to try to reduce their infectiousness. When HIV-1 infection was first recognized, the associated stigma limited the number of people who sought to determine their infection status. Today, advances in treatment offer HIV-1–infected persons compelling reasons to seek testing. Opportunistic infections associated with seropositivity for HIV-1 can be prevented through the use of well-established, inexpensive regimens that are widely available. Effective antiretroviral therapy is available in developed countries and may become available in some developing countries as well.

Antiretroviral therapy reduces the viral burden in both blood and genital secretions.⁶ It would therefore be reasonable to assume that antiretroviral therapy would reduce the sexual transmission of HIV-1. But the results from the Ugandan study do not prove this point. HIV-1 can still be cultured from the genital secretions of some patients who are receiving antiretroviral therapy and who have undetectable levels of HIV-1 RNA in blood,⁷ a finding that means that one cannot reassure patients that they are not contagious. Indeed, if the use of such therapy increased the likelihood that HIV-1–infected patients would practice unsafe sex in the mistaken belief they were unable to transmit the virus, it could offset the benefit of viral suppression.⁸ Furthermore, antiretroviral therapy is currently too expensive and the treatment regimen is too complex for routine use in developing countries. However, there are other ways to reduce the viral burden, such as treatment of some systemic infections⁹ or genital tract infections.¹⁰ As research addresses these issues, those who provide care for people with HIV-1 infection must be provided with the best behavioral and biologic approaches to prevention that are available for patients in a given community. The development of a spectrum of interventions to reduce the infectiousness of HIV-1 deserves the same attention afforded strategies designed to reduce susceptibility to infection with the virus (e.g., vaccines, topical microbicides, and safe sex).

Quinn et al. found that none of the 50 HIV-1–negative male partners who had been circumcised became infected despite exposure to their HIV-1–positive partners.¹ This observation is consistent with the

results of many other studies.^{5,11} The protection afforded by circumcision most likely reflects changes in cutaneous barriers after the procedure that reduce the prevalence of inflammation and genital ulcers and the access of HIV-1 to receptive cells. Countries where HIV-1 infection is endemic or epidemic might well consider promoting circumcision for its public health benefits. However, the promotion or institution of a procedure that has profound cultural implications, risks of complications, and benefits that are realized only decades later represents a formidable public health and political challenge.

Although the forces fueling the HIV-1 epidemic in sub-Saharan Africa have not been fully defined, the magnitude of this epidemic has been ascribed primarily to high-risk sexual behavior.¹² Yet in a recent cross-sectional study of several thousand subjects who were 15 to 49 years of age, Buve¹¹ found no differences in sexual behavior between people living in parts of Africa where the prevalence of HIV-1 was high (20 to 30 percent) and those who lived in parts where the prevalence was much lower (3 to 8 percent).

Biologic factors also have a major role. The viral subtype dominant in parts of Africa (clade C) has unique properties that favor sexual transmission.¹³ The plasma HIV-1 RNA levels in seropositive people in sub-Saharan Africa may be higher than those in HIV-1-infected people with the same stage of disease who live in more developed countries.¹⁴ Furthermore, people in sub-Saharan Africa often lack host factors that can reduce the risk of infection. Mutations in the gene for chemokine receptor 5, which confer resistance to HIV-1 infection, are rare among Africans.¹⁵ Men in most of Africa are uncircumcised,^{1,5,11} and conditions such as bacterial vaginosis¹⁶ that cause changes in vaginal flora that favor the acquisition of HIV-1 are common among women in Africa. Finally, the high prevalence of classic inflammatory or ulcerative sexually transmitted diseases in the same areas where HIV-1 infection is prevalent probably increases both the infectiousness of the virus (as demonstrated by Quinn et al.) and susceptibility to the infection.³

It is unlikely that any single strategy of prevention, whether directed at those who are infected or those who are susceptible, will end the pandemic. Accordingly, the field of "prevention sciences" has evolved to bring together unlikely and sometimes unwilling partners from diverse disciplines so that political, social, behavioral, and biologic interventions can be better utilized. Working with remarkable diligence in a remote part of sub-Saharan Africa, Quinn and his colleagues have collected data that provide critical new insights into the biologic requirements for the sexual transmission of HIV-1. Tragically, results such as these could be obtained only in places with a very high incidence and prevalence of the virus and few practical or affordable means of preventing transmission. The challenge now is to use these results to develop prevention strategies that can benefit everyone, especially those who participated in this research.

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