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## The development of microbicides: A new method of HIV prevention for women

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## Programs Division

The Development of  
Microbicides: A New Method of  
HIV Prevention for Women

Christopher J. Elias  
Lori Heise

WORKING PAPERS

1993

No. 6

The Development of Microbicides:  
A New Method of HIV Prevention for Women

Christopher J. Elias  
Lori Heise

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Christopher Elias is Associate, The Population Council, New York. This paper was prepared as part of the Robert H. Ebert Program on Critical Issues in Reproductive Health and Population and supported by grants from the John D. and Catherine T. MacArthur Foundation and the Rockefeller Foundation. Lori Heise is a Project Associate with the Center for Women's Global Leadership at Rutgers University, New Brunswick, New Jersey and directs the Center's Violence, Health and Development Program. Her work on this paper was supported, in part, by a grant from the Ford Foundation.

## ABSTRACT

A critical review of current epidemiological trends and social science research demonstrates that there is an urgent need for expanding the range of female-controlled HIV prevention methods. Existing efforts to control the spread of HIV infection primarily through the encouragement of a reduction in the number of sexual partners, widespread condom promotion, and the control of other sexually transmitted infections are inadequate for many of the world's women. Underlying gender power inequities severely limit the ability of many women to protect themselves from HIV infection, especially in the absence of a prevention technology they can use, when necessary, without their partner's consent. Current understanding of biology suggests that developing such methods is a feasible and potentially cost-effective endeavor. This paper describes the growing risk of HIV infection faced by women throughout the world; examines the serious limitation of contemporary AIDS prevention strategy in meeting the needs of women; reviews the existing data on female-controlled HIV prevention methods; and outlines the challenges for future microbicide development.

## ACKNOWLEDGEMENTS

This paper evolved from our joint commitment to integrating a woman-centered analysis into the scientific and policy-making process related to HIV disease. As a document that couples fundamental biological and social science with an explicitly feminist analysis, we hope it will encourage dialogue across disciplines and a more realistic and informed approach to meeting women's protection needs in the age of AIDS.

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#### A NOTE CONCERNING TERMINOLOGY

This paper is concerned primarily with the development of female-controlled microbicides for intravaginal use in preventing the heterosexual transmission of the human immunodeficiency virus (HIV) and other sexually transmitted infections (STI). In our view, a microbicidal compound, appropriately formulated to allow women to use it without the consent of their sexual partners, is the most important new prevention option to pursue. In several parts of the text, however, we apply the cumbersome term "prevention technology" to refer to the full range of potentially female-controlled methods, including, most notably, the "female condom" or "vaginal pouch." We review the data concerning this method, as well as other physical barrier methods, in Section IV.

In considering the challenges for future development, however, we focus exclusively on microbicides. Strictly speaking, a "microbicide" is a substance that "kills microbes" -- understood in this paper to refer to all infectious agents, including bacteria, parasites, and viruses, and especially, HIV. While an intravaginal compound could theoretically prevent the transmission of HIV without actually killing the virus (e.g., by preventing its attachment to the vaginal mucosa), we do not make this semantic distinction in the text. For our purposes, the term "microbicide" refers to any compound capable, when applied intravaginally, of preventing the transmission of sexually transmitted pathogens.

It is important to clarify our reasons for using the term "microbicide" as opposed to the more narrow, but increasingly common, term "virucide." Frustration with the limitations of the existing AIDS prevention strategy has generated a search for new prevention options and, in particular, a female-controlled virucide. This paper is predominantly focused on the need for such a compound as an essential component of a comprehensive response to the AIDS pandemic. In calling for the resources to pursue the development of new prevention technologies, however, we must remember that a broad range of sexually

transmitted pathogens other than HIV cause considerable morbidity and mortality among women, especially in the developing world. In view of this reality, it is obvious that the most desirable compound would be one that also killed or inactivated the pathogens responsible for other widely prevalent sexually transmitted infections, such as gonorrhea and chlamydia. Such a broadly microbicidal compound could be an important means of preventing the very common problems of pelvic inflammatory disease, ectopic pregnancy, chronic pelvic pain, and infertility.

There is considerable reason to be hopeful that intravaginal compounds effective against HIV would have extended activity against other STIs. Alternatively, virucidal compounds could potentially be formulated with agents active against the viral, bacterial, and parasitic organisms that cause other sexually transmitted infections. The pursuit of "microbicides," therefore, would obviously not exclude compounds with a specific or narrow range of activity against HIV or other viruses. We feel that for the purposes of general discussion, however, the term "virucide" should be used as a specific subset of the broader term "microbicide." The breadth of the latter term will serve to remind us of the serious, and largely unattended, problem of reproductive tract infections among women throughout the world.



## INTRODUCTION

Slightly more than a decade after the first recognition of the AIDS epidemic, the means we have to prevent the spread of HIV remain remarkably primitive. We suggest that people not have sex, or imbue this basic freedom with the burdens of risk and fear. We promote condoms as prevention devices without serious thought concerning their interference with women's childbearing intentions or the fact that they are male-controlled. And we face the embarrassing reality that services to identify and treat other sexually transmitted infections (now recognized as an important AIDS prevention tactic) are among the most poorly funded health-sector programs in both industrialized and developing countries. In addition, at present our armamentarium lacks a critical tool -- a method of HIV prevention that is within the personal control of women.

Several authors have presented a strong case for developing such an HIV prevention technology (Stein, 1990; Elias, 1991; Germain, 1992; Cates and Stone, 1992). The proponents of such technology acknowledge the significant and growing risk of HIV infection faced by women throughout the world and, simultaneously, recognize the serious limitations of the current AIDS prevention strategy. Existing efforts to control the spread of HIV infection primarily through the encouragement of a reduction in the number of partners, widespread condom promotion, and the control of other sexually transmitted infections are inadequate for many of the world's women (Worth, 1989; Stein, 1990; Ulin, 1992). Underlying gender power inequities severely limit the ability of many women to protect themselves from HIV infection, especially in the absence of a prevention technology they can use, when necessary, without their partner's consent. The development of new prevention methods controllable by women would fill an important gap in the global response to the AIDS pandemic.

We must be clear, however, that the complexities of AIDS

will not be met adequately with a "technological fix." As outlined in more detail in Section III, efforts to develop female-controlled prevention options must be complemented by more concerted attempts to address the underlying gender power imbalances that shape women's risk of sexually transmitted infection, as well as their ability to protect themselves using the currently existing range of prevention strategies.

Although technology development is not a solution in itself, women's overall vulnerability to HIV would be greatly reduced if they had access to a prevention method within their personal control. The absence of a female-controlled method puts women in a uniquely vulnerable position. If men choose to ignore behavior-change messages to reduce their number of sexual partners, they still have a technology -- condoms -- to use to protect themselves. If injection drug users continue to inject, they still have a technology -- clean needles and/or bleach -- that is both effective and within their personal control. Only women, who confront centuries of social conditioning that grants sexual license to men, are expected to protect themselves without a technology they can control.

Obviously, the development of any additional prevention technology, including a female-controlled method, will also have a considerable benefit for men. It is reasonable to assume that a female-controlled microbicide that afforded women protection from HIV infection during heterosexual intercourse would also provide similar, if not greater, protection to men, thus expanding the options men have for avoiding infection. Protecting men, obviously, indirectly protects women. Through a general decrease in sexual transmission, the overall population of women and men will face a diminished risk of HIV infection.

The advancement of female-controlled prevention technology will require a long-term commitment to research and development. This effort will complement current attempts to develop preventative vaccines. It must be stressed that, despite remarkable progress in our understanding of the molecular biology

of retroviruses, there is no immediate hope for an effective pre-exposure HIV vaccine in humans. We must, therefore, pursue jointly both of these important prevention technologies, while simultaneously addressing the more immediate challenge of fundamental behavioral change.

We begin our review with a critique of existing AIDS prevention strategy. We do not intend to discredit the importance of this strategy for reducing women's risk of HIV infection or to portray women as helpless victims. "Women have been functioning as actors and prime movers, not just victims, in response to this epidemic -- not only as activists and professionals, but also as ordinary women, at the personal level and in their sexual relationships" (Berer, 1992). We also do not argue that resources should be diverted from these efforts to microbicide research. It should not be a zero-sum game. At present, all AIDS prevention efforts lack sufficient resources to stop the pace of the epidemic (Funders Concerned About AIDS, 1992). Among other things, we need more condoms, lower cost STI diagnostics, and greater insight into human sexuality and behavior change. Microbicide development is a complementary need arising from the limitations of the current strategies to be pursued within the broad range of tactics employed by women to reduce their risk of infection, morbidity, and death.

We do not want to imply that there has been a complete lack of interest or effort in this area for the past decade. A number of important starts have been made. In the United States, the United States Agency for International Development (USAID), the National Institute for Child Health and Human Development (NICHD), and the National Institute for Allergy and Infectious Disease (NIAID) have all invested resources in microbicide development. In the United Kingdom, the Medical Research Council has recently mounted a coordinated research and funding strategy for the development of intravaginal virucides (Stone, 1992). We do want to suggest, however, that this investment has been far too limited and too exclusively focused on the development of

contraceptive microbicides. As presented in the text, the feasibility of developing noncontraceptive microbicides is unresolved, given our limited knowledge concerning several critical questions of reproductive biology. Compared to contraceptive microbicides, the pursuit of such compounds presents a number of additional challenges and will most certainly take a longer time to be realized, but is an essential goal when viewed from the perspective of women.

To illustrate the level of investment, consider the fiscal year 1993 contraceptive research and development budget of the National Institute of Child Health and Human Development (NICHD, 1993). While directed research on potentially microbicidal spermicides represents 20 percent of this budget, the total dollar amount for such microbicide research is only \$1.3 million. This can be compared to a fiscal year 1992 investment of \$43.9 million in government-directed HIV vaccine research by the National Institute of Allergy and Infectious Disease (NIAID, 1993). Clearly there is a need for greater investment of resources in this important topic.

This paper has several objectives: to describe the growing risk of HIV infection faced by women throughout the world; to examine the serious limitations of contemporary AIDS prevention strategy in meeting the needs of women; to review the existing data on female-controlled HIV prevention methods; and to outline the challenges for future microbicide development. A critical review of current epidemiological trends and social science research demonstrates that there is an urgent need for expanding the range of female-controlled prevention methods. Current understanding of biology suggests that developing such methods is a feasible and potentially cost-effective endeavor. It is our hope that by assembling this information in a single review we will promote a more careful discussion of this vital topic. Although we have drawn most of our examples from research concerned with women in developing countries, we believe that the essence of our argument applies equally as well to poor women in

industrialized countries.

## I. WOMEN AT RISK

The early and persistent stereotype of AIDS as a "gay male" disease has perpetuated the notion that women are not at risk for HIV infection. The reality is that in sub-Saharan Africa and other regions of the world where HIV is predominantly transmitted through heterosexual intercourse, there are as many infected women as there are men. As of early 1992, the World Health Organization (WHO) estimated that over three million women in sub-Saharan Africa had been infected with HIV, along with one-half million infants who contracted the virus before, during, or shortly after birth (Global Programme on AIDS, 1992a). Of the one million individuals who have contracted HIV in the year since January 1992, slightly over one-half live in sub-Saharan Africa, about one-quarter live in Asia and the Pacific, and a little more than a tenth live in Latin America and the Caribbean (Global Programme on AIDS, 1992b). Developing countries now account for over 90 percent of all new infections (Global Programme on AIDS, 1992a).

Surveillance data reveal the degree to which HIV has penetrated vulnerable female populations. Among female sex workers, whose contact with multiple sexual partners increases their risk of having sex with someone who is infected, rates of HIV infection exceed 50 percent in some urban centers (Table 1). Rates among sex workers can increase dramatically in a very short time. In the six months between December 1990 and June 1991, the seroprevalence of HIV among sex workers in Chiang Mai, Thailand increased from 22.1 percent to 36.7 percent (Center for International Research, 1992a; Weniger et al., 1991). For the year ending June 1991, Thailand's sentinel surveillance system documented a near doubling of HIV infection among individuals attending STI clinics in all regions of the country (Center for International Research, 1992a).

Table 1: Percentage of Women Who are HIV Positive,  
Selected Countries

	Female Sex Workers	Female STI Patients	Pregnant Women
Cameroon			
Douala (1989)	10.9	-	-
Yaounde (1990)	9.3	-	-
Central African Republic			
Bangui (1989)	17.0	-	8.0
Congo (1990)			
Pointe Noire	64.1	-	9.0
Ethiopia (1989)			
Addis Ababa	18.2	36.8	-
Kenya (1990)			
Nairobi	87.8	-	5.8
Malawi (1990)	55.9	-	22.8
Rwanda (1989)			
Kigali	-	-	30.3
Tanzania			
Arusha (1988)	75.0	-	5.5
Tanga (1988)	52.6	-	7.0
Uganda			
Kampala (1990)	-	54.6	34.0 (a)
Zambia (1990)			
Northern Province	-	71.0	9-30
Lusaka	-	69.0	24.5
India			
New Delhi (1988)	30.1	-	-
Bombay (1986)	18.1	-	-
Haiti (1989)			
Port-au-Prince	41.9	-	11.6
Honduras (1990)	35.0 (b)	-	-

a) AIDS surveillance Report Fourth Quarter, 1990. AIDS Control Programme, Ministry of Health, Kampala, Uganda.

b) Global Programme on AIDS. 1992a. "Current and Future Dimensions of the HIV/AIDS Pandemic." Document WHO/GPA/RES/SF1/92.1. p.8.

**Source:** Center for International Research. "Recent seroprevalence by country." 1992. Research Note No. 6. Washington, DC: US Bureau of the Census.

Sex workers, however, constitute only a small percentage of the women affected by HIV. Studies show that by 1992, between one-quarter and one-third of all women aged 15-49 had become infected in some large urban centers in East and Central Africa (Global Programme on AIDS, 1992a). While the prevalence of HIV infection among women is significantly lower in other parts of the world, the incidence of new infection is increasing rapidly. In Central America, for example, the number of reported AIDS cases among women has increased 40-fold in the last four years (Global Programme on AIDS, 1992a). Not surprisingly, the number of infants born with HIV is rising in step. In some cities, between 18 and 32 percent of pregnant women presenting at prenatal care clinics are HIV-infected (Table 1). Between 15 and 33 percent of the children born to these women will become infected during pregnancy or birth (European Collaborative Study, 1992; Italian Multicentre Study, 1988). WHO estimates that in sub-Saharan Africa, infant and child deaths from AIDS may increase by as much as 50 percent during the 1990s, wiping out the significant gains in child survival achieved over the past two decades (Global Programme on AIDS, 1992a).

In industrialized countries, such as the United States and the nations of Western Europe, the primary populations affected by HIV continue to be gay and bisexual men and injection drug users, the majority of whom are male. But here too, women now comprise the fastest growing population of persons living with AIDS and HIV infection (Brettelle and Leen, 1991). Women are exposed to the virus through their own use of injectable drugs or through sexual activity with an infected partner. According to 1984 figures compiled by the Centers for Disease Control, 6.4 percent of all people diagnosed with AIDS in the United States were female. By September 1992, this figure had risen to 11.5 percent (Centers for Disease Control, 1992). AIDS became the leading cause of death for African American women aged 15 to 44 in the states of New York and New Jersey in 1987, and is

predicted to become the fifth leading killer of all U.S. women of reproductive age by the end of 1992 (V. Alexander, 1991). Worldwide, by the year 2000, the annual number of AIDS cases in women will equal or exceed the number in men (Petros-Barvazian and Merson, 1990; and Viravaidya, Obremskey, and Myers, 1991).

A host of biological, cultural, and economic factors conspire to heighten women's vulnerability to AIDS in comparison to men's. For example, it is likely that per-exposure transmission from man to woman during heterosexual intercourse is significantly more efficient than from woman to man. In one study of 42 discordant couples\* in Nairobi, for example, Clemetson et al. (1990) found that the rate of transmission from man to woman was 2.5 times greater than from woman to man. A comparable study of 563 couples in nine European countries estimated the risk ratio as 1.9\*\* (European Study Group on Heterosexual Transmission of HIV, 1992). A greater efficiency of transmission from man to woman has also been suggested for other STIs, such as gonorrhea (Hook and Handsfield, 1989).

The efficiency of HIV transmission appears even greater if the woman or her partner has another sexually transmitted infection. There is strong evidence that STIs that cause genital sores, such as herpes, chancroid, and syphilis, can significantly facilitate the transmission of HIV by creating a site of entry for the virus (Laga, 1992a; Wasserheit, 1991). Other, nonulcerative STIs that nonetheless cause inflammation, such as gonorrhea, chlamydia, and trichomoniasis, may also enhance susceptibility by concentrating more lymphocytes -- target cells of HIV -- in the genital tract (Manoka et al., 1990). Evidence suggests that the presence of either type of STI increases the risk of HIV transmission at least 3- to 5- fold (Wasserheit, 1991). Most researchers now believe that the widespread presence

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\* Stable unions where only one partner is infected with HIV.

\*\* (95% confidence interval 1.1 - 3.3)



of untreated STIs in the developing world may partially explain why heterosexual intercourse appears to transmit the virus more efficiently in these regions than in industrialized countries (Wasserheit, 1991).

Women are at a further biological and social disadvantage because the same diseases that generally cause burning and itching in men are often asymptomatic in women, leaving them unaware that they are in need of treatment (Dixon-Mueller and Wasserheit, 1991). Researchers estimate that from 10 to 50 percent of women with trichomoniasis, 25 to 30 percent of women with gonorrhea, and probably over 50 percent of women with chlamydia and bacterial vaginosis have no symptoms at all (Wasserheit, 1989). Others with pelvic pain or vaginal discharge may accept this discomfort as a woman's "lot in life," not recognizing that they can and deserve to be treated (Dixon-Mueller and Wasserheit, 1991). Even those who would welcome treatment often feel too embarrassed or ashamed to seek care at STI clinics, whose clients are primarily men or female sex workers (Cates and Stone, 1992). As with health care in general, women are often too busy, too modest, or too poor to seek treatment for STIs.

The precarious state of women's reproductive health in the world's poorer nations also places women at an augmented risk of infection through increased exposure to blood transfusion. The lifetime risk of dying from a pregnancy-related cause for third world women is 200 times that for women in the industrialized world (Petros-Barvazian and Merson, 1990). Overburdened with work and exhausted from too many pregnancies and chronic malnutrition, women in developing countries continue to bear children and manage their households with little time or energy left to attend to their own needs. Chronic iron deficiency, malaria, complicated pregnancies, and lack of access to safe and legal abortion predispose women to the need for blood

transfusion.\* While much blood is now tested in the capital cities of the developing world, adequate quality assurance procedures are still evolving, and the equipment necessary to screen blood is often nonfunctional and generally not available in smaller cities or rural areas.

## **II. LIMITATIONS OF THE EXISTING AIDS PREVENTION STRATEGY**

As of July 1992, the World Health Organization estimated that at least 10 to 12 million adults had become infected with HIV, 75 percent of whom contracted the virus through heterosexual intercourse (Global Programme on AIDS, 1992b). Among individuals infected during 1992, over 90 percent acquired their infection through heterosexual sex. This reflects the continuing trend toward heterosexual transmission in both the industrialized and developing worlds. Changing the nature of sexual behavior of men and women thus becomes a necessary cornerstone of any global strategy to combat AIDS.

As currently conceived, the global AIDS prevention strategy consists primarily of three interrelated tactics: 1) encouraging people to reduce their number of sexual partners; 2) promoting the widespread use of condoms; and 3) treating concurrent STIs in populations at risk of HIV. Together, these three themes constituted the backbone of the \$88 million the U.S. government spent on AIDS prevention in developing countries in fiscal year 1991 (United States Agency for International Development, 1992). As the following discussion will show, however, this three-pronged attack is inadequate for meeting the protection needs of many of the world's women. Disproportionately poor and with little power to negotiate the terms of sexual encounters or to find livelihoods outside of marriage that do not require sexual contact, women often cannot avail themselves of these life-saving

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\* Women and children receive roughly 80 percent of all blood transfused in sub-Saharan Africa (Lampety and Mitchell, 1990).

strategies. Women need both a new commitment to addressing the underlying inequities that heighten their risk, and new technologies that provide them with a means of HIV protection within their personal control.

#### **A. Critique of Partner Reduction Strategies**

The first line of defense in many AIDS prevention campaigns has been to counsel individuals to avoid exposure to HIV by limiting their number of sexual partners. Teenagers are told to abstain from sex until marriage, couples are exhorted to remain monogamous, and others are encouraged, at the very least, to reduce their number of sexual partners. There are a number of realities in women's lives, however, that limit the utility of this prevention advice. First, for many of the world's women, monogamy is a largely irrelevant strategy because they are already monogamous. It is the sexual or drug-using behavior of their sexual partner that puts them at risk. Second, for a significant portion of those women who are not monogamous, having multiple partners is not a pleasure-seeking strategy, but a way to gain access to resources that only men control. These women cannot easily reduce the number of their sexual partners; multiple partners are their key to survival. Third, partner-reduction messages assume that women are always in control of when they have sex and with whom. As data on rape and coercive sexuality indicate, however, this is far from the case in many sexual encounters. This section -- which deals with the problems that partner-reduction messages pose for women -- will examine each of these issues in turn, exploring how they limit women's ability to protect themselves from HIV.

#### The Danger of Relying on Presumptions of Monogamy

What has been forgotten in the rush to "educate" populations considered to be at "high risk," such as prostitutes, is that the mass of women in need of protection are not sex workers, but

women with one partner -- their husband or the man with whom they live. In Sao Paulo, Brazil, married women who have only one sexual partner constitute 49 percent of all new AIDS cases among women (Pitanguy, 1993). In a recent article from the United States, Kost and Forrest (1992) review the limited data available from the General Social Survey and National Survey of Family Growth concerning reported multiple heterosexual partnership for men and women and estimate ranges for the direct and indirect risk of exposure to STIs among reproductive-age women. (Direct risk of exposure relates to a woman reporting that she has had multiple sexual partners; indirect risk of exposure relates to her only male partner having multiple partners.) Even in their most conservative, low-end estimates, Kost and Forrest find that women are roughly at equal risk of STI exposure through the nonmonogamous behavior of their male partner (12.2 percent) as they are through their own nonmonogamous behavior (14.3 percent). In the high-end estimates, women are almost twice as likely to face an indirect risk of STI exposure through their male partner's sexual behavior (24.4 percent).

Unfortunately, many of the most popular AIDS prevention messages -- "Stick to Your Partner," "Love Faithfully" -- give women the mistaken impression that if they remain monogamous, they will be safe from HIV. Data from around the world, however, indicate that it is not safe for women, or for AIDS prevention programs, to make this presumption. Monogamous women are increasingly at risk of AIDS through both the heterosexual and homosexual behavior of their steady male partners. To date, AIDS prevention programs have not included these women, leaving them without adequate information or skills to protect themselves from infection.

#### Male Infidelity With Women

In many cultures there persists a sexual double standard that gives men license to be sexually adventurous while

restricting female sexuality.\* As a result, many surveys of sexual behavior document a higher rate of partner change among married and single men than among women (Handwerker, 1991; Sittitrai et al., 1991b; Rwabukwali et al., 1991; and Anarfi, 1992).\*\* In Thailand, for example, 28 percent of a stratified random sample of men nationwide admitted to having sex outside of their marriage or steady partnership within the last year, compared to only one percent of women (Sittitrai et al., 1991b). Likewise, an island-wide random survey of men and women on Barbados showed that during the age period 25 to 34, men had five sexual partners on average, while women had only one. (Not surprisingly, sticking to one sexual partner did not reduce a woman's odds of reporting a history of STIs) (Handwerker, 1991). Results from a six-country, WHO-sponsored survey on African sexuality found that more than twice as many men as women reported extramarital affairs in the 12 months prior to the survey. Men also reported significantly more lifetime sexual partners (Crael et al., 1990).

A study from Kigali, Rwanda (Allen et al., 1991) illustrates starkly the danger women face in assuming that monogamy "protects" them from AIDS. Of 1,458 women aged 18 to 35 years attending the outpatient pediatric and prenatal clinics at the Centre Hospitalier de Kigali, 86 percent reported being married or in a common-law union with a man. All but 10 reported being monogamous, although only 496 (34 percent) felt certain of the fidelity of their partners. Overall, 24 percent of women who thought they were in mutually monogamous relationships were HIV positive. Even among the two-thirds of women who had only one

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\* The following focuses on data from communities where polygyny is not a formal social institution. For an evocative discussion of the influence of formal polygyny on the transmission of HIV, as well as other STIs, see Frank, 1992.

\*\* Some of this difference may be the result of overreporting of sexual conquests by men and/or underreporting of extramarital sex by women.

lifetime partner -- their husband -- 21 percent were infected. The authors suggest that it is likely that a good portion of these women married men who were already infected with HIV. "A striking finding," they note, "was the high prevalence of infection among women who had been living with a partner for less than seven years." Apparently, men in Kigali become sexually active several years before they take a wife, and during that time their sexual partners are a small group of "free women" (often single mothers) who have many partners. The prevalence of infection in 1983 among "free women" in another Rwandan city was 88 percent (Clumeck et al., 1985; Allen et al., 1991). "If the rise in prevalence in this group increased rapidly in one or two years and peaked in 1982 and 1983," the authors note, "this would explain the high prevalence of infection in wives whose partners had premarital sex in 1982 or later."

The tendency for young girls to be partnered with men many years their senior increases the likelihood that they will be exposed to HIV (Table 2). This age gap is likely to increase as older men seek out younger and younger partners in the hopes of avoiding AIDS -- a pattern already documented in parts of Africa (Amnesty International, 1992). It will also increase as harsh economic times lengthen the time it takes for African men to accumulate the "bridewealth" they must pay a woman's family to secure her hand in marriage (Palloni and Lee, 1990).

Table 2: Age Difference Between Spouses in Years

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<u>COUNTRY</u>	<u>MEDIAN DIFFERENCE</u>
Nigeria	9.7
Ghana	7.6
Sudan	8.4
Bangladesh	9.1
Morocco	6.5

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**Source:** Casterline, J., Williams, L. and P. McDonald. 1986. "The age difference between spouses: Variations among developing countries," Population Studies, 40, 3.

Mathematical models of the AIDS epidemic show that a woman's risk of contracting HIV increases dramatically as her age at first intercourse goes down and/or the age difference between her and her partner goes up (Palloni and Lee, 1990; Anderson et al., 1986). Older men have had more sexual partners and, therefore, have a greater chance of being infected with HIV or other STIs. It has also been suggested, however, that early intercourse may represent an additional, independent, risk (Cates, 1991; Kost and Forrest, 1992; Moscicki et al., 1989). Data suggest that if a young woman is exposed to HIV before genital maturation is complete, she may face a greatly augmented likelihood of HIV infection. This dynamic may account for the very high rates of clinical AIDS among young women that have been found in areas where sexual initiation with older men occurs at a very early age (United Nations Development Programme, 1992).

As the Rwandan example illustrates, in highly infected areas a young woman's first sexual partner could easily be infected with HIV, effectively eliminating the utility of advocating "monogamy" as a means of AIDS control. These women need strategies of HIV prevention that they can use throughout their sexual and reproductive lives. This reality, and the desire of most women to bear children, underscores the need for a method of HIV prevention that will allow conception.

Many women feel incapable of challenging their husband's infidelity -- to do so places their relationship, their economic security, and their physical safety at risk. During focus-group discussions in Zambia, for example, many women felt powerless over their partner's sexual behavior. "I can be faithful to my husband, but my husband will not be faithful to me," observed one woman. "There are very few men who are faithful to their wives" (Mushingeh, Chama, and Mulikelela, 1991). Similarly, from a 27-year-old woman in the Mukono district of Uganda, "My husband has lost a girlfriend of AIDS and now he is dealing with another whose husband died of AIDS this year. So I think I have got the

virus and with time I will get the symptoms" (Moodie et al., 1991). Likewise, preliminary data from research projects on women and HIV in India, Brazil, South Africa, and Guatemala, reveal that an overwhelming number of women report being monogamous themselves but aware that their partners are not (Rao Gupta, 1992). These women also express a sense of helplessness over their inability to change their partner's sexual behavior.

#### Male Infidelity With Men

Elsewhere, other "low-risk" women are contracting HIV through the hidden homosexual behavior of their male partners. To date, this phenomenon has been studied primarily in Latin America and the Caribbean, although similar patterns are now being documented in other places, such as Thailand (Sittitrai et al., 1991a). Because homosexuality is not accepted in many cultures and the pressure to have children is acute, many men who engage in homosexual activity nonetheless marry or have steady female sexual partners. This sets the stage for increasing AIDS incidence among women and children, a pattern already documented in Trinidad and Tobago, Brazil, the Dominican Republic, and other Latin American countries (PAHO, 1988). As of 1991, bisexuality was the risk factor for 28 percent of AIDS cases among men in both Brazil and Mexico\* (Huang et al., 1992; Valdespino et al. 1991).

Unfortunately, men who engage in bisexual behavior are very hard to reach with AIDS prevention messages because many do not consider themselves "gay" or "bisexual." In Brazil, for example, only men who take the receptive, passive role in anal sex are considered homosexual; the man who "inserts" is seen as masculine regardless of the gender of his sexual partner (Parker, 1992). Research from Rio de Janeiro documents that as of 1990,

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\* In the Mexico study an additional 16 percent of cases among men were listed as "heterosexual," although the authors estimate that more than 80 percent of these men were really bisexual.



unprotected penetrative intercourse was still dangerously common among men having sex with other men, especially among those who reported sexual contact with both women and men.\* Fully 56 percent of bisexual men had engaged in anal intercourse with a male partner during the last six months, 43 percent without a condom. Of the 100 percent who also had vaginal sex with a woman, 89 percent did not use a condom with their female partner (Parker, 1992). Not surprisingly, the male to female ratio among reported AIDS cases in Brazil decreased from 30:1 in 1985 to 6:1 in 1991 (Vilela et al., 1992).

These examples emphasize the importance of reaching all women with AIDS prevention messages, not just those who themselves engage in "high risk" activity. In fact, it is precisely those women who appear least at risk of contracting HIV -- married women who have no outside partners and do not use drugs -- who are left exposed due to the failure of most AIDS prevention campaigns to reach out to women other than those who identify themselves as sex workers. Women's risk of HIV is also exacerbated by the failure of most programs to target men. As the epidemic proceeds, sexual partners of men at high risk are destined to make up an ever larger share of individuals contracting AIDS.

### Sexual Networking as an Economic Strategy

Many partner-reduction messages are based on the premise that individuals seek multiple partners to further their own pleasure; reducing one's risk is thus only a question of exerting self-control. While pleasure is surely a factor in many cases, there is also a need to replace partners lost through separation, divorce, or death. Likewise, for many women, having more than

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\* Studies from Lima, Peru (Bossio, 1990) and Trinidad and Tobago (McCombie et al., 1990) also document that bisexual men report lower levels of perceived self-risk than heterosexual men and significantly lower levels of condom use with their female partners compared to their male partners.

one partner is an economic survival strategy that is central to their ability to support themselves and their children.

"Stick to One Partner" slogans ask many women living on the edge to forego income vital to meeting today's needs to avoid an ill-defined risk of AIDS 10 years hence. Increasing poverty, especially among women, has made this type of balancing act ever more present in women's sexual decision-making. In the decade prior to 1990, three-fourths of the world's women lived in countries whose per capita gross domestic product either declined or increased by an average of less than \$10 per person annually (UNDIESA, 1991). With declining real income, women have had to compensate by working longer hours, competing with men in a labor market that severely undervalues women's work.

This period of economic deterioration coincided with and contributed to an unprecedented rise in the number of households headed by females. Estimates indicate that women are now the sole earners in one-fourth to one-third of all the world's households (Agarwal, 1990). Given women's lack of access to wage employment and their responsibility for child care and family upkeep, it is not surprising that households headed by women are disproportionately poor. Data from five Latin American cities, for example, document that the median monthly income of poor households headed by women is consistently lower than that of households headed by men (Arriangada, 1990).

With few marketable skills, many women have come to rely on "sexual networking"\* as an economic strategy to sustain their families in the face of growing economic uncertainty. Although the composition of sexual networks varies, research has shown that women often have relationships with more than one man to gain access to resources -- resources they do not command themselves because of entrenched gender discrimination in access

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\* "Sexual networking" is a phrase increasingly being applied by anthropologists and public health experts to describe patterns of multi-partnered sexual relationships.

to education, to credit, and to the formal wage economy (Bledsoe, 1990a; Guyer, 1988; Schoepf et al., 1990). These women cannot practically "reduce" the number of their sexual partners.

In urban areas of Africa, for example, it is not uncommon for women to form relatively stable unions with several partners, each of whom contributes in some way to the maintenance of their families. These relationships may and often do involve affection, but their primary motive is economic. A woman may have ties to several long-distance truck drivers, for example, whom she sees on occasion when they pass through town. They, in turn, help buy groceries and pay the school fees for her children. These women -- known as "spares" in Zimbabwe, "deuxièmes bureaux" in Francophone Africa, and "girl friends" or "town wives" elsewhere in Africa -- draw strong distinctions between themselves and "prostitutes," making them unlikely to respond to standard messages linking AIDS with the explicit exchange of money for sex (Lampsey and Potts, 1990).

Women clerical workers, school girls, and female traders are examples of the larger population of urban women who often survive by occasionally bartering sex for the resources and upward mobility that older men can provide (Ulin, 1992). It is quite common for secondary school girls, for example, to take up with a "sugar daddy" who helps pay the fees and expenses that allow her to stay in school. As anthropologist Caroline Bledsoe explains in her study of urban school girls in Sierra Leone, girls from poor families have little choice but to seek outside support if they want to continue their education (Bledsoe, 1990b). According to Bledsoe, even better-off parents often hesitate to spend money on school fees for adolescent daughters, fearing that they will get pregnant early and drop out of school. "Ironically," she notes, "parental reluctance itself often makes this outcome a self-fulfilling prophecy." Each year, thousands of school girls in Africa are forced to drop out of school because they get pregnant as a result of providing sexual favors to older men in exchange for school money. Many of these young

women are then repudiated by their families, forcing them to engage in more high-risk sexual behavior. One study of prostitutes in Nairobi found that the majority were unwed girls who had dropped out of school due to pregnancy. The rest were primarily divorced, separated, or widowed women (Ngugi, 1991).

The Nairobi study is just one among many that demonstrates that prostitution is often an economic survival strategy, especially for women who have been ostracized or abandoned by their husbands, family, or community. Depending on the culture, a wide variety of social "transgressions" can precipitate repudiation -- among them divorce, unwed pregnancy, AIDS, infertility, widowhood, or surviving a rape. A study by the Indian Housewives Federation, for example, found that 80 percent of New Delhi prostitutes in their sample were women cast out from their communities after having been raped (Rad, Vaid, and Juneja, 1992). The migration of abandoned or rejected barren women to urban prostitution has also been noted in Niger, Uganda, and the Central African Republic (Frank, 1983). Ironically, many of these women are abandoned due to infertility caused by an STI acquired from their husbands.\*

As these examples suggest, cultural and economic constraints make it difficult for women who have no husbands to survive without multiple sexual partnerships and the added risk they entail. Research in both Uganda and Rwanda, for example, has shown that women who are separated, widowed, or divorced have significantly higher levels of HIV infection than do married or cohabitating women (Allen et al., 1991; Ankrah, 1991). Although most women marry early in developing countries, divorce, male outmigration, widowhood, and abandonment mean that many will have to survive at least part of their lives on their own. In Ghana, for example, the average woman spends 50 percent of her

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\* Studies show that in some parts of sub-Saharan Africa, 30 to 50 percent of women are infertile, compared to the 3 to 7 percent that would be expected to result from genetic, anatomic, or endocrinological causes (Wasserheit and Holmes, 1992).

reproductive years (15-49) without a man in residence (Blanc and Lloyd, 1990). In some developing countries, more than half of all marriages will be dissolved by the time a woman reaches her forties (Table 3). Some of these women will remarry and others will be supported by an elder son, but many will find themselves alone with few skills and little education to fall back on. One researcher estimates that there are roughly 10.5 million widows in India who are either without adult sons to support them or have been abandoned entirely by their families (Chen, 1992).

Table 3: Proportion of Ever-Married Women Whose First Marriage is Dissolved by Age 40-49

<u>COUNTRY</u>	<u>PERCENT</u>
Cameroon	35
Cote D'Ivoire	45
Ghana	40
Mauritania	56
Colombia	35
Dominican Republic	53
Haiti	53
Bangladesh	36
Indonesia	55
Malaysia	33
Thailand	27

**Source:** United Nations. 1987. Fertility Behavior in the Context of Development. New York: United Nations. As cited in Bruce, Judith and Lloyd, Cynthia. 1992. "Finding the ties that bind: Beyond headship and household." Research Division Working Paper No. 41. New York: Population Council.

Evidence suggests that even among married women, access to economic resources is often a factor in the decision to take on additional partners. Among the Yoruba of southwestern Nigeria, Orubuloye and colleagues found that, in contrast to men, married women who had affairs seldom said it was for their own pleasure; rather, it was in exchange for some form of economic assistance or support withheld by their husbands (Orubuloye, Caldwell, and Caldwell, 1991). Likewise, Rwabukwali and colleagues (1991) argue that among women in Kampala, Uganda, economic necessity was

the primary reason for sexual risk taking among 72 percent of HIV+ women and 54 percent of matched controls. Both authors conclude that sexual networking is in fact a form of economic networking, making it difficult for women to eliminate outside partners without access to alternative forms of income.

These examples demonstrate the difficulty of applying Western categories -- "prostitution," "multiple partners," "monogamous relationship" -- to the reality of third-world women's lives. Such labels do not begin to capture the subtlety or fluidity of sexual networks under conditions of economic scarcity, nor do they acknowledge the degree to which economic vulnerability shapes the sexual decision-making of third-world women. Until women have realistic economic alternatives, many will be unable to heed AIDS prevention messages that advocate "partner reduction" as a means to protect oneself from AIDS.

#### The Role of Nonconsensual Sex

Partner reduction messages are only actionable insofar as women are truly free to control when and with whom they will have sex. A growing body of literature documents that women are frequently denied this basic freedom and forced to have intercourse against their will. The pervasiveness of nonconsensual sex in women's lives is a reality that prevention programs have yet to confront, despite its ability to undermine significantly the effectiveness of conventional AIDS prevention strategies.

Rape is an extreme example of the type of sexual coercion that women confront daily in both the industrialized and developing world. In the United States, for example, population-based surveys suggest that one in five American women has been the victim of a completed rape (Koss, in press). Studies worldwide also demonstrate a remarkable consistency in the demographics of sexual assault. Contrary to popular perception, the majority of rape survivors (60 to 78 percent) know their assailants, a reality confirmed by surveys and service statistics

from rape crisis centers in Malaysia, Mexico, Panama, Peru, and the United States (Heise, 1993). Also, a large percentage of rapes are perpetrated against girls 15 years and under, with a disturbing percentage of assaults against girls younger than 10 (Table 4).

Unfortunately, evidence indicates that even women in consensual unions often lack control over the dynamics of their sexual lives. A study of home-based industrial workers in Mexico, for example, found that wives' bargaining power in marriage was lowest in the area of deciding if and when to have sexual intercourse (Beneria and Roldan, 1987). Studies of natural family planning in the Philippines, Peru, and Sri Lanka (Liskin, 1981) and sexual attitudes among women in Guatemala (DataPro and Asociacion Guatemalteca para la Prevencion y Control de SIDA, 1991) also mention the frequency of forced sex by men, especially when they arrive home drunk. The summary document of the Guatemalan focus groups observes, "It is clear from the replies the women gave...that being forced through violence to have sex by their partner is not an uncommon experience for Guatemalan women."

Studies show that the percentage of women who experience forced sex in marriage is even higher among women who live with physically abusive men. Whereas 14 percent of U.S. wives report being raped, the prevalence among battered women is between 33 and 46 percent (Council on Scientific Affairs, 1992).<sup>\*</sup> Reports from Bolivia and Puerto Rico (Isis International, 1988) estimate that 58 percent of abused women in these countries have been raped by their husbands, as have 46 percent of abused women in Colombia (Profamilia, 1992). When one considers the percentage

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\* According to a recent review article in the Journal of the American Medical Association, "Victims of marital rape suffer many of the same reactions as other rape victims and are likely to exhibit particularly severe sequelae, both emotionally and physically (including very severe depression and suicidality)" (Council on Scientific Affairs, 1992).

Table 4 Statistics on Sexual Crimes, Selected Countries<sup>a</sup>

	Percent of perpetrators known to victim	Percent of victims 15 years and under	Percent of victims 10 years and under
Lima, Peru	60	--	18 <sup>d</sup>
Malaysia	68	58	18 <sup>b</sup>
Mexico City	67 <sup>c</sup>	36	23
Panama City	63	40	--
Papua New Guinea	--	47	13 <sup>e</sup>
United States	78	62 <sup>f</sup>	29

<sup>a</sup> Studies include rape and sexual assaults such as attempted rape and molestation, except for U.S data that includes only completed rapes.

<sup>b</sup> Percentage of victims age 6 and younger.

<sup>c</sup> Data from Carpeta Basica. 1991. Mexico City: Procurador de Justicia del Distrito Federal de Mexico.

<sup>d</sup> Percentage of victims age 9 and younger.

<sup>e</sup> Percentage of victims age 7 and younger.

<sup>f</sup> Percentage of victims age 17 and younger.

Table updated from (Heise, 1993)  
**Data sources:** Malaysia data from (Consumer's Association, 1988); Panama City data from (Perez, 1990); Peru data from (Portugal, 1988); Papua New Guinea data from (Bradley, 1990); Mexico City data from (COVAC, 1990); United States data from (Kilpatrick et al., 1992).

of women around the world who live with physically abusive partners, the true dimensions of sexual coercion in relationships begins to emerge. As Table 5 shows, in many countries one-third to one-half of all women have been beaten by their partners, suggesting that a substantial portion of the world's women have faced coercive sex as well. Since women have little say over their partner's sexual behavior outside of marriage, their lack of control over the sexual encounter within marriage is even more problematic.

Regrettably, there is ample evidence as well that early



forced sex is an all-too-common dimension of growing up female. Especially vulnerable are young girls who are forced to have intercourse by a male relative or are foisted prematurely into the world of adult sex after being married off as a child. In the Maternity Hospital of Lima, Peru, for example, 90 percent of young mothers aged 12 to 16 had been raped by their father, stepfather, or another close relative.\* In Jamaica, 40 percent

Table 5 - Percentage of Women Reporting Physical Abuse, Selected Countries

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- o In Papua New Guinea, 67 percent of rural women and 56 percent of urban women have been victims of wife abuse, according to a national survey conducted by the PNG Law Reform Commission (Bradley, 1988).
  - o In a detailed family planning survey of 733 women in the Kissi district of Kenya, 42 percent said they were beaten regularly by their husbands (Raikes, 1990).
  - o In a random sample of Norwegian gynecological patients, 25 percent of women who had ever lived in a relationship had been physically and/or sexually abused by their partner (Schei and Bakketeig, 1989).
  - o In a study of 1,388 women seeking services (not related to violence) at Costa Rica's national child welfare agency, one in two report being physically abused (Chacon et al., 1992).
  - o Colombia's detailed, country-wide Demographic and Health Survey revealed that one in three women have been emotionally or verbally abused by their partner, one in five have been physically abused, and one in ten have been raped by a partner (Profamilia, 1991).
  - o In one study of an Indian village, more than 75 percent of men from lower caste classes admitted to beating their wives (Mahajan, 1990).
  - o A 1990 study of 1,000 women in the department of Sacatepequez, Guatemala found that 49 percent have been physically, sexually or emotionally abused; 74 percent by an intimate male partner (Castillo et al., 1992).

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\* This figure is quoted in Rape: Can I Have This Child?, a booklet published by Movimiento Manuela Ramos, a nongovernmental women's organization in Lima, Peru.

of pregnant girls aged 11 to 15 reported the reason for their first intercourse as "forced" (Allen, 1982). And in Zaria, Nigeria, 16 percent of female patients attending one STI clinic were children under the age of five; another 6 percent were girls under the age of 15 (Kisekka and Otesanya, 1988).

#### **B. Limitations of Condom Promotion Strategies**

Another major thrust of AIDS prevention programs has been the promotion of condoms as a way to protect oneself from AIDS. To a large extent, the global effort to increase condom use has just begun. In many parts of the world high cost, poor quality, and limited availability impair the implementation of this important element of AIDS prevention strategy. Greater political commitment and community leadership are needed to make the use of condoms widely acceptable to individual men and women throughout the world. Along with this commitment must come increased resources for improved condom design, procurement, and distribution.

As a strategy for women, however, condom promotion has some major limitations that highlight the need for complementary, female-controlled, prevention technologies. Condoms are a technology that women may influence, but ultimately do not control. This means that women's safety is often predicated on their ability to "negotiate" condom use with an often unwilling partner. There are a variety of powerful forces -- social, economic, cultural, and emotional -- that limit women's ability to negotiate successfully on their own behalf.

#### Obstacles to Proposing Condom Use

For a condom-based strategy to work for women, they must first feel able to discuss sex and condom use with their partner. Open communication about sexual matters, however, is not a part of many relationships. A survey of spousal communication in Asian countries, for example, found that close to a third of the

women interviewed in the Philippines never talked to their husbands about sexual matters, nor did 47 percent in Singapore or 53 percent in Iran (UNESCAP, 1974). Caldwell and colleagues (1989) report that frank discussion between partners about sex is uncommon in many parts of sub-Saharan Africa as well. Elsewhere, strong cultural factors work against the open discussion of sex. In traditional Latina culture, for example, a "good woman" is expected to be naive about sexual matters; knowledgeable or assertive women are considered to be "loose" (Maldonado, 1991).

There are also strong emotional barriers that prevent women from raising the subject of condom use. Especially in the context of an ongoing relationship, discussion of condoms often raises painful issues of fidelity and trust that many women and men would rather not confront. In focus-group discussions in places as diverse as the Caribbean, sub-Saharan Africa, and Sri Lanka, men and women uniformly said that use of condoms symbolized distrust between partners, rather than care and concern (Johns Hopkins School of Hygiene and Public Health, 1990). Not surprisingly, these beliefs make the discussion of condom use an emotionally loaded topic, especially in the context of a valued relationship.

Experience has shown that women also suffer abandonment, physical abuse, and accusations of infidelity by bringing up condom use. The family planning literature documents how for some men, the desire to use any form of birth control signals a woman's intentions to be unfaithful. (Their logic is that protection against pregnancy allows a woman to be promiscuous.) Where children are a sign of male virility, a woman's attempt to use birth control may also be interpreted as an affront to her partner's masculinity. In focus-group discussions with women in Mexico and Peru, for example, many women were afraid to bring up birth control for fear of being beaten, deserted, or accused of cheating on their partner (Folch-Lyon, Macorra, and Schearer, 1981; Fort, 1989). The connection to infidelity is even stronger for condoms, which are widely associated with promiscuity,

prostitution, and disease in many parts of the world. By bringing up condom use, women either insinuate their own infidelity or they implicitly assert the right to protect themselves from husbands who have outside relationships. This assertion may trigger violent reactions.

Raising such issues can be equally as difficult and threatening for women in industrialized nations. In 1987, the National Institutes of Drug Abuse (NIDA) launched a major research and advocacy initiative to test strategies for reaching and intervening with two groups of women at high risk of contracting HIV -- injection drug users (IDUs) and sexual partners of IDUs (mostly low-income, minority women). One of the most dramatic findings of the study -- which included large surveys and in-depth interviews with 200 women in five cities -- was the prevalence of violence in these women's lives, often at the hands of a male sexual partner. "For women in currently abusive relationships," argues Gloria Weissman, the former director of the project at NIDA, "the risks of introducing condoms are very real indeed and may, in fact, be much more immediate than the risk of contracting HIV. Telling such women that they should learn to 'negotiate' with their partners is neither sensitive nor relevant advice" (Weissman, 1991).

Besides fear, complex psychological factors often keep women from raising the topic of condom use with a partner. Among such factors is the tendency of individuals to feel personally immune from risks that they readily acknowledge for others. This type of denial is especially dangerous in the realm of sexuality, where strong emotions often supersede the tug of reason. Many a

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\* Based on an evaluation of the original 63 interventions, NIDA has developed a model AIDS prevention program for women, which was further tested at five locations during 1992. The new model emphasizes women's empowerment, both within relationships and within society at large, and includes a new research instrument that examines in detail the nature of women's relationships and the impact of sexual and physical abuse on women's risk-taking behavior.

teenage pregnancy has been born of the belief that only "other people" get pregnant, or "it can't happen the first time." Likewise, many a married woman has undoubtedly clung to the belief that her partner is faithful, even when evidence suggests the contrary. A study of women's risk perception in Mexico, for example, found that while two-thirds of women thought married women should use condoms because Mexican men have affairs, the vast majority of women did not perceive themselves to be personally at risk (Del Rio et al., 1991). The understandable need women have to believe that their partners are faithful works to their disadvantage, especially in cultures where male infidelity is the norm.

#### Difficulties in Gaining Male Compliance

The obstacles to discussing the use of condoms can be formidable, but even when the issue is raised, women often face entrenched male resistance to their use. Because women are often dependent on men economically and socially, they have little leverage for gaining male compliance (Mushingeh, Chama, and Mulikelela, 1991). The more limited the options a woman has outside of a particular relationship or sexual encounter, the less she can afford to lose her partner or her paying customer. A woman's cultural conditioning may also limit her ability to assert dominance in the sexual realm, a domain largely controlled by men in most parts of the world. Likewise, "negotiating" condom use requires behaviors, expectations, and attitudes that are foreign to women who have been socialized to be deferent to male authority and control. As the consensus statement from the First International Workshop on Women and AIDS in Africa observes: "Forces ranging from early childhood training to state laws governing marriage, divorce, and property rights, prepare women to defer to their male partners, not to instruct or oppose them...especially in the context of marriage [quoted in Ulin, 1992]."

Indeed, it is clear from conversations with women in both

the industrialized and developing worlds that many feel unable to influence their partner's behavior with respect to condom use. In focus-group discussions, women in rural South Africa felt it was a "waste of time" to bring up condom use with their husbands; they strongly emphasized the need for a preventive method they could use without their partner's knowledge (Karim, 1992). Partners of injection drug-using men in New York City expressed similar frustration at being made to feel responsible for men's sexual behavior. "The men decide what is going to happen sexually," they said. If the staff wanted men to wear condoms, they would have to talk to the men (Worth, 1989). And in Rwanda, when women were counseled on HIV infection and encouraged to try prevention, three-fourths of participants opted for a method that they could use themselves without their partner's cooperation (nonoxynol-9 foam or cream). Only one-fourth decided to try condoms (Allen et al., 1988).

Consistent condom use appears to be difficult to maintain even with substantial outside support and counseling. In Zaire couples where one partner had HIV infection needed frequent home visits as well as clinic counseling to help them use condoms regularly. Despite intensive counseling, infection or pregnancy occurred in nearly 10 percent of couples followed for six months or more (Kamenga et al., 1991). Likewise, in Mexico AIDS educators found that HIV-infected homosexual men needed at least three months of weekly support-group sessions to encourage and sustain condom use (Rossi et al., 1989). These studies suggest the magnitude of the task women face in negotiating consistent condom use each and every time they have sex.

This is not to say that all women are powerless in sexual situations that put them at risk. Kline and colleagues (1992) report that many of the low-income, minority women they interviewed in New Jersey were able to exert considerable power in their relationships by withholding sex if a partner refused to use condoms. Generally, these women were involved with drug-using men who contributed little to the family's economic

support.

Orubuloye and colleagues (1992) also report that among the Yoruba of southwest Nigeria, women have been able to refuse sex, without violent reprisal, if their partner is known to be infected with a traditional STI. (Only 36 percent of women said they would consider using a condom in place of abstinence). The authors note that Yoruba women have certain advantages when it comes to controlling their sexuality; they tend to be financially independent, their families welcome back wives in cases of conflict, and they traditionally have had the role of enforcing abstinence during pregnancy, menstruation, and up to two years postpartum. Polygamy and a tolerance of male infidelity also mean that men can seek pleasure elsewhere. The authors note, however, that refusal is likely to be tolerated only until the man is treated. Long-term refusal, as would be required by HIV infection, "would likely result in the husband driving away the wife...or becoming threatening or violent, in which case the wife would leave."

Several studies have shown that sex workers seem to have more leverage than women in the general population when negotiating condom use, probably because bargaining is already an explicit part of the sexual encounter and the balance of power is more equal between buyer and seller. Most peer-education programs for sex workers have shown that condom use can increase substantially if women are educated about their risk and taught how to use condoms properly (Plummer et al., 1988; Monny-Lobe et al., 1989; Liskin et al., 1989). But here too, women experience difficulty getting clients to comply. Six separate studies reported at the Fifth International AIDS Conference found that the main reason sex workers did not use condoms was male refusal (Liskin et al., 1989). Even after extensive role-playing concerning how to overcome client resistance, for example, only one-third of sex workers in the Dominican Republic were able to get all 10 of their previous clients to use condoms (Rosaria, Pareja, and De Lister, 1988).

As a consequence, many AIDS prevention programs in developing countries have begun to place greater emphasis on targeting men. This is a welcome shift from placing all responsibility for changing male behavior on women. It would be a mistake, however, to switch entirely away from educating sex workers and other women to programs targeted exclusively at men, a response that could evolve from disillusionment over women's ability to influence their partner's sexual behavior. Such a wholesale shift would leave women unacceptably exposed. AIDS prevention programs must reach out to both men and women to be successful.

#### Other Impediments to Condom Use

It is not always men, however, that stand between women and condom use. Among women, the fact that condoms prevent pregnancy is also a major barrier to their use. In many cultures, childbearing is a woman's only route to status, and having children is an important way for women to gain power within the narrow political realm of the family. Pregnancy is often the primary motivation for sex: "If a man uses a condom on me, I cannot even become pregnant, and what is the use of sex without conceiving?" asked a key informant in the Zambia study cited above (Mushingeh, Chama, and Mulikelela, 1991). Likewise, in Kinshasa, Zaire, despite the well-recognized risk of infection, the desire to have children was the single most common reason women gave for not using condoms (Panos Institute, 1990).

Also operative in women's resistance to condoms appears to be the symbolic significance of unprotected sex -- a sign of intimacy with which condoms interfere. One of the strongest and most consistent findings to emerge from AIDS research to date is that women and men alike have proven far more willing to use condoms with prostitutes, clients, or casual sex partners than with steady lovers or spouses (Handwerker, 1991; Bossio et al., 1990). Similarly, sex workers who regularly use condoms in their profession have proven unwilling to introduce them into their



private lives (Liskin et al., 1989; Worth, 1989; Hooykaas et al., 1989). This appears to be related to the need to distinguish work or recreational sex from relationships that have more emotional significance. In many different contexts, a willingness to engage in unprotected sex has become a cultural marker of intimacy (Cohen, 1989).

Moreover, like men, women can find condoms unpleasant because they reduce sensation and interfere with notions of spontaneous or "natural" sex (Kline, Kline, and Oken, 1992; Mushingeh, Chama, and Mulikelela, 1991; Del Rio et al., 1991). As one female informant noted in the study of sexuality among fish traders in northwestern Zambia: "If there is no sperm, I can't enjoy sex. If I am in love with you, I have also accepted the risk of disease - even death" (Mushingeh, Chama, and Mulikelela, 1991). Similar concerns about interrupting the passionate flow of lovemaking have been mentioned by low-income, minority women in the United States (Kline, Kline, and Oken, 1992). Elsewhere, female sex workers have expressed dislike for condoms because they prolong intercourse, which can lead to painful and dangerous friction sores (Pyne, 1992). Clearly, a "condom-only" approach to AIDS prevention must overcome resistance on the part of both women and men.

### **C. STI Control as an AIDS Prevention Strategy**

Recently, the strategy of preventing and controlling other sexually transmitted infections has been accepted as a major component of the global AIDS response. After considerable debate, most researchers now agree that STIs, particularly genital ulcer diseases, significantly augment the sexual transmission of HIV (Laga, 1992a). In fact, a recent review suggests that, on a population basis, much of the risk of HIV transmission in Africa may be attributable to the presence of other STIs (Berkley, 1991). Many programs have thus come to see STI control as a priority public health intervention in the fight

against AIDS.

Prior to the AIDS era, STI control programs were among the most poorly funded of all health-sector activities. Strengthening district, state, and national STI control programs will require additional resources to train providers, establish diagnostic facilities, and develop clinical infrastructure. Given these challenges and existing resource constraints, initial efforts at improved STI control have been highly targeted, concentrating primarily on "core" groups, such as sex workers, their clients, and men with repeated STIs. A programmatic bias toward targeting has been reinforced by econometric modeling that suggests that targeted interventions are considerably more cost-effective (in terms of "healthy years of life saved") than broad-based efforts aimed at the general population (Over and Piot, 1992). In keeping with this logic, the bulk of STI investment has gone toward improving the existing network of STI clinics (whose clientele are primarily men and, in some settings, sex workers) and establishing new services for reaching these core groups.\*

While such highly targeted efforts may make sense in the short term, given existing resource constraints, the long-term reproductive health of women and men depends on a commitment to promote an expanded development budget that affords reproductive health services, including routine STI screening and treatment, the priority it deserves (Sewell et al., 1992). Ideally, STI services for women in the general population will need to be integrated with other health services, because women are seldom

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\*An interesting and potentially important exception to this rule is the innovative strategy of providing STI treatment through social-marketing approaches currently being initiated by Population Services International (PSI). In a demonstration project in Cameroon, PSI is developing an STI "kit" containing antibiotics, educational materials, and condoms, which will be marketed for men through existing private-sector distribution channels. These kits will include information regarding the need to refer female partners for clinical evaluation (Population Services International, 1992a).

willing to endure the stigma attached to attending an "STI clinic." The development of integrated services, in turn, will require reorientation of service providers, improved clinical facilities, and practical research aimed at identifying effective and sustainable service models (Elias, 1991).

As outlined in the proceedings of a recent meeting on reproductive tract infections,\* cosponsored by the International Women's Health Coalition and the Rockefeller Foundation, the establishment of adequate services for the recognition and appropriate treatment of STIs in women will require a significant investment of resources (Germain, 1991). This investment is essential, given the considerable morbidity and mortality that women experience as a result of these infections. While the AIDS epidemic has attracted global attention, in most parts of the world reproductive tract infections caused by pathogens other than HIV still account for the bulk of reproductive morbidity suffered by women (Wasserheit, 1989; Liskin, 1992).

Given the current economic and political climate, however, it appears unlikely that governments will commit to the type of expanded budget that would allow for the development of comprehensive reproductive health services capable of reaching the majority of the world's women. As a result, it is unlikely that most women will directly benefit in the short term from the "STI control" measures currently promoted as part of the global AIDS prevention strategy.

This reality creates an even greater urgency to develop

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\*The term "reproductive tract infection" refers to sexually transmitted infections of the female reproductive tract, infections that may be transmitted nonsexually (such as those caused by the overgrowth of organisms normally found in the genital tract of healthy women -- e.g., bacterial vaginosis and candidiasis), and iatrogenic infections (such as those caused by unsterile abortion and delivery procedures). Given that sexually and nonsexually transmitted infections of the reproductive tract often present with similar clinical syndromes (e.g. vaginal discharge, itching, or lower abdominal pain), the broader term more accurately describes women's need for clinical services.

effective microbicides that can be made widely available through commercial channels. Of course, political pressure must be maintained on both fronts -- to develop microbicides and to increase greatly national and international funding for reproductive health services. After all, the unacceptable state of women's health services and the "orphan" status of microbicide development result from the same underlying dynamic -- a development agenda that is not sufficiently considerate of women's needs.

### **III. STRENGTHENING WOMEN'S ABILITY TO PROTECT THEMSELVES**

As the previous section demonstrates, the existing strategies for AIDS prevention are of limited utility to many of the world's women. Women often have too little power within their relationships to insist on condom use, and they have too little power outside of these relationships to abandon partnerships that put them at risk. What can then be done to reduce women's risk?

Ultimately, empowering women to have more control over their sexual lives will require a fundamental change in the dynamics of male/female relations and a concerted effort to eliminate the inequities that leave women economically dependent on men. In large measure, women's vulnerability to HIV infection derives from their low status in society. Reducing their vulnerability will mean changing the cultural beliefs and gender stereotypes that perpetuate the belief that women are inferior to men.

Empowering women will also require redefining what it means to be male. In many societies, the right to dominate women is considered the essence of maleness itself. Culturally created norms tolerate, indeed encourage, sexual behavior by men that puts both them and their partners at risk. New norms must be established -- through education and advocacy -- that stress mutuality, responsibility, and equality between men and women.

By its very nature, however, this type of fundamental social

change takes time -- time that women at risk of HIV today do not have. The AIDS epidemic therefore creates two imperatives: to begin in earnest to work on changing the underlying causes of women's vulnerability and to pursue vigorously every means possible to strengthen women's immediate ability to protect themselves in the face of the economic and cultural forces that are currently allied against them. This latter mandate, in turn, involves two priority tasks: 1) placing a greater emphasis within existing AIDS programs on empowering women; and 2) developing HIV prevention technology that is within the personal control of women.

#### **A. Long-Term Approaches to Reduce Women's Vulnerability**

Advocates working toward women's empowerment have come to distinguish between efforts that address women's strategic gender needs (i.e. those that seek to transform society and male/female relations) and women's practical gender needs (i.e. what women need for survival today given the reality of their roles and status) (Moser, 1989). Constructive social change requires both, as does any effort to respond to the AIDS prevention needs of women. The limitations of the existing AIDS prevention strategies, described above, argue strongly for the development of a female-controlled prevention method. Without a concomitant dedication to addressing the inequalities that underlie women's risk, however, a new prevention technology could become a "technological fix" that allows male dominance to continue unchallenged. It is important to remember that it is women's subordination that is their primary risk factor for HIV (Hamblin and Reid, 1991).

Strategic efforts toward establishing gender equality are many, including the revision of laws and labor codes to guarantee women the right to own and inherit property, earn salaries on a par with men, and have equal access to credit and training. These efforts also include promoting female education, educating women concerning their rights, changing the cultural beliefs and

biases that denigrate women and value boy children over girls, and helping women organize on their own behalf. Until women become part of the dialogue that establishes policy and distributes resources, women's issues will remain vastly underattended. And until women share power more equally with men -- in both the public and the private sphere -- they will remain at heightened risk of AIDS.

#### **B. Changing Current Programs to Strengthen Women's Position**

Short of transformational change, there is much that can be done to empower women within existing AIDS prevention programs. Promising projects in Thailand, the Dominican Republic, and Nigeria, for example, have helped sex workers enforce condom use by improving their assertion and negotiation skills, implementing "condom-only" policies in brothels, and giving women more power through self-organization (Bruyn, 1992). A project in Calabar, Nigeria has helped sex workers change the basic economics of their trade (Buchan, 1992). Together, these women decided to raise their fee for sex simultaneously so that they could afford to refuse clients who would not use condoms. Project organizers also persuaded hotel owners not to raise the price of the rooms that the women use for clients, arguing that "safe sex" was in the owner's long-term financial interest. The project, which was started by a group of volunteers, is now largely self-supporting, with the women themselves taking over most of the organizing functions.

The key to the Calabar project's success is that it built upon women's capacity for collective action. Women throughout the world have a history of rallying together to solve common problems -- a strength that has yet to be widely utilized by AIDS prevention programs. As behavioral scientist, Priscilla Ulin (1992), observes, "Women's collective perception of their ability to act on AIDS prevention messages could be a critical determinant of both male and female behavior change." To date, there has been little effort to initiate dialogue among women

about the strategies they have used successfully to change their own or their partners' behavior. Nor have most projects sought to organize women to exert collective pressure on men to change their ways. Examples abound, however, of instances where, through collective action, women have managed to affect and change male behavior (e.g., successful campaigns against male alcoholism in India and community policing against wife battering in Peru) (Kanhere, 1980; Isis International, 1987).

Elsewhere, projects that seek to empower women have learned that it is impossible to deal with a woman's HIV risk divorced from the other issues in her life -- relationship problems, drug use, lack of job skills. Groups like PROTOTYPES in Los Angeles and AWARE in San Francisco help women take charge of their lives one step at a time. PROTOTYPES, for example, uses peer educators -- other women who have turned their lives around -- to reach out to injection drug-using women and partners of injection drug users (Reback, 1992). Women are invited to join the project's program, which includes six months of one-on-one counseling, as well as group workshops that allow women to share experiences, build self-esteem, and learn new skills through role plays. Recognizing that HIV risk is exacerbated by underlying dependencies, PROTOTYPES also runs a residential program where women can live with their children for up to a year and receive drug treatment and vocational training in computer science.

The AWARE program also uses peer counselors, but they work on the streets in poor neighborhoods. The program provides special support, health and sex education, and free comprehensive health examinations. Staff also provide referrals and advocacy for women needing access to specialized health care and other treatment programs. Although many of AWARE's participants have remained in high-risk relationships, their ability to use safer sex practices has significantly increased, and, as of 1992, only one woman had become infected with HIV since the program began in 1986 (Dorfman, Derish, and Cohen, 1992).

### C. Developing New Prevention Technologies

The challenge of microbicide development is historically analogous to the development of female-controlled contraceptive technology 40 years ago. Although the development of female-controlled methods, like the pill, was not sufficient in itself to address women's need to control their fertility comprehensively, it did provide an essential tool that allowed many women to reduce their risk of unwanted pregnancy.

There are many important lessons from contraceptive development that bear on the search for new HIV prevention technologies. One is the general principle that increasing the range of contraceptive methods available to women improves overall use (Jain, 1989). In family planning, expanded method choice affects use both by recruiting new users and by facilitating the continuation of contraceptive use over time.\* The availability of multiple methods means that more women will find at least one that meets their particular needs.

A similar dynamic can be expected to apply to technologies for the prevention of HIV. Women differ in terms of their childbearing aspirations and the nature of their sexual relationships. Even within a single relationship, sexual encounters may vary across time (i.e., from voluntary, consensual intercourse to violent, coercive sex when a partner arrives home drunk). All of these variables affect the type of prevention method that may work for a woman in a particular setting. As

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\* In a recent review of the literature, Jain (1989) found that the widespread addition of one new method of contraception to a country's family planning program increased the number of couples practicing contraception by 12 percent. In addition, data from Bangladesh show that two-thirds of women still practicing contraception 18 months after acceptance had switched methods (Bhatia et al., 1980). In the Philippines, 34 percent of acceptors still contracepting at 24 months had switched methods at least once (Laing and Alcantara, 1980). Women switched methods because of unpleasant side effects or because their life circumstances changed. If alternative methods had not been available to accommodate these changes, many women would likely have discontinued family planning altogether.



with avoiding unwanted pregnancy, we must recognize that the sexual encounter is the most relevant focus for prevention strategies. In many cases this is more important than a more general focus of "high-risk" relationships. Whereas a condom may be used for some encounters or with some partners, other situations may require more secrecy. Indeed, for many nonconsensual encounters, a method that can be used after intercourse might be required. As with contraceptive choice, the availability of multiple methods would help ensure that at any given time, at least one method would be available and be used (Bruce, 1990).

Another important lesson from the history of contraception is that new technologies, especially when they are the first of their kind, have a capacity to help crystallize social movements. The introduction of "the pill" in the early 60s helped to usher in and validate a whole generation of new expectations. As the first simple and effective female-controlled contraceptive, it assisted in bringing about and consolidating social discussion of women's entitlement to control their own fertility. An important role of technology in a postmodern society is to focus social discourse.

In the area of AIDS prevention, the introduction of a female-controlled technology could serve a similar function, focusing attention on the protection needs of wives and adolescent girls. As discussed in the foregoing sections, many AIDS prevention programs have focused almost exclusively on sex workers and, more recently, their clients. The failure to reach out to other women does not necessarily reflect a lack of concern; rather, it derives from a profound pessimism regarding women's ability to change the behavior of their sexual partners. In short, current programs take women's powerlessness as a given, and therefore fail to include them. The availability of a female-controlled microbicide, however, would incite a discussion regarding its use and accessibility by all women, thus creating an incentive and a demand to throw the prevention net more

widely. In this way, rather than being a substitute for the empowerment of women, a new technology might be a tool for such empowerment.

A final lesson from the contraception field returns us to the first point of this section. Practical solutions to women's vulnerability cannot be pursued in isolation from the longer term strategic needs of women for societal change. Several decades after the development of highly effective female-controlled contraceptive technologies, many of the world's women remain at risk of unwanted pregnancy and its complications. This reality reflects a lack of political will to invest in health care, to improve the status of women, and to make abortion legal and safe, as well as an often too-narrow focus on the introduction of new technology without adequate attention to provider training, client education, and the development of appropriate counseling services. Similarly, a female-controlled microbicide will not be a "magic bullet" that eliminates the need for fundamental social change. A technology for women, however, is an essential element of any viable global response to AIDS.

#### **IV. FEMALE-CONTROLLED HIV PREVENTION TECHNOLOGY: CURRENT OPTIONS**

Most women are at greatest risk of acquiring HIV infection through heterosexual vaginal intercourse with an infected man.\* To avoid infection a prevention method must establish an effective barrier between the infectious elements in the male

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\* On a per-exposure basis, unprotected anal intercourse appears to be more likely than vaginal intercourse to result in HIV transmission from man to woman (European Study Group, 1992). Anal intercourse is a common sexual practice among homosexual men, as well as heterosexual men and women (Bolling, 1977). In some communities it is commonly substituted for vaginal intercourse as a means of fertility regulation. Given very different biological considerations (for example, radical differences in pH and normal flora), potential microbicides would have to be separately formulated and evaluated for safe use intrarectally. Although we do not address the biology or clinical testing of rectal preparations in this paper, we recognize that this is an extremely important area for future research.

genital secretions/ejaculate and those cells of the female reproductive tract susceptible to infection. Such a barrier might be physical (such as that provided by condoms), chemical (such as that provided by an intravaginal microbicide), or immunological (such as the mucosal immunity that might result from an effective vaccine). Ideally, such a barrier would be selective, providing effective protection against HIV and other sexually transmitted infections without impairing a woman's ability to conceive. Such an ideal barrier could be combined with a spermicide (or another method of birth control) for use when contraception was explicitly desired.

As discussed below, a large number of unanswered questions remain regarding the biology of heterosexual HIV transmission. For example, does transmission result from the free virus or cell-associated virus found in semen? Which cells in the female reproductive tract are most susceptible to infection? Are all mucosal cells susceptible? What is the role of vaginal pH? Answers to these and other questions are needed to define more precisely the required characteristics of an effective barrier, as well as the feasibility of identifying methods that are noncontraceptive. This section reviews the current, somewhat limited, state of knowledge regarding existing female-controlled options for preventing the sexual transmission of HIV infection. The subsequent section outlines the major issues and challenges to be faced in broadening women's options for exercising personal control over their risk of HIV infection.

#### **A. The "Effectiveness" of Female-Controlled Prevention Methods**

One might assume that a vaginal microbicide -- a chemical barrier -- would be less efficacious in preventing HIV transmission than a condom -- an impermeable physical barrier. But when considering HIV protection, it is important to distinguish between the theoretical effectiveness of a method and the level of protection it achieves in real life. As in the case

of contraceptives, an HIV prevention technology that is highly efficacious in the laboratory may be only moderately effective in preventing transmission, because couples fail to use it properly or consistently. Even the best barrier cannot prevent infection if it is not used.

This distinction -- known in the contraceptive field as the difference between "theoretical effectiveness" and "use effectiveness" -- has important implications for AIDS prevention.\* Under ideal conditions, for example, condoms have been shown to be highly effective physical barriers for preventing the transmission of a wide range of sexually transmitted pathogens, including HIV. In other words, condoms appear to have a high theoretical effectiveness (Centers for Disease Control, 1988; Rietmeijer et al., 1988). Under actual use, however, there is reason to believe that condoms might be less effective in preventing HIV transmission, despite their higher theoretical effectiveness, than would female-controlled methods. By virtue of being female-controlled, methods such as contraceptive sponges and vaginal spermicides *have the potential to be used in a greater percentage of sexual encounters*, thereby achieving a greater long-term use effectiveness than condoms (Stein, 1990).

Indeed, the results of a recent retrospective study of STI transmission in a Denver STI clinic reflect just such a conclusion (Rosenberg et al., 1992). Employing a comparison group consisting of women using no contraceptive or with tubal ligations, Rosenberg et al. compared the rates of reproductive tract infection among users of condoms, diaphragms, and sponges as a means of contraception. Users of all three barrier methods

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\* **Theoretical effectiveness** refers to the effectiveness of a particular method when used perfectly. **Use effectiveness** refers to a method's effectiveness under real life conditions and reflects failure to use the method, as well as its inherent limitations. In epidemiological terms, theoretical effectiveness refers to a method's efficacy.

had lower rates of infection with Neisseria gonorrhoeae, Trichomonas vaginalis, and Chlamydia trachomatis when compared to controls.\* More significantly, users of sponges and diaphragms had a lower risk of gonorrhea and trichomoniasis than did condom users, even after adjusting for age, race, partner exposure, symptoms, and history of prior STI. The adjusted odds ratios were 0.45 [95% C.I. 0.22 - 0.92] and 0.33 [95% C.I. 0.17 - 0.64], respectively. While the Denver study did not address HIV infection directly, its findings provide strong circumstantial evidence that a female-controlled microbicide would play a significant role in averting such infection, even if it were less efficacious than condoms on a per-exposure basis (i.e., had a lower theoretical effectiveness). This dynamic would be most prominent among vulnerable women who are least able to negotiate condom use with their partners.

Another retrospective study among U.S. prostitutes showed that use of a spermicide and/or diaphragm was associated with a markedly decreased risk of Hepatitis B virus (HBV) infection in some groups of women, specifically black and Hispanic IDU sex workers (Rosenblum et al., 1992). This association was not found in all groups of sexually active women at risk of HBV infection, however. Also, in a recent prospective randomized controlled trial, although the use of spermicide containing nonoxynol-9 was found to be protective against cervical infection, this effect was only noted in women with >75 percent compliance (Niruthisard, Roddy, and Chutivongse, 1992). In the same study, condom use was found to be partially protective at lower levels of compliance. The strengths and weaknesses of these findings, along with conflicting views regarding their public policy implications, have recently been presented in a series of commentaries in the American Journal of Public Health (Stein, 1992; Rosenberg and

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\* These lower rates reached statistical significance only for N. gonorrhoeae and T. vaginalis, given the generally low incidence of C. trachomatis infection.

Gollub, 1992; Cates, Stewart, and Trussel, 1992).

#### **B. The "Vaginal Pouch" or "Female Condom"**

One new technology designed to expand women's options for preventing HIV infection is the "vaginal pouch" or "female condom," now available in Switzerland and the United Kingdom. There are currently three such products, including two latex devices and a polyurethane sheath. The vaginal sheath (to be marketed as Reality® in the U.S. and Canada and as Femidom® in other countries) has received the most extensive evaluation to date (Bounds, Guillebaud, and Newman, 1992; Liskin and Sakondhavat, 1992). This sheath is made of soft polyurethane with a flexible ring at each end. The smaller ring is used for insertion, much like a diaphragm, but without the need for individual fitting. The larger, more flexible, ring hangs outside the vagina (Townsend, 1991).

Like the male condom, the vaginal sheath attempts to prevent HIV infection by providing an impermeable physical barrier. Indeed, by providing more complete coverage of the vulva, this device may theoretically provide greater protection than standard male condoms. While the vaginal sheath has been shown to be impermeable to HIV in laboratory testing (Drew et al., 1990; Leeper, 1990), there are yet no clinical data that evaluate its effectiveness in preventing HIV transmission in real life (Feldblum and Fortney, 1988). Initial studies indicate that its use effectiveness as a contraceptive method is comparable to that of the male condom (Trussel and Kost, 1987). In a recent study, 100 self-selected women used the device as their sole method of contraception for 437 person-months of observation and had a failure rate of 15 percent at 12 months (Bounds, Guillebaud, and Newman, 1992). There were seven conceptions, of which four were associated with inconsistent use. The remaining three appeared to be true method failures.

Preliminary field trials have also shown the vaginal pouch to be effective in preventing the transmission of some common

STIs (Shangold, in press). In one trial, women were given the female condom and instructed in its use following treatment for trichomonas or chlamydia. Consistent users showed substantially lower reinfection rates than did intermittent or nonusers. This study, together with the laboratory data and the results of the contraception trials, suggest that the female condom will serve as a reliable barrier to HIV and other sexually transmitted pathogens. In December 1992, an advisory committee of the U.S. Food and Drug Administration recommended that the device be approved for use in the U.S. with labeling indicating it has the potential to prevent both pregnancy and sexually transmitted infection (Wisconsin Pharmacal, 1992).

Despite this high theoretical effectiveness, there are several reasons to doubt whether the vaginal sheath will greatly expand women's control over their HIV infection risk. Acceptability studies have shown that a substantial number of users (both male and female) indicated that they would use the method again, but the majority stated a preference for male condoms (Liskin and Sakondhavat, 1992). Men and women cited physical discomfort during intercourse, objectionable noise, slippage into the vagina, and unaesthetic appearance as barriers to use. Moreover, because the female condom still requires male cooperation and consent, it does not fulfill women's need for a surreptitious method. In the Kenya acceptability study, men's objections were the major reasons why 40 percent of the women discontinued use after the first three weeks of the study (Ruminjo and Steiner, 1991). The investigators of the largest acceptability study, conducted in the United Kingdom, concluded that "although the majority of study participants did not find the product acceptable, we can confirm the existence of a sub-population of sexually active couples who like this new contraceptive and if it were available would continue to use it" (Bounds, Guillebaud, and Newman, 1992).

Beyond the acceptability issues, concern exists that the projected cost of the sheath will make it unavailable to the

majority of the world's women. When it comes to market in the U.S., Reality® will be priced in the range of \$2.00 to \$2.25 per sheath, more than three times the current price of male condoms. The cost of this method will be prohibitive to most women, especially in developing countries, unless a substantially reduced public-sector price can be negotiated. Public subsidies of this new method, however, will have to be balanced directly against the current needs for expanding the procurement and distribution of male condoms.

An additional concern relates to the still unquantified risk associated with reuse of the female condom, a possibility made more likely by its high cost, as well as the greater durability of the thicker polyurethane sheaths compared to typical latex male condoms. A small minority of women in the acceptability studies reported reusing the sheath, including some sex workers who did not clean the sheath between clients (Monny-Lobe and Joanis, 1991; Ruminjo and Steiner, 1991). There are currently no data on breakage rates associated with reuse of the product or on the risk of facilitating STI transmission in the absence of careful washing (Liskin and Sakondhavat, 1992).

In conclusion, it is clear that the female condom is not the final answer to women's need for an expanded range of HIV prevention technologies. This device is female-applied; however, because male consent and cooperation are required, for many women it will not be sufficiently "female-controlled." Nevertheless, for a small subpopulation of women and couples, it may provide an additional, acceptable method of protection against both unwanted pregnancy and sexually transmitted infection. Given the limited options currently available for these purposes, the importance of this incremental addition to the range of HIV prevention technologies should not be understated. In addition, it must be remembered that the current devices are essentially prototypes and, therefore, there is still much room for improvement in design. Subsequent generations of vaginal sheaths may prove acceptable to a broader range of women and couples.



### C. The Controversy over Nonoxynol-9

At present there are only two spermicides approved for use in the United States, nonoxynol-9 and octoxynol-9. Nonoxynol-9 is the active ingredient in the vast majority of over-the-counter contraceptive products, including diaphragm jelly, vaginal suppositories, and the Today® sponge. Since the early days of the AIDS epidemic, public health workers have suspected that nonoxynol-9 in its various preparations might offer some protection against HIV infection. Researchers have shown that nonoxynol-9 kills a wide variety of STI pathogens *in vitro*, including HIV (Alexander, 1990; Hicks et al., 1985; Voeller, 1986; Malkovsky, Newell, and Dalgeish, 1988). Like other "biodetergent" compounds, nonoxynol-9 acts by indiscriminately disrupting cell membranes and viral envelopes. It remains unclear, however, whether the demonstrated virucidal action of nonoxynol-9 in the laboratory translates into reduced transmission of HIV to women during actual sexual intercourse.

There is considerable circumstantial evidence to suggest that nonoxynol-9 has the potential to provide women some protection from HIV. Nonoxynol-9 has been shown in a number of clinical trials, for example, to reduce the sexual transmission of common bacterial STIs, such as gonorrhea and chlamydia (Louv et al., 1988; Rosenberg et al., 1987; Niruthisard et al., 1991; Washington, Cates, and Wasserheit, 1991). Clinical trials of the Today® sponge, as well as spermicidal jelly, have reported reductions of 10 to 69 percent for gonorrhea and 25 to 40 percent for chlamydia (Rosenberg and Gollub, 1992; Centers for Disease Control, 1988; North, 1990). Other research shows that a woman can significantly augment her protection from these common STI pathogens by using a diaphragm in conjunction with nonoxynol-9 (Rosenberg and Gollub, 1992; Alexander, 1990; Cates and Stone, 1992). In one study, nonoxynol-9 plus a diaphragm reduced the incidence of gonorrhea by 55 percent as compared to a 10 percent reduction with the spermicide alone (Austin, Louv, and Alexander, 1984). The added efficacy of a physical cervical barrier makes

sense in the case of gonorrhea and chlamydia, because both pathogens infect the cervix primarily.

The relevance of these findings for HIV remains unclear, however, since different pathogens have different mechanisms of infection. For example, the role of the cervix in HIV transmission has yet to be defined precisely (Alexander, 1990). Compared to its demonstrated clinical efficacy in preventing gonorrheal and chlamydial infection, the ability of nonoxynol-9 to prevent other reproductive tract infections (including viral infections other than HIV) is less well established (Barbone et al., 1990). As mentioned above, a retrospective study of factors affecting the sexual acquisition of Hepatitis B virus revealed a beneficial effect from nonoxynol-9 in only some groups of at-risk women (Rosenblum et al., 1992). It has also been suggested that nonoxynol-9 may reduce a woman's risk of developing cervical cancer, a disease associated with certain strains of the human papilloma virus and widely considered to be sexually transmitted (Peters et al., 1986). Likewise, in animal models, researchers have shown that nonoxynol-9 applied intravaginally in macaque monkeys can provide at least partial protection against infection with the simian immunodeficiency virus (SIV), an animal retrovirus. In one experiment, only 7 out of 12 female macaques became infected after receiving almost 1000 times the viral load normally found in the ejaculate of infected monkeys\* (Miller et al., 1992). Few other studies, however, provide direct evidence of the ability of nonoxynol-9 to prevent viral transmission.

In the last five years, there have been only a handful of studies designed to test directly whether nonoxynol-9 helps prevent the sexual transmission of HIV in human beings. The results of these studies are mixed and contradictory. A recent study of sex workers in Cameroon, for example, found that women who consistently used nonoxynol-9 suppositories reduced their

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\* This represents a 100 percent infectious dose in this model.

risk of seroconversion by 80 percent compared to infrequent users (Zekeng et al., 1991). This effect persisted after controlling for condom use, average number of partners per week, and other potentially confounding factors. This observational study, however, could not exclude the possibility of significant selection bias. It is possible that the self-selected group of women who consistently used the spermicide suppositories also had in common some confounding characteristic not measured or controlled for in the study that protected against HIV seroconversion.

In a similar study among discordant couples in Zambia, researchers have also documented a protective effect from nonoxynol-9. Consistent use of nonoxynol-9 suppositories resulted in a 40 percent decrease in HIV transmission to seronegative women. Again the possibility of selection bias cannot be ruled out (Feldblum, 1992).

The two studies above, which suggest that nonoxynol-9 does offer protection from HIV, contradict a randomized controlled trial among female sex workers in Nairobi that found that daily use of the nonoxynol-9-impregnated Today® sponge appeared to be associated with increased risk of HIV seroconversion (Kreiss et. al., 1992). In 1987, Kreiss and colleagues enrolled 138 prostitutes in a clinical trial and randomly assigned 74 to receive the nonoxynol-9-impregnated sponge and 64 to use a placebo suppository. All of the women received intensive counseling on the importance of using condoms in addition to the sponge or placebo, and all were given a free supply of condoms. In July 1990, however, the trial was stopped, because women using the sponge appeared to have a higher rate of HIV seroconversion than did the placebo controls. Further analysis revealed that the risk of seroconversion for sponge users was almost twice that of women using the placebo (hazard ratio of 1.7 with a 95 percent

confidence interval of .9 to 3).<sup>\*</sup> In addition, sponge use was associated with a 3.3-fold increased risk of genital ulcers and vulvitis, leading the authors to postulate that perhaps the frequent use of high-dose nonoxynol-9 increased a woman's risk of seroconversion by causing local lesions that allow the virus to enter the body more freely.

Not surprisingly, these results (which were first reported several years earlier than the Cameroon or Zambian studies) put a pall over further research into the possible usefulness of nonoxynol-9 in the fight against AIDS. Given the conflicting data, some commentators have concluded that spermicides should not be recommended to women for HIV prevention in the absence of clear evidence of preventive efficacy (Bird, 1991). Others argue that it is premature to dismiss nonoxynol-9, because the Kreiss study had design limitations that rendered its results inconclusive (Gollub and Stein, 1992; Voeller, 1992). Gollub and Stein, for example, point out that the Today<sup>®</sup> sponge used in the Kreiss study had an extremely high dose of nonoxynol-9 (1000 mg/ml) compared to other nonoxynol-9-containing products, such as vaginal creams, gels, or film, which usually contain 350 mg/ml of nonoxynol-9 or less. Also, the placebo group in the Kreiss study used a vaginal suppository instead of a placebo (no spermicide) sponge. Gollub and Stein further speculate that the irritation and ulcers could have been a function of the high dose or the sponge itself rather than of nonoxynol-9 per se. Also puzzling was Kreiss' finding that the increased ulcers were found on the vulva, not the vagina or the cervix, where one might expect to find lesions created by an intravaginal sponge.

In an editorial accompanying the publication of the Kreiss findings, Stone and Peterson further suggest that the increased

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<sup>\*</sup> A Data Safety and Monitoring Committee recommended stopping the study in July 1990 because the HIV seroconversion data available at that time, although not statistically significant, were inconsistent with any clinical benefit from nonoxynol-9 (Kreiss et al., 1992).

ulceration could be the result of selection bias (Stone and Peterson, 1992). Even though an attempt was made to assign subjects randomly to use the sponge or placebo, the women in the sponge group had a significantly greater prevalence of genital lesions (16 percent) at baseline than did women in the control group (3 percent). This finding may indicate that sponge users differed from the placebo group in regard to some important factor unmeasured by this study, such as the frequency of their exposure to partners with other, unrecognized, STIs. Such an unmeasured confounding variable might account for the increased incidence of ulcerative lesions and/or HIV seroconversion observed.

Since this early work, a number of studies have explored further the impact of nonoxynol-9 on the vaginal mucosa. Evidence has emerged to suggest that the epithelial irritation and disruption caused by nonoxynol-9 may be dose-dependent, raising the possibility that it may be an appropriate HIV prevention strategy for some women under more typical use conditions (i.e., the infrequent application of low-dose preparations), but not for high-frequency users, such as sex workers. In one study of high-frequency use, for example, women in Thailand were asked to insert four (150 mg) nonoxynol-9 suppositories a day for 14 days without having intercourse. Six of the 15 women experienced epithelial disruption of the cervix or vagina (Niruthisard, Roddy, and Chutivongse, 1991). In two other clinical trials conducted in Cameroon and Thailand, however, nonoxynol-9 suppositories, film, or gel (all containing 100 mg/ml or less) were not shown to damage the vaginal mucosa or cause genital ulcers (Zekeng et al., 1991; Niruthisard et al., 1991). Another study from the United States found no increased disruption or vaginal irritation among women using nonoxynol-9 under average conditions (five to eight times a month) (Louv et al., 1988).

Perhaps the most convincing evidence of a dose-related response comes from a study recently completed in the Dominican

Republic (Roddy et al., 1992). The study compared four groups of users to a placebo control: women who used nonoxynol-9 preparations every other day, once a day, twice a day, and four times a day. Researchers found that women using nonoxynol-9 every other day had no more epithelial disruption than did women using the placebo; those using these preparations once or twice a day experienced slightly more than twice the disruption (2.6 and 2.1 times); and those using them four times a day experienced five times the incidence of mucosal damage compared to the controls.

These results suggest that, to the extent that nonoxynol-9 does cause mucosal inflammation, micro-ulcerations, or sores, the effects may be limited to situations of high-dose and/or high-frequency use. What remains to be established is whether nonoxynol-9 offers women measurable protection from HIV in typical use and at what point the negative consequences of potentially disrupting the epithelium outweigh the positive benefits of killing the virus. It is impossible to say at this point whether a woman's risk of HIV transmission is lower in the situation where there is a totally intact vaginal epithelium and a high dose of live virus, or a low dose of live virus with some epithelial disruption.

Given the incomplete and conflicting evidence on the efficacy of nonoxynol-9, public health officials have disagreed on what should be the appropriate message to women regarding nonoxynol-9 use and HIV risk (Bird, 1991; Rosenberg and Gollub, 1992; Voeller, 1992; Rekart, 1992). In most instances, health officials have abdicated responsibility for this matter by remaining silent. The New York State Department of Health, however, has recently developed a policy that recommends a hierarchy of protection options for women (New York State Health Department, 1992). When abstinence or a condom are not feasible, the protocol suggests that women use a diaphragm and a vaginal spermicide containing nonoxynol-9. As a last resort, the policy suggests that women use nonoxynol-9 alone, although it makes

clear that this offers the lowest degree of potential protection. Such a policy recognizes the limits women often face in negotiating condom use. Given these limits, many women have already come to rely on various preparations of nonoxynol-9 as their primary HIV prevention strategy (Vermund, 1992). Clarifying the safety and efficacy of nonoxynol-9 for preventing the sexual transmission of HIV, therefore, must be a high-priority research area.

#### **D. Other Spermicides**

There are a number of other spermicidal compounds that have potential activity against HIV, as well as a range of other sexually transmitted infections. These compounds include octoxynol-9, benzalkonium chloride (Chermann et al., 1987; Wainberg and Bleau, 1987; Wainberg et al., 1990), Betadine® (Harbison and Hammer, 1989), chlorhexidine (Chantler, 1990; Chantler, 1992, Harbison and Hammer, 1989), menfegol, and gossypol (Polsky et al., 1989; Segal and Ueno, 1989). Of these compounds, only octoxynol-9 is approved in the U.S. for use as a spermicide. Benzalkonium chloride and chlorhexidine are approved as spermicides in the United Kingdom. At present, only in vitro data are available to suggest that these compounds may have the potential to be useful as microbicides. Recently, menfegol was used in a phase I trial in Senegal to assess toxicity. This trial had to be stopped early because a very high rate of inflammation and ulceration was observed (Laga, 1992b). Some evidence exists that chlorhexidine may provide better penetration into cervical mucous and retain a greater spermicidal activity once in cervical mucous than other spermicides, suggesting it could be a more effective spermicide (Sharman et al., 1986).

The importance of these data for preventing HIV infection is unknown, given current uncertainties about the precise biological mechanisms of HIV transmission. A new contraceptive sponge has recently been developed (to be marketed under the name Protectaid®) that incorporates low concentrations of both

nonoxynol-9 and benzalkonium chloride (AXCAN, 1992). Product information for this new sponge suggests that it has the ability to rapidly inactivate HIV-1 in vitro. No data from clinical tests are presented, however. Regarding gossypol, Segal and Ueno (1989) have reported on the characteristics of a preparation that might be tested as a vaginal protective cream for spermicidal and virucidal activity. A recent report of the ability of orally administered gossypol to eliminate HIV from the semen of HIV-infected men provides circumstantial evidence of its probable in vivo efficacy (Garza-Flores et al., 1992).

In addition, a considerable amount of effort is going into the in vitro screening of new compounds that are potentially microbicidal. In 1992, for example, the Contraceptive Research and Development (CONRAD) Program, a cooperating agency of USAID, assayed 131 potentially spermicidal products (40 new experimental formulations of nonoxynol-9, along with 91 materials containing a different potentially active ingredient). Fifty-six of these compounds were tested for activity against HIV in vitro, and 26 of them proved to be active. Several of these compounds are currently being evaluated in rabbit models for vaginal irritation and fertility effects. In vivo tests for antiviral activity have not yet been initiated (Doncel, 1992).

#### **E. Other Barrier Methods**

There are no data concerning the ability of other existing barrier methods (e.g., a diaphragm or cervical cap) without spermicide to prevent HIV infection, since these methods are usually recommended for use with a spermicide. There is, however, some evidence that the cervical cap may be effective as a contraceptive in the absence of spermicide (Richwald et al., 1989). Also, in a recent study of diaphragm acceptability in Brazil, investigators found that the lowest pregnancy rates occurred at the one clinical research site where women were counseled to use a diaphragm around the clock without spermicide (Ferreira, 1992). In interpreting these results, it was



suggested that when used in this manner, the diaphragm became a noncoitally-dependent method and, therefore, had a greater use-effectiveness as a method of contraception. These findings may have some relevance for women seeking to avoid cervical infections, such as gonorrhea and chlamydia, in situations where they cannot use a condom or spermicide. These data are probably of limited relevance for HIV prevention, however, given evidence that HIV transmission can occur through vaginal mucosa in the absence of a cervix (Alexander, 1991).

#### **V. CHALLENGES FOR FUTURE DEVELOPMENT OF MICROBICIDES**

Despite the rapidly increasing number of women infected with HIV and the inability of many women to negotiate condom use successfully with their male partners, there has yet to be an adequate mobilization of effort and resources for the development of prevention methods that are under the personal control of women. More than a decade into the global AIDS epidemic, we still do not have answers to some of the most basic questions regarding the biology of heterosexual transmission (Alexander, 1990; Forrest, 1991). We still do not know what to counsel women with respect to the safety and microbicidal efficacy of vaginal spermicides. And there has been virtually no discussion of the serious need for a microbicidal compound that allows conception.

Why have the needs of women been overlooked? The answer lies in a complex interplay between gender bias within the medical research community and the entrepreneurial factors that drive private-sector investment. It is now well documented, for example, that the health concerns of women have received far less than their fair share of public-sector research dollars (Society for the Advancement of Women's Health Research, 1991). In fact, only recently has the research establishment begun to acknowledge that women are at substantial risk of HIV (Correa, 1992).

The neglect of microbicide research in the public sector has been matched by an even greater disinterest among private pharmaceutical companies. Microbicides are largely perceived as

not profitable, due to the difficulty in securing patent protection for such products and an extremely complex regulatory environment. Companies also fear the costly product-liability suits that may result from a compound's inability to provide complete protection from a fatal disease despite cautionary product labeling, as well as litigation related to alleged low-level associations with birth defects. This latter issue has occasionally threatened the availability of vaginal spermicides, such as nonoxynol-9 (Mills et al., 1982; Shapiro et al., 1982). As a result, the development of a microbicide active against HIV infection will require a concerted public-sector research and development effort. This has long been the case with new contraceptive technologies (Bardin, 1987; Mastroianni, Donaldson, and Kane, 1991; Harr and Johnson, 1991).

There is an urgent need for the further testing of existing compounds and devices, as well as the innovative search for newer, less toxic microbicidal compounds. Ideally, this latter effort would include the identification of both contraceptive and noncontraceptive preparations. The following discussion outlines some of the salient issues pertaining to the development of vaginal microbicides within the personal control of women.

#### **A. Biological Issues**

A broad range of basic scientific issues relates to the development of new microbicidal compounds for preventing the sexual transmission of HIV. These range from understanding the chemical and physical properties of potential microbicides and product formulations, to defining more precisely the exact biological mechanism of HIV transmission. Although a comprehensive review of such issues is beyond the scope of this paper, this section will highlight some of the most prominent concerns.

Despite a considerable amount of research effort, much remains to be learned about the basic biology of sexual transmission of HIV (Alexander, 1990; Alexander et al., 1990).

Epidemiological studies suggest that a person is most infectious both very early and very late in the course of his or her infection. During the period immediately following infection, a person experiences high levels of virus in the blood and bodily secretions prior to the development of anti-HIV antibodies (Goudsmit et al., 1987; Stramer et al., 1989). Advanced infection is also associated with high levels of infectiousness, a phenomenon that mirrors the decline in measurable immune function (Osmond et al., 1988). Recent studies of HIV-infected men show that HIV is more commonly found in the semen of men with advanced infection (Anderson, 1992).

HIV-infected lymphocytes and macrophages are primary infectious elements in semen (Alexander, 1990; Anderson, 1992). These immune cells are abundant in normal semen and have been shown to increase in the presence of genital tract inflammation (such as that resulting from common STIs) and HIV infection (Wolff and Anderson, 1988). Significant amounts of cell-free virus have also been found in semen (Borzy, Connell, and Kiessling, 1988; Krieger et al., 1991; Anderson et al., 1992). Discerning whether HIV transmission involves cell-associated virus, cell-free virus, or both, is a critical question for microbicide development. For example, if it were convincingly demonstrated that only virus associated with immunologically competent cells, such as lymphocytes and macrophages, was capable of infecting the female reproductive tract, this would have significant implications for the types of microbicidal compounds one would pursue. In such a scenario, the virucidal action could target the infected host cells instead of the virus itself.

Some recent evidence suggests that cell-associated virus is a principal means of HIV transmission. Phillips and coworkers at the Population Council's Center for Biomedical Research have developed an in vitro model of viral transmission using a confluent epithelial cell culture (Bourinbaiar and Phillips, 1991; Phillips and Bourinbaiar, 1992; Phillips and Tan, 1992). In this model, HIV did not become associated with the epithelium

after exposure to cell-free virus. When the test was repeated with HIV-infected CD4 lymphocytes, however, these lymphocytes were soon observed in close association with the epithelial surface. Subsequent observation by electron microscopy demonstrated the directional release of mature viral particles into the space between the lymphocyte and epithelium, as well as the rapid uptake of virus by the epithelial cells. It is also well established that Langerhan's cells are present in the vagina and cervix and could be recipients of cell-free or cell-associated HIV (Hussain et al., in press; Edwards and Morris, 1985). These observations obviously do not exclude a role for cell-free virus in the transmission of HIV, however, and therefore require corroboration with in vivo studies of viral transmission.

Speculating from the above, one possible scenario is that cell-associated virus is primarily responsible for transmission across intact epithelial surfaces, but that cell-free virus can infect mucosa when present in high concentration or when epithelial surfaces are disrupted.\* Studies of discordant couples, for example, have demonstrated that older/postmenopausal women are at increased risk of HIV seroconversion (Peterman et al., 1988; European Study Group, 1992), a finding attributed to their increased risk of epithelial disruption during sex due to low estrogen levels and atrophic vaginal mucosa.\*\* This may also partially explain why HIV transmission is augmented in the presence of genital ulcerative diseases that result in mucosal disruption (Quinn et al., 1988). Further, this explanation might help with interpreting the conflicting data reviewed above regarding the safety and efficacy of currently available vaginal

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\*Data from monkey studies show that transmission can occur when high concentrations of cell-free virus are nontraumatically inoculated intravaginally (Miller et al., 1989)

\*\*Others speculate that this could be a pH effect (Voeller and Anderson, 1992a, 1992b).

spermicides in preventing HIV infection. Given the nonselective detergent properties of compounds such as nonoxynol-9, there may be a narrow range between "enough" microbicidal spermicide and "too much."

This line of reasoning suggests the need to develop more specific intravaginal compounds that prevent the attachment of HIV-infected lymphocytes to epithelial surfaces, the secretion of virus from these cells, or the uptake of virus by the mucosal epithelium, without indiscriminantly disrupting cell membranes. One such compound may be dextran sulfate, one of a class of polyanionic polysaccharides. Dextran sulfate has been demonstrated to inhibit HIV replication in vitro (Bagasra and Lischner, 1988). It has also been shown to inhibit the cell-associated transmission of HIV using the in vitro epithelial cell culture model described above (Pearce-Pratt and Phillips, 1992). This activity has been demonstrated at concentrations 100-1000 times lower than those associated with significant cytotoxicity. The hypothesized mechanism of action of these polyanionic compounds is that, by coating the epithelial surface with a highly charged macromolecular film, they may physically repel HIV and HIV-infected cells from the epithelium and thereby prevent the directional release of HIV that occurs when these infected lymphocytes attach to mucosal cells. As nondetergent compounds, polyanionic polysaccharides should have considerably less local toxicity than existing vaginal spermicides and may potentially allow conception, since they have little effect on sperm (Phillips, 1992). It should be emphasized, however, that although this is certainly a promising class of compounds to begin evaluating, no clinical data currently exist regarding their safety or effectiveness for intravaginal use in preventing HIV transmission.

Another basic issue related to the biology of HIV transmission is our incomplete understanding of the precise cells and tissues within the female reproductive tract that are infected in the course of transmission. Disruptions of

epithelial surfaces probably augment susceptibility to infection, but data from animal models, as well as case reports of infections acquired during artificial insemination, indicate that such disruption is not required for transmission to occur (Miller et al., 1989; Stewart et al., 1985). The work of Bourinbaiar and Phillips suggests that cell-associated virus may infect typical mucosal cells. But, does this happen throughout the vagina? Is the cervix a more or less susceptible site? What is the role of the upper genital tract structures, if any? Recent studies of SIV transmission in hysterectomized macaque monkeys suggest that the presence of a cervix is not required for transmission (Alexander, 1991). Given the limitations of simian animal models,\* however, this finding may not easily generalize to humans and, even if applicable, does not exclude an additional (and potentially more important) route of infection via the cervix or upper genital tract. Answers to such questions of basic biology are essential to understand fully the interactions of various contraceptive methods with HIV infection, as well as the possibility of identifying a noncontraceptive microbicide (Alexander, 1990; Cates and Stone, 1992).

Another important issue that bears directly on the feasibility of developing a noncontraceptive microbicide is the question of whether HIV infects or attaches to sperm. Several authors have suggested that HIV may become associated with sperm, either by attaching to the surface or crossing the cell membrane

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\* Because of the relatively low probability of infection resulting from a single exposure, the simian models of SIV transmission have depended on the identification of a "100 percent infectious" dose of SIV (i.e., the concentration of SIV that, when introduced intravaginally, results in infection in all cases) (Miller et al., 1989). This dose is approximately 1,000 times the usual concentration of SIV in macaque semen. When this dose was used in macaques following surgical removal of the uterus, infection was noted to occur (Alexander, 1991). Whether or not this model accurately reflects the transmission dynamics in macaques under natural circumstances could be questioned, as well as the generalization of this finding to humans.

(Bagasra et al., 1988; Scofield, 1992). Others have refuted these findings after failing to find a physical association between HIV and sperm in careful assays used to separate motile sperm from other elements of semen, as well as failure to identify HIV DNA using genetic amplification techniques on the sperm fractions of semen from more than 200 seropositive men (Anderson, 1992). Current consensus favors the lack of a significant relationship between HIV and viable sperm; but the data are by no means complete, leaving open the possibility of an uncommon, but perhaps biologically relevant association (Anderson, 1991). Obviously, a significant association of virus with sperm would make the development of a noncontraceptive microbicide extremely problematic.

Emerging data further suggest that the complex chemical, microbiological, and immunological environment of the male and female reproductive tracts may play a major role in determining the likelihood of HIV transmission. Understanding the ecology of the vaginal environment is essential for future microbicide development, because any compound introduced intravaginally has the potential to disrupt the balance of vaginal flora, pH, or immune function. For example, recent evidence has shown that the normally low pH of the vagina may be virucidal in its own right (Voeller and Anderson, 1992a,b). Voeller and Anderson have shown that at pH levels below 5.5 both HIV and HIV host cells are rapidly inactivated. Semen typically neutralizes the acidic pH of the vagina. This finding suggests that a microbicidal preparation should be formulated to include a strong acidic buffer if feasible. It also raises the possibility of developing a prevention strategy based on keeping the pH of the vagina low.

The disturbance of vaginal pH may also partially explain why nonulcerative genital tract infections have been shown to augment the transmission of HIV to women (Wasserheit, 1991). Vaginal infections, such as trichomoniasis and bacterial vaginosis, are very common and often remain unrecognized or untreated in many women (Wasserheit, 1989). These infections are commonly

associated with an alkaline change in pH (Hillier and Holmes, 1989; Rein and Muller, 1989). This suggests that the routine screening and treatment of women for these common reproductive tract infections may help reduce HIV transmission, especially in areas where heterosexual transmission predominates.

Another mechanism by which reproductive tract infections augment women's susceptibility to HIV infection is by attracting large numbers of potential "host cells" into the genital tract mucosa through the inflammatory process. Data indicate that, unlike semen, healthy female vaginal secretions contain relatively few CD4 lymphocytes and macrophages, except during menstruation (Anderson and Hill, 1991). Future preparations of vaginal compounds for use as microbicides must take into account effects on the vaginal flora. Disruption of the vaginal flora might result in subclinical inflammation or pH alteration that could potentially impair the natural defenses of the reproductive tract. The potential for such effects, for example, have recently been reported for nonoxynol-9 (McGroarty et al., 1990a; 1990b).

A final set of issues crucial to microbicide development relates to the mucosal immunity of the male and female reproductive tracts. In addition to the systemic immune defenses of the body, most mucosal surfaces exhibit immune protection against potential pathogens through the local activity of immunologically competent cells and the secretion of antibody that prevents primary infection of epithelial surfaces. Currently, very little is known about the local immunity of the reproductive tract (Forrest, 1991; Anderson and Pudney, 1992). The data that do exist on women suggest that the mucosal secretory immune system of the endocervix provides a primary immune defense against lower reproductive tract pathogens, primarily through the local production of Immunoglobulin A (IgA) (Anderson and Hill, 1991; Rebello, Green, and Fox, 1975; Underdown and Schiff, 1986).

The majority of people acquiring HIV today are infected by



mucosal exposure to cell-free or cell-associated virus through heterosexual contact. The most pressing question, therefore, is whether candidate vaccines, many of which are primarily targeted to stimulate systemic immunity, will provide an adequate immunological barrier at the mucosal surfaces of the reproductive tract. Experience with other mucosal pathogens suggests that there may be a fair amount of segregation between the systemic and secretory immune systems. As highlighted in a recent review, "systemic immunity alone may not be adequate to interrupt the heterosexual transmission of HIV" (Forrest, 1991).

This uncertainty provides an important reason to pursue microbicide development even in the face of possible advances in vaccine research. While much insight has been gained through vaccine research, it is clear that there are no extremely promising pre-exposure vaccine candidates in the offing at present (Harvard AIDS Institute, 1992). Further, most candidate vaccines nearing clinical trials in humans may affect only systemic immunity. Therefore, even if one of these should prove effective against blood-borne transmission of HIV (e.g., through sharing contaminated needles), there is no assurance it will offer women protection against infection through vaginal intercourse. Women may still need a microbicide even after the first generation of vaccines becomes available.

Indeed, microbicide and vaccine research should be seen as mutually reinforcing. It may turn out, for example, that to be most effective, HIV vaccines will have to be administered mucosally. Although it may be possible to consider administering such vaccines orally, it may also turn out that such vaccines would need to be delivered intravaginally, in which case experience gained with microbicidal agents regarding vehicles for their storage, formulation, and dispersal may be highly relevant. Also, given that the design of clinical efficacy trials for microbicides and vaccines share some important similarities, there may be significant opportunity for combined or sequential testing of these prevention technologies. For example, the

vaccine trials branch of the National Institute for Allergy and Infectious Disease is actively considering the benefits of expanding its research infrastructure developed for vaccine evaluation to include the testing of other prevention measures, including microbicides (Vermund, 1992).

## **B. Issues of Clinical Testing**

One of the most common concerns expressed about microbicide development is that it would be impossible to design clinical trials that are both scientifically valid and ethically defensible. Although clearly a complex and costly endeavor, the task of testing a candidate microbicide is both feasible and considerably less problematic than testing a vaccine\*. Below we explore some of the more salient issues around the design of clinical trials for a female-controlled microbicide.

Before entering human testing, a candidate compound would go through standard testing for toxicity in rabbits and rats, as well as efficacy evaluation in a simian species. With minor modification (i.e., the addition of efficacy testing in a simian species), the typical product-development sequence for a new contraceptive could be applied to the pursuit of new microbidental compounds. The sequence of preclinical, animal testing required for evaluation of new intravaginal compounds, as well as the simian models for retrovirus transmission, are discussed elsewhere and will not be reviewed here (Chvapil et al., 1980; Miller et al., 1992). The preclinical evaluation of potential compounds will obviously require serious attention to the potential mutagenicity of vaginal compounds, especially those that are noncontraceptive.

Following successful testing in vitro and in animal models, a carefully selected group of potentially microbidental compounds

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\*Vaccine evaluations will require the establishment of a testing infrastructure that can answer the question of how long immune protection lasts once established (i.e., how many months, years, or decades of protection does a candidate vaccine provide?).

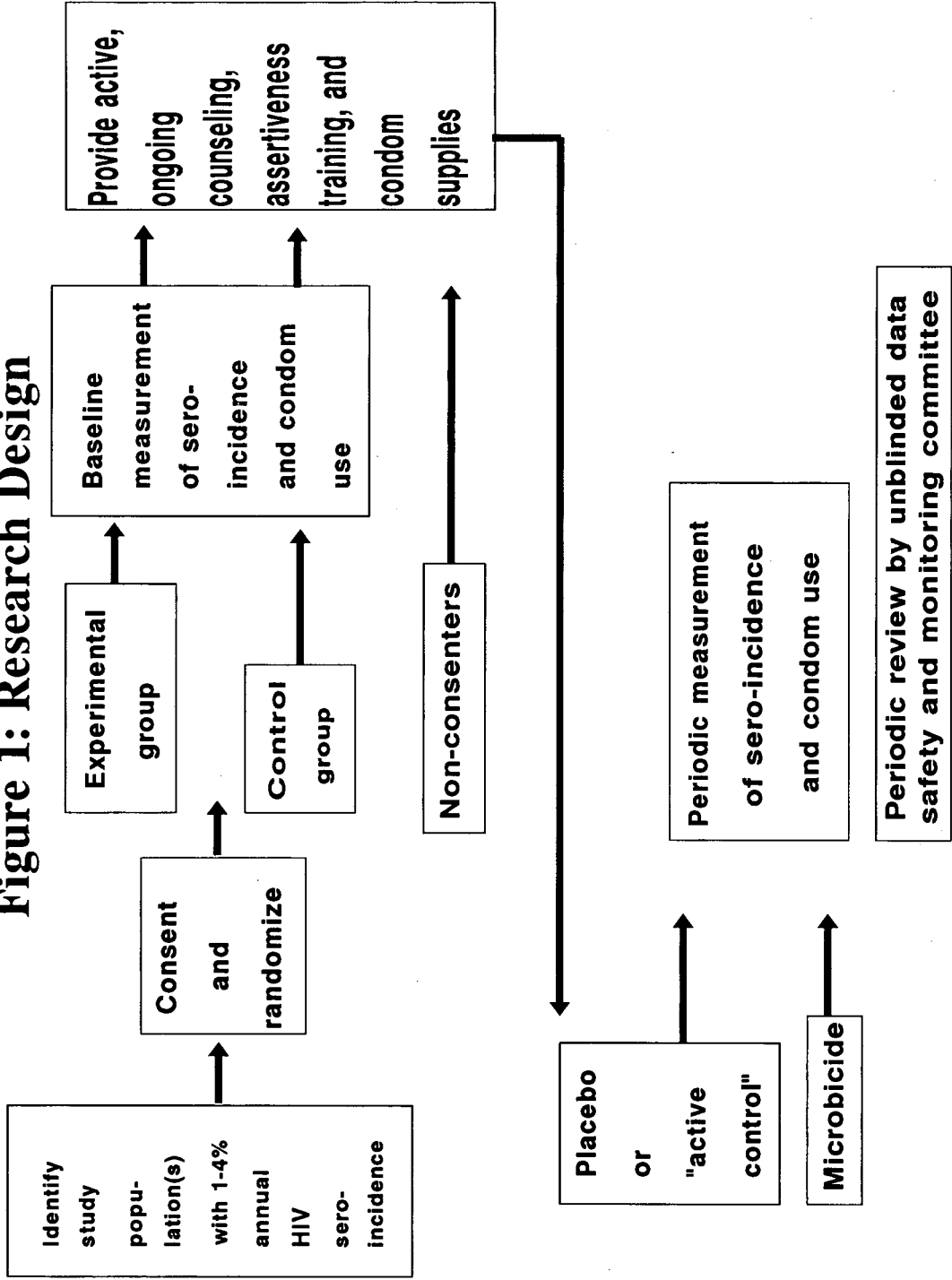
would be brought to human trials. Human trials involve three phases: Phase I trials evaluate the safety, toxicity, and acceptability of a compound in a limited number of women; Phase II trials generally involve 50 to 200 women and are designed to establish some evidence of effectiveness; and Phase III trials expand the safety and effectiveness testing to 1,000 or more women. For a typical compound, completion of all three phases of human clinical trials can take at least five years, but may take longer for microbicide evaluation, given the sample size requirements and special requirements of study populations described below.

The challenge with respect to microbicide development is to design an effectiveness trial that is both scientifically rigorous and ethically defensible. From a scientific standpoint, the most rigorous, and therefore the most desirable, design is a randomized controlled trial (RCT), where trial participants are randomly assigned to receive either the compound under investigation or a placebo (or an "active control" if there exists a compound with previously demonstrated effectiveness).<sup>\*</sup> Since it would be unethical to withhold a form of HIV prevention known to be protective, participants in a microbicide trial would also receive free supplies of condoms and be counseled to use both the vaginal product and a condom during each act of intercourse. Researchers would then use statistical techniques to determine any incremental benefit offered by the experimental compound over condom use alone (Figure 1). Many of the practical issues of clinical trial design for evaluating the effectiveness of spermicides in preventing more common STIs (including a discussion of study population, site selection, and follow-up procedures) have recently been reviewed (Foldes et al., 1990).

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<sup>\*</sup> If conducted today, the control group in a microbicide trial would be a placebo formulation, since there is no convincing evidence of an existing microbicidal agent that is both safe and effective. One could also consider a three-armed study comparing a new microbicide with nonoxynol-9 and placebo.

**Figure 1: Research Design**



This type of trial design raises important ethical issues.\* One of the most significant concerns in conducting an RCT is that, at best, some members of the comparison group will become infected with HIV while participating in the study. The critical ethical question here, however, is whether all study participants will benefit from participation in the trial. According to the ethical principle of "beneficence," researchers have an obligation to minimize harm and to maximize the benefits to all trial participants (Table 6). In the optimal design, therefore, all participants, including those in the control group, would benefit from receiving condoms, reproductive health care, and intensive HIV counseling. If the trial were performed properly (i.e., if condom counseling were active and sustained), the women in the control group should have a lower HIV seroconversion rate than women not participating in the study. Historical controls could be used to document improved use of condoms by all participants as a direct measure of the benefit of participating in the trial.\*\*

To illustrate how this might work, consider the hypothetical results laid out in Figure 2. Researchers randomly assign a

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\* The analysis offered here is based on recent guidelines developed to assist in the design of clinical trials of HIV therapeutic agents and vaccines (Levine, Dubler and Levine 1991; U.S. Public Health Service, 1991; Council for International Organizations of Medical Sciences, 1991). It should be emphasized that any clinical trials of new microbicides undertaken by the Population Council, in either developed or developing countries, would be under an investigational new drug (IND) application to the U.S. Food and Drug Administration and would follow the rigorous procedural requirements of this regulatory body as well as be subject to its inspection and monitoring authority.

\*\* From a research perspective, there is a subtle disincentive to promote condoms vigorously, because doing so decreases the power of the study (i.e., it makes it more difficult to measure a protective effect in the test compound). A direct measure of benefit would therefore provide an important check, furnishing measurable assurance of program effort to reduce the HIV infection risk of all trial participants.

group of sex workers with a seroincidence rate of 4 percent per year to receive either the test compound or a placebo. In addition, both groups receive extensive counseling and free condoms, which raise their condom use from 10 percent before the trial to 50 percent after. In the control group, the women's seroincidence declines from 4 percent to 3 percent, a 25 percent drop, whereas in the experimental group, the rate declines to 1.5 percent, a 62.5 percent drop. This design would confirm the protective effect of the test substance while at the same time reducing the rate of seroconversion in the control group.

The principle of beneficence also requires that no one be refused access to a substance known to be protective. Applied to microbicides, this means that randomization can only be justified when there is a legitimate dispute as to whether the substance under investigation is beneficial or not (Levine, Dubler, and Levine, 1991; Freedman, 1987). A good case can be made that nonoxynol-9 meets this criterion, given the conflicting data available on its ability to protect women from HIV infection, and the possibility that it may actually increase women's risk of HIV. Hence, a randomized control trial of nonoxynol-9 at low or moderate doses would be justified to settle the existing debate over its effectiveness. It may be necessary, however, to delay effectiveness trials in high-frequency users until further

Table 6: Definition of Ethical Principles

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**Respect for Persons:** Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The notion of "informed consent" derives from this principle.

**Beneficence:** Two general rules have been formulated as complementary expressions of beneficent actions - 1) to minimize harm; and 2) to maximize possible benefits.

**Justice:** Justice refers to the equitable distribution of both the burdens and benefits of research.

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**Source:** (Levine, Dubler, and Levine, 1991)

# Figure 2: Hypothetical Results

Initial measurement of seroincidence	Initial measurement of condom use	Post-intervention condom use	Post-intervention seroincidence
4%	10%	50%	1.5%
4%	10%	50%	3%

Random assignment:

Study population:  
 Commercial sex workers with 4% annual HIV seroincidence

Experimental group

Control group

toxicity data become available regarding the safety of nonoxynol 9 in various doses and formulations.

A final justification for a randomized control trial is the need to have the highest degree of scientific certainty possible in the results of a clinical trial of potential microbicides. A less than rigorous trial (i.e., a poorly controlled study) would leave women, counselors, and program directors in a nebulous position not unlike the uncertainty they face today regarding the effectiveness of nonoxynol-9. Presently, decision-makers are forced to make policy in the absence of clear scientific data, potentially exposing women to unnecessary risk. Likewise, an inconclusive trial would complicate further research: If results "suggested" that a compound were protective, it would be difficult to identify an appropriate control group for future trials. There is, therefore, a strong ethical imperative to design trials that are scientifically, as well as ethically, rigorous.

Researchers would have to undertake a variety of other safeguards to guarantee the ethics of microbicide trials. Among them is the need to ensure informed consent, an imperative that derives from the ethical principle of "respect for persons" (see Table 6). Informed consent requires both the absence of direct or structural coercion and full disclosure of trial procedures, including the randomization process and the use of a placebo if applicable. With respect to microbicide testing, this would require that counseling, condoms, and reproductive health care be made available to women who choose not to be in the trials (as well as to participants), so that women would not feel obliged to participate just to gain access to these often scarce resources. Also, researchers would have to take special care to ensure that women understood the contraceptive activity of both the test substance and the control. Some women may wish to protect themselves further from pregnancy during the trial, while others may choose not to participate if doing so might prevent them from



conceiving.\* Discussing the issue of contraceptive activity is especially important in settings where access to abortion is restricted by law or by lack of services.

A relatively new aspect of the ethics of clinical-trial design that has gained currency during the AIDS era is the need to invite community participation in trial design (Levine, Dubler, and Levine, 1991). In the case of microbicides, "community consultation" would mean soliciting input from both the community of women actually involved in the trial as well as from women's health advocates. Also critical is the establishment of an independent, unblinded, "safety and data monitoring committee" that can periodically review the progress of the study and recommend its early cessation if the experimental compound proves either clearly beneficial or clearly detrimental to the trial participants before the planned termination of the study.

Perhaps the most difficult ethical issue, however, derives from the principle of justice, which mandates that the burdens and benefits of research be equitably distributed (Levine, Dubler, and Levine, 1991). A particularly gross example of injustice would be where a new vaccine is extensively tested in sub-Saharan Africa, but once proven, is unavailable to Africans due to its high cost (Freedman, 1992; Ndinya-Achola, 1991). This precise example has been the focus of much debate, given the high cost of vaccine development, the prominence of private-sector interest, and the long-term investment that would be required to make vaccines available in many developing countries.

There are a variety of scientific exigencies that make it almost certain that phase III testing of a microbicide would have

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\* It is also possible, especially in the case of new compounds, that complete data on contraceptive efficacy might not be available at the time of preliminary evaluation for microbicial efficacy. In this event, initial tests would need to be conducted with women who have been sterilized or are otherwise protected from unwanted pregnancy.

to take place primarily in the third world. Two preconditions are required to measure a significant decrease in HIV seroconversion attributable to an effective microbicide:

1. A population of women with a high seroincidence rate attributable primarily, if not exclusively, to the sexual transmission of HIV;\* and
- 2) A sufficiently large study population to achieve statistical significance.

As Table 7 illustrates, the number of trial participants required to achieve statistical significance quickly becomes unmanageable in populations with annual HIV seroincidence rates of less than 2 to 4 percent.\*\* For example, the number of participants required in each arm of a clinical trial seeking to establish 50 percent efficacy of a test compound in three years drops from 3,039 women to 743 women as the seroincidence of the study population increases from 1 to 4 percent (Table 7). Note that even at a high seroincidence rate of 4 percent, however, it is likely that data from multiple sites would have to be pooled for analysis. As with vaccine evaluations, the greatest chance for success lies in the design of multicenter, multicountry studies that include both developed and developing country populations of

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\* It is important to avoid any study effect that may result from "contamination" with other routes of transmission, such as injection drug use. Compared to sexual transmission, it is relatively easy to become infected through parenteral exposure; hence, any significant contamination could potentially obscure the effects of the product under study or greatly increase the required sample size.

\*\* Active program effort to reduce HIV transmission through means other than microbicide use has the effect of significantly increasing the required sample size for a clinical effectiveness trial. The required increase in sample size is directly proportional to the success of these alternative interventions. Sample size calculations, therefore, should be made from estimates of the seroincidence that can be expected in a given study population after the initiation of such alternative intervention strategies.

women.

Study populations that fit the criteria outlined above are found more commonly in the developing countries and often involve vulnerable women, such as sex workers, who are subject to economic and physical exploitation. Although there are populations of women with annual seroincidence rates in the range of 2 - 3 percent in the United States (e.g., in the major urban centers of New York and New Jersey), a large proportion of these women are injection drug users, making them less ideal for

Table 7 - Number of Participants Required for Microbicide Trials

Effectiveness	Annual HIV Seroincidence			
	1 %	2%	3%	4%
25%	29,008	14,376	9,499	7,061
30%	19,521	9,677	6,396	4,755
50%	6,078	3,016	1,996	1,486
70%	2,552	1,268	840	626
90%	1,118	556	369	276
99%	646	322	214	160

Assumptions: Alpha = 0.05, 1 - Beta = 0.90, 2-tailed test  
N = total sample size, two-armed study  
3 year trial (participants enrolled for 2 years and followed for 1 year each.) No loss to follow-up.  
For formula see Cohen, 1977.

microbicide testing because of their risk of acquiring infection through nonsexual means. Clearly, the political and ethical questions raised by this reality would have to be resolved prior to initiating Phase III testing. If the developing world is to bear the major burden of clinical research related to microbicides, women in developing countries must realize the benefits of such compounds once proven. Similar concerns about the distributive justice of vaccine testing are currently under

debate and may provide some guidance in this important area.

The issues of North/South equity raised by microbicide testing may be slightly less charged than those raised by vaccines, because the distribution of an effective microbicide, while requiring attention to manufacturing, storage, and transportation logistics, would not necessarily depend on extensive health-system support. There is some reason to expect that these compounds, once proven, could be incorporated into existing condom-distribution systems and social marketing campaigns. Even though, as described above, microbicide development will most likely depend on a public sector-supported research effort, efficient manufacture and distribution will require some degree of profitability. Therefore, the major challenge (as with condom supplies today) will be identifying resources to finance the recurrent costs of commodity procurement and distribution. In many places, this will require substantial infrastructure development, as well as the political will to provide public subsidy for the purchase and distribution of these commodities for individual use in the public good.

A final ethical question concerns the appropriate study populations to use in Phase I safety testing. Since studies on safety, tolerance, and absorption can be done in populations not at significant risk of AIDS, there is little justification for doing Phase I research among vulnerable populations.\* Special caution should be applied in the recruitment of sex workers from developing countries for Phase I trials. Given the economic, political, and violent realities of many of these women's lives, it is impossible to ensure (even through cash payments) that they will not "work" during the trial, thereby exposing themselves to

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\* There are compelling reasons to repeat Phase I safety and toxicity testing in developing countries and among high-risk women following the initial testing in the country of origin and the accumulation of adequate safety data in low-risk populations. The U.S. National Institutes of Health, for example, has adopted this policy for Phase I testing of candidate vaccines (Vermund, 1992).

HIV while using an intravaginal compound whose safety in humans has not yet been demonstrated. Preferably, Phase I trial participants should not be at risk of contracting HIV during initial safety and acceptability testing.\*

### **C. Programmatic Issues**

In addition to the challenges of designing ethical and scientifically valid clinical trials, a number of important programmatic issues must be considered in relation to microbicide development. Perhaps most important is a commitment to seeking women's input at each stage of the research and development effort. Soliciting women's needs and preferences at the outset will help ensure that the product, once developed, will be used and accepted. The importance of this type of consultation for contraceptive development has recently been summarized by the International Women's Health Coalition and the World Health Organization's Special Programme of Research on Human Reproduction in their publication entitled "Creating Common Ground: Women's Perceptions on the Selection and Introduction of Fertility Regulation Technologies" (1991).

Women's input is especially critical with respect to the initial design criteria for a new microbicidal product. Table 8 lists some of the dimensions along which a new product might vary. In all likelihood, a broad range of product formulations will ultimately be necessary. The ideal formulation for an adolescent in the United States, for example, might be quite different from that required by a married woman in rural India. An important step in product development will be to conduct field research to establish women's needs and preferences in different geographic and cultural settings.

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\* We gratefully acknowledge the help of Priscilla Alexander at the WHO Global Programme on AIDS in articulating this important point.

Table 8: Some Dimensions of Microbicide Product Specification

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Contraceptive activity  
Interaction with existing contraceptive use  
Capacity for covert use ("detectability")  
Method of application (e.g. jelly, film, etc.)  
Coital dependence  
Postcoital effectiveness  
Onset and duration of action  
Spectrum of microbicidal activity  
Disposability  
Affordability  
Smell/taste  
Messiness  
Shelf life  
Stability at room temperature  
Ease of insertion  
Appropriateness for anal/oral sex

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Experience from testing the acceptability of various contraceptives suggests that one of the more critical design features for microbicide development will be its method of application. A microbicidal compound could be manufactured in a number of ways, each with unique implications for its acceptability among users. Cultural factors, for example, might affect whether women would prefer a vaginal cream applied with an applicator or a vaginal sponge inserted by hand. In parts of Africa, for example, women use a variety of astringent substances to dry and tighten the walls of the vagina before sex (Dallabeta et al., 1990). Where this form of "dry sex" is common and preferred, a moist vaginal creme would probably receive little use.

Fortunately, there is great potential for improvement in the design of new delivery vehicles. One approach that holds much promise is the adaptation of the contraceptive vaginal film (CVF), a delivery vehicle for nonoxynol-9 now gaining currency. These films, which resemble small squares of cellophane, dissolve rapidly when inserted into the vagina and wash away with body fluids (Hatcher, 1992). That they can be easily hidden and stored and are not "messy" like foams and jellies also make them a potentially surreptitious method. This fact should make the

films especially attractive to women who are afraid or unwilling to broach the subject of HIV protection with their partner.

Contraceptive research also suggests that the timing of insertion will be another factor critical to the acceptability of new microbicides. Couples tend to prefer methods that do not interrupt the spontaneity of intercourse, a property determined in part by the product's onset and duration of action. Microbicides that become effective quickly and/or that can be inserted long before intercourse are likely to be preferred. A great need also exists for a product that could be used postcoitally to protect women subject to nonconsensual sex. It is reasonable to expect, given our current understanding of HIV transmission, that a product could be developed that would offer at least some protection if administered immediately after intercourse. The need for such a product is evidenced by the reality that some rape crisis centers in the United States have been using nonoxynol-9 for this purpose, although there are no data substantiating its efficacy when used in this manner (Dattel, 1992). A postcoital method might also have some utility for women, especially adolescents, in communities where "planning" to have sex is unacceptable (Pick de Weiss et al., 1991).

Another set of programmatic issues revolves around the introduction, distribution, and postmarketing surveillance of any new microbicide product. The development of appropriate information, public education, and counseling materials must complement the development of any new biotechnology to ensure that women realize the maximum benefit of such new products and that providers supply proper guidance regarding correct usage. A major advantage of a microbicide over a vaccine is that it could be distributed and sold through existing commercial channels rather than be dependent on health-care workers and an already overburdened health-care system. Vaccines often require delicate handling, constant refrigeration, and trained personnel, making vaccine programs considerably more difficult to administer than

distribution networks based on commercial marketing. Several decades after the development of a highly effective measles vaccine, for example, measles remains one of the most common causes of child mortality (UNICEF, 1992), a fact that speaks to the difficulty of achieving coverage, given the virtual absence of health services in many resource-poor areas.

By contrast, the programmatic challenge of microbicides will be to adapt and apply the lessons learned from condom promotion to a new product targeted to women. In many cases, microbicides could potentially be incorporated into the same procurement, storage, and distribution systems presently used for condoms. Moreover, many of the same social-marketing techniques used to create demand for condoms could also be used to promote microbicides. Even in very poor countries like Zaire, social-marketing campaigns have been able to increase greatly the sale of condoms using a skillful mix of media, packaging, pretested slogans and ads, and aggressive, widespread distribution through multiple outlets (Population Services International, 1992b). Also promising are opportunities to distribute and promote microbicides through family planning programs, mothers' clubs, and other women's organizations. Indeed, for this type of product, word-of-mouth, "woman to woman" promotion may be the most effective.

## **CONCLUSION**

We can no longer ignore the urgent need to develop an expanded range of female-controlled options for HIV prevention. The discovery and testing of both contraceptive and noncontraceptive compounds for intravaginal use in preventing the sexual transmission of HIV and other STIs, as well as further evaluation of existing spermicidal compounds, should command a high priority for immediate research. The information reviewed here suggests that this is a difficult, yet feasible, challenge.

The development and testing of microbicidal compounds will require advancing our basic understanding of human reproductive



biology. It will rely on careful attention to the ethics of clinical trial design and require a lasting dialogue between scientists and advocates. And it will require the collaboration of professionals from various academic disciplines, as well as the coordination of efforts among various governmental, nongovernmental, and intergovernmental organizations.

The world is waiting for the development of these compounds as an important addition to the global campaign against the spread of AIDS. And, the world will not wait patiently. The AIDS epidemic has precipitated a new type of social activism. Persons living with HIV infection, as well as communities at risk, have organized and begun to demand an accountability from the scientific community that is without precedent. Activist organizations have articulated specific demands regarding access to experimental therapies, the design of clinical trials, the allocation of research funds by governmental agencies, and the generation of research funds themselves. This activism has begun to shape and accelerate the global response to AIDS.

As recognition has grown concerning women's risk of HIV infection and the limitations of the current AIDS strategy, women's health advocates have begun to advocate for more research in this important area (Juffer, 1992; International Women's Health Coalition, 1992). At a meeting held in Barbados in March 1992, cosponsored by the International Women's Health Coalition and the Women and Development Unit of the University of Barbados, West Indies (WAND), leading women's health advocates from over 40 countries outlined an agenda for future research regarding women's health (International Women's Health Coalition, 1992). This agenda included a strong call for the development of female-controlled microbicides.

In June 1992, the Population Council sponsored a meeting in New York involving over 50 advocates and scientists from around the world to outline the feasibility and challenges of microbicide development. Our conclusion was that the development of such technology was an achievable, if demanding, goal. The

Population Council has subsequently taken steps to make microbicide development a high-priority area for its technology development program. Other organizations have also begun to accelerate their efforts concerning this important endeavor.

Only a persistent and conscious neglect of women's needs will explain continued inattention to this important area of research. Fortunately, as the brief history of AIDS has taught us, not only is the world waiting -- history is watching.

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