Commentary

Primary HIV Infection—A Public Health Opportunity

ABSTRACT

Primary human immunodeficiency virus (HIV) infection should be considered a key target for HIV prevention activities. Mathematical models suggest that the primary HIV infection interval makes a disproportionate contribution to the HIV epidemic, perhaps accounting for as many as half of the existing infections at any point in time. If this is true, primary infection presents a special window of opportunity within which to exert a maximum impact on the spread of HIV. A combination of biological, behavioral, and social factors may account for the influence of primary infection on the HIV epidemic. HIV prevention measures can be focused on each of these factors. Biologically, detecting individuals early in the course of infection and offering treatment can reduce viral load and possibly an individual's infectiousness. Behaviorally, counseling newly infected persons about the importance of adopting safer practices may instill prevention behaviors at a critical time. Socially, using a network approach to notify persons exposed to those with primary infections can dampen the amplification effect of rapid HIV spread through high-risk environments. By focusing prevention efforts on the primary HIV infection interval, public health officials could increase their leverage in slowing the HIV epidemic. (*Am J Public Health*. 1997;87:1928–1930)

Willard Cates, Jr, MD, MPH, Margaret A. Chesney, PhD, and Myron S. Cohen, MD

Introduction

Primary human immunodeficiency virus (HIV) infection, the time during which the viral burden set point is achieved, includes the acute symptomatic and early infection phases (Figure 1). Primary HIV infection should be considered an important public health opportunity. The relatively short interval (several months) of high viral load during early infection, followed by a long period of low viral load,[1] suggests a special window of time during which focused HIV prevention efforts could be particularly effective.

The Primary HIV Infection Interval

Primary HIV infection represents the initial stage of the disease, when viral replication is associated with dissemination in lymphoid tissue and a distinct immunologic response.[2,3] From half to three quarters of patients with acute infection have symptoms during this stage, including fever, skin rash, headache, diarrhea, malaise, and lethargy lasting about 1 month. In many patients with acute HIV infection, p24 antigen and HIV RNA can be detected in the blood. As patients recover from acute infection, the concentration of HIV in the blood is reduced to a "set point" that probably reflects the balance between viral growth and host defenses. The final level of the viral set point is inversely correlated with disease prognosis.[4] We believe that the level of HIV transmission occurring in the community during the primary infection interval also affects the prognosis for the epidemic.

Effect of Primary HIV Infection on the Epidemic

At the population level, primary HIV infection makes a disproportionate contribution to the spread of HIV. Mathematical models have assessed the role of this interval on different endemic levels of HIV infection. According to the most widely accepted set of assumptions, as much as half of HIV transmission occurs during the primary infection interval.[5] Three complementary possible explanations might account for the influence that primary HIV infection has on the spread of HIV—biological, behavioral, and social. Each has specific implications for prevention.

The biological explanation involves the high level of cell-free HIV in blood during primary infection relative to most other phases of the disease.[1] Vertical,[6] hematogenous,[7] and sexual[8] transmissions of HIV appear to reflect the concentration of the virus in blood. In recent studies, the concentration of HIV in blood best predicted the concentration in semen,[9] although these observations are not universal.[10,11] HIV may also be shed in higher concentrations in genital secretions during primary infection; high levels of HIV RNA were detected in semen from three men with acute HIV infection.[12]

The behavioral explanation for the spread of HIV infection recognizes that the

Willard Cates, Jr, is with Family Health International, Research Triangle Park, NC. Margaret A. Chesney is with the Center for AIDS Prevention Studies, Department of Medicine, University of California, San Francisco. Myron S. Cohen is with the Department of Medicine, University of North Carolina, Chapel Hill.

Requests for reprints should be sent to Willard Cates, Jr, MD, MPH, Family Health International, PO Box 13950, Research Triangle Park, NC 27709.

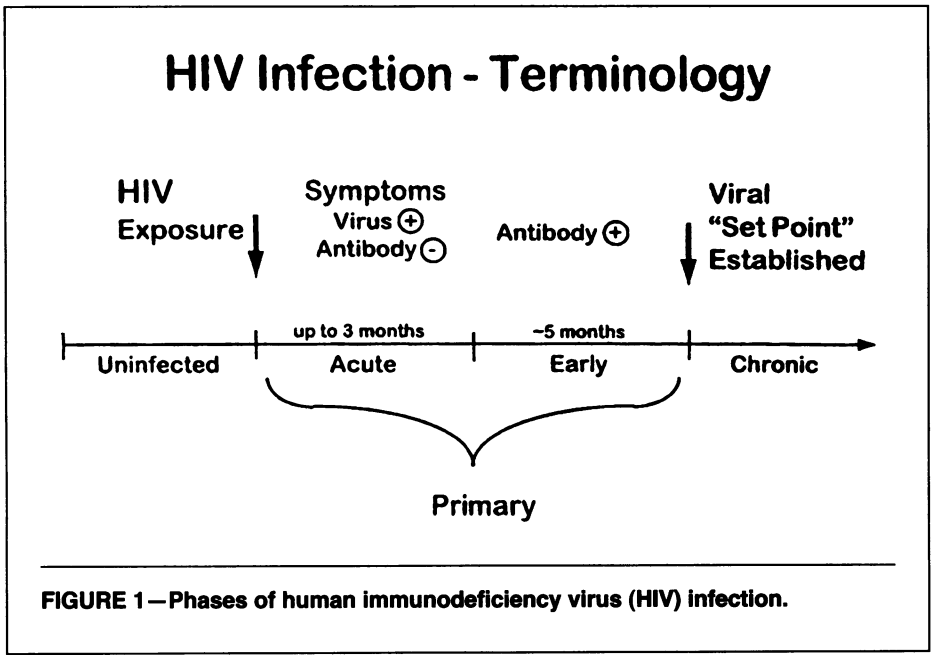

FIGURE 1—Phases of human immunodeficiency virus (HIV) infection.

risk behaviors (sexual or drug-sharing) that led to the individual's becoming infected with HIV are likely to continue.[13] Unless the symptoms of primary HIV infection are so severe as to limit the person's activities, a temporal clustering of risky behaviors in the recently infected individual could be expected to fuel the epidemic.

The social explanation is possibly the most important. The index infection occurs in the context of a network of people who share the same high-risk behaviors, which produces a marked amplification effect on the epidemic. The multiplicative dynamics of HIV infection among population networks engaging in risky behaviors is the strongest factor affecting the spread of HIV infection.[5] Accordingly, concurrency of sex partnerships is a more important factor than the aggregate number of sex partners in spreading HIV.[14]

Prevention Implications

Primary HIV infection presents a special window of opportunity in which prevention efforts may exert a maximum impact on the spread of HIV. Prevention strategies employed after the first several months of infection (such as current HIV antibody testing), while useful for identifying infected persons and referring them to care, may miss the best chance for slowing the epidemic. Efforts under way to work with communities to identify individuals in this primary infection window are of the utmost importance and need to be matched by innovative strategies to reduce any factors potentiating spread during this interval.

Both individual-level and population-level interventions are necessary. At the individual level, administering antiviral therapy early in the course of infection will reduce the level of viremia and may lower infectivity.[15] This approach would require educating vulnerable populations to seek HIV testing and antiviral therapy on the basis of such indicators as a known exposure to HIV or early recognition of symptoms. This individually based approach is characteristic of typical sexually transmitted disease (STD) control strategies[15] and includes such activities as educating patients about symptoms, screening, diagnosis, and early treatment to prevent the disease from progressing and the infection from being transmitted more widely.

These individual-level approaches can be complemented by interventions at the population level. Reducing factors that potentiate the transmission of HIV during the primary infection period could have a marked impact on slowing the epidemic.[16] Such population-directed strategies include changing social norms to reduce the rate of sex partner change, increasing condom use to lower the number of unprotected sexual acts, and targeting treatment of synergistic STDs in high-prevalence communities. Indeed, these approaches are currently the basis for international HIV prevention efforts. However, targeting them toward the primary infection interval would leverage their impact.

As persons with primary infection are identified, intervening in their sociosexual or drug-sharing networks could abort the amplified spread that occurs in these environments.[5] Locations such as crack houses where sex is exchanged for drugs[17] or brothels where new sex workers are imported every 3 months[18] are prime targets. Encouraging "environmentally protective" behaviors in these settings can reduce the population-level prevalence of all STDs, including HIV infection. The 100% condom policy of Thailand—a national policy requiring clients of sex workers to use condoms during all sexual acts—is one example of a successful environmental intervention.[18]

Other interventions—even if imperfect—that can decrease infectiousness during the primary HIV infection interval would also help.[19] We offer a few suggestions, realizing that all would need to be carefully evaluated for their ultimate impact on HIV transmission.

1. *More convenient identification of primary infection.* At this moment, we have no convenient method for detecting primary HIV infection. However, research in this area continues and technological developments abound.[1] In the meantime, we must educate the community about symptoms and encourage testing earlier in the course of HIV infection. Our current HIV testing program has primarily identified those in later stages of infection.[20] We must make detection of primary HIV infection more convenient and acceptable, possibly by using home detection systems and newer techniques for amplifying HIV in plasma.

2. *Early antiviral therapy.* The development of antiviral drugs for treating HIV disease is a source of new optimism. A combination of drugs can reduce the viral burden in both blood and semen for an extended period. If early viral burden predicts long-term health status,[2-4] individuals have a great incentive to recognize symptoms of primary HIV infection. Moreover, if therapy reduces early infectiousness, communities will reap marked prevention benefits.

3. *Network notification.* Many prevention programs stress individual partner notification for those found to be HIV seropositive. Typically, persons found to be seropositive are asked to provide information about their sex partners during the previous year. However, because the primary infection window is a shorter period of time, focusing notification efforts on more recent sex partners (for example, within the previous 3 months) would be more efficient. Timely epidemiological analysis and follow-up might help identify those sociosexual networks in which HIV is being transmitted most efficiently during the primary infection interval.[5] Interventions targeted directly toward these networks might dampen the amplification effect of the rapid spread of HIV through high-risk social environments.

4. *Innovative STD control at population levels.* Other STDs that cause ulcers or inflammation have an epidemiologic synergy with HIV transmission.[21] Therefore, population-level interventions that lower the overall prevalence of symptomatic STDs will reduce the likelihood of their occurring during primary HIV infection.[22] A randomized community trial in Tanzania demonstrated that syndromic STD treatment reduces the incidence of HIV infection.[23] In addition, a large study in Malawi demonstrated that treatment of urethritis in men reduces the concentration of HIV in ejaculate.[24] However, syndromic treatment is applicable only to those persons who recognize that they have STD symptoms. Thus, mass prophylactic treatment in high-prevalence populations may help to further reduce levels of asymptomatic STDs and thus lower the incidence of HIV infection.[25]

5. *Vaccine trials.* Because of the importance of infectiousness during the primary HIV infection interval, any vaccine that could reduce the concentration of HIV in blood or semen could contribute to slowing the epidemic. Most vaccine trials are being designed to test susceptibility rather than infectiousness. Alternatively, designs that enroll couples,[26] rather than individuals, could allow for more efficient measurement of the HIV vaccine's effect on infectiousness.

We realize that these suggested prevention strategies directed toward both individuals and populations in the primary HIV infection interval are unproven and might even have adverse consequences. For example, our concept of network notification could further stigmatize populations already marginalized in our society. Environmental discrimination could worsen, rather than improve, conditions under which accelerated HIV transmission occurs. Likewise, administering early antiviral therapy might lead some persons to believe that they have eliminated the risk of new HIV infection and thus can ignore messages recommending continued protective behaviors. These potential adverse consequences, however, can be minimized by acknowledging their possibility, monitoring their occurrence, and designing interventions to prevent them.

Conclusion

The primary HIV infection interval should be the main target of prevention efforts. We are already implementing a multitude of reinforcing prevention strategies at both the individual level and the population level.[22] We must be creative in suggesting and evaluating innovative approaches to preventing HIV transmission during the primary infection interval. We can view these as combination prevention approaches just as we use combination therapies for persons with HIV infection. These combined strategies, albeit imperfect individually, will have a strong cumulative impact on overall HIV transmission.[19] Moreover, focusing these multiple strategies on the primary HIV infection window provides an opportunity for maximum public health impact. □

Acknowledgments

This work was partially funded by National Institute of Allergy and Infectious Diseases (NIAID) contract N01-AI-35173 (HIV Network for Prevention Trials, Family Health International), National Institute of Mental Health (NIMH) grant P50MH42459 (Center for AIDS Prevention Studies), and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) grant R01 49381, NIAID grant GCRC RR00046, and NIAID grant UI 931496 (University of North Carolina).

References

1. Fauci AS, Pantaleo G, Stanley S, Weissman D. Immunologic mechanisms of HIV infection. *Ann Intern Med.* 1996,124:654–663.
2. Quinn TC. Acute primary HIV infection. *JAMA.* 1997;278:58–62.
3. Kinloch-de Loës S, Hirschel BJ, Hoen B, et al. A controlled trial of zidovudine in primary human immunodeficiency virus infection. *N Engl J Med.* 1995;333:408–413.
4. Mellors JW, Rinaldo CR Jr, Gupta P, White RM, Todd JA, Kingsley LA. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science.* 1996;272:1167–1170.
5. Koopman JS, Jacquez JA, Welch GW, et al. The role of early HIV infection in the spread of HIV through populations. *J Acquir Immune Defic Syndr.* 1997;14:249–258.
6. Dickover RE, Garratty EM, Hemman SA, et al. Identification of levels of maternal HIV-1 RNA associated with risk of perinatal transmission: effect of maternal zidovudine treatment on viral load. *JAMA.* 1996;275:599–605.
7. Busch MP, Operskalaki EA, Mosley JW, et al., for the Transfusion Safety Study Group. Factors influencing HIV-1 transmission by blood transfusion. *J Infect Dis.* 1996;174:26–33.
8. Lee T-H, Sakahara N, Fiebig E, Busch MP, O'Brien TR, Hemman SA. Correlation of HIV-1 RNA levels in plasma and heterosexual transmission of HIV-1 from infected transfusion recipients. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1996;12:427–428. Letter.
9. Vernazza PL, Gilliam BL, Dyer J, et al. Quantitation of HIV in semen: correlation with antiviral treatment and immune status. *AIDS.* 1997;11:987–993.
10. Rasheed S, Zhiliang L, Xu D, Kovacs A. Presence of cell-free human immunodeficiency virus in cervical vaginal secretions is independent of viral load in the blood of human immunodeficiency virus-infected women. *Am J Obstet Gynecol.* 1996;175:122–130.
11. Liuzzi G, Chirianni A, Clementi M, et al. Analysis of HIV 1 load in blood, semen and saliva: evidence for different viral compartments in a cross-sectional and longitudinal study. *AIDS.* 1996;10:F51–F56.
12. Dyer JR, Gilliam BL, Eron JJ, Fiscus SA, Vernazza P, Cohen MS. Effects of disease stage and CD4+ lymphocyte count on shedding of HIV-1 in semen. In: Program and Abstracts of the XI International Conference on AIDS; July 7–12, 1996; Vancouver, BC, Canada. Abstract We.C. 335.
13. Catania JA, Moskowitz JT, Ruiz M, Cleland J. A review of national AIDS-related behavioral surveys. *AIDS.* 1996;20(suppl):S183–S190.
14. Morris M, Kretzschmar M. Concurrent partnerships and transmission dynamics in networks. *Soc Networks.* 1995;17:299–318.
15. St. Louis ME, Wasserheit JN, Gayle HD. Editorial: Janus considers the HIV pandemic—harnessing recent advances to enhance AIDS prevention. *Am J Public Health.* 1997;87:10–12.
16. Garnett GP, Anderson RM. Strategies for limiting the spread of HIV in developing countries: conclusions based on studies of the transmission dynamics of the virus. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1995;9:500–513.
17. Edlin BR, Irwin KL, Faruque S, et al. Intersecting epidemics: crack cocaine use and HIV infection among inner city young adults. *N Engl J Med.* 1994;331:1422–1427.
18. Wiwat R, Hanenberg R. The 100 percent condom program in Thailand. *AIDS.* 1996;10:1–7.
19. Cates W Jr, Hinman AR. AIDS and absolutism: the demand for perfection in prevention. *N Engl J Med.* 1992;327:492–494.
20. Wortley PM, Chu SY, Diaz T, et al. HIV testing patterns: where, why, and when were persons with AIDS tested for HIV? *AIDS.* 1995;9:487–492.
21. Wasserheit JN. Epidemiological synergy: interrelationships between human immunodeficiency virus infection and other sexually transmitted diseases. *Sex Transm Dis.* 1992;19:61–77.
22. Aral SO, Holmes KK, Padian NS, Cates W Jr. Overview: individual and population approaches to the epidemology and prevention of sexually transmitted diseases and human immunodeficiency virus infection. *J Infect Dis.* 1996;174(suppl 2):S127–S133.
23. Grosskurth H, Mosha F, Todd J, et al. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet.* 1995; 346:530–536.
24. 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;349:1868–1873.
25. Wawer MJ, Sewankambo NK, Gray RH, et al. Community-based trial of mass STD treatment for HIV control, Rakai, Uganda: preliminary data on STD declines. In: Program and Abstracts of the XI International Conference on AIDS; July 7–12, 1996; Vancouver, BC, Canada. Abstract Mo.C.443.
26. Koopman JS, Little RJ. Assessing HIV vaccine effects. *Am J Epidemiol.* 1995;142:1113–1120.