

Sexually Transmitted Infections



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Sexually transmitted infections (STIs) are responsible for an enormous burden of morbidity and mortality in many developing countries because of their effects on reproductive and child health (Wasserheit 1989) and their role in facilitating the transmission of HIV infection (Laga, Diallo, and Buvé 1994).

INTRODUCTION

Largely because of the HIV epidemic, interest in STIs has increased over the past two decades. During that time, the epidemiology of STIs has changed in developing countries, partly as a result of modifications in STI case management approaches and partly because of behavioral changes in response to the HIV epidemic. At the same time, advances in STI prevention have enhanced understanding of the intricacies of STI transmission dynamics and the role of interventions in the control of STIs. However, what has not changed is as significant as what has changed: the epidemiology of STIs still differs substantially in the industrial countries and the developing world. The sociocultural and economic contexts in developing countries influence the epidemiology of STIs and help make them an important public health priority.

Incidence and prevalence rates of STIs are generally high in both urban and rural populations and vary considerably across areas. Because diagnosis and treatment of STIs are often delayed, inadequate, or both, rates of STI complications are also high in developing countries. Those complications include pelvic inflammatory disease, ectopic pregnancy, and chronic abdominal pain in women; adverse pregnancy outcomes, including abortion, intrauterine death, and premature delivery;

neonatal and infant infections and blindness in infants; infertility in both men and women; urethral strictures in men; genital malignancies, such as cancer of the cervix uteri, vulva, vagina, penis, and anus; arthritis secondary to gonorrhea and chlamydia; liver failure and liver cancer secondary to hepatitis B or human T cell lymphotropic virus type I; and central nervous system disease secondary to syphilis (Holmes and Aral 1991; Meheus, Schulz, and Cates 1990; van Dam, Dallabetta, and Piot 1999). Thus, STI sequelae affect mostly women and children.

In developing countries, high levels of STIs and high rates of complications and sequelae result largely from inadequacies in health service provision and health care seeking (Aral and Wasserheit 1999). STI care is provided by a large variety of health care providers, many of whom are poorly trained in STI case management, and the quality of care they provide is often less than desirable (Moses and others 1994; WHO 1991). Health care seeking for STIs is frequently inadequate, particularly among women (van Dam 1995), because of the low levels of awareness regarding sexual health, the stigmatization associated with genital symptoms, and the asymptomatic nature of many STIs. A study in Nairobi, Kenya, found that 42 percent of patients had been symptomatic for more than a week before coming to a clinic and that 23 percent had been symptomatic for more than two weeks (Moses and others 1994).

Setting up good-quality STI services is considerably more difficult in resource-poor settings than elsewhere. Variables that affect the duration of infectiousness include adequacy of health workers' training, attitudes of health workers toward such marginalized groups as sex workers, patient loads at health centers, availability of drugs and clinic supplies, and

costs of care (Moses and others 2002). Thus, improvements pertaining to all these factors would greatly improve STI-related services, help reduce the duration of infectiousness, and decrease the incidence of STIs (Aral 2002a). However, in many countries in the developing world, worsened economic conditions and the increasing burden of HIV/AIDS have negatively affected these variables. For example, in South Africa, the ratio of hospital beds to population declined from 6.5 per 1,000 in 1976 to 2.3 in 1996; during 1999, approximately 300 professionally trained nurses left the country each month; and student enrollments in nursing school declined from 12,282 in 1996 to 10,398 in 1999 (Aral 2002a).

Sexual behaviors also contribute to the STI burden in developing countries. These behaviors are heavily influenced by the sociocultural, economic, and political contexts, which in the past two decades have deteriorated at an accelerated rate in many areas. Societal change has included rising levels of inequality within countries, growing inequality between countries, increased levels of globalization, increased proportions of people who live in cultures they were not born in, and a larger proportion of the world's population living in postconflict societies (Aral 2002a). One effect of these changes is an increase in multipartner sexual activity, which in turn increases the rate at which infected and susceptible individuals are sexually exposed to each other and consequently the rate at which STIs spread.

Changes in STI Epidemiology, Management, and Prevention since 1993

Since 1993, STI epidemiology and management have evolved interactively, particularly in developing countries. Technological advances in diagnosis, screening, and treatment; evaluation and widespread implementation of new case-management algorithms; and changes in risk behaviors in response to the AIDS epidemic have all influenced the dynamic typology of STIs (Wasserheit and Aral 1996).

The introduction of nucleic acid amplification tests, which have improved the sensitivity and expanded the repertoire of usable specimens, has heralded a new era in STI diagnosis. The use of urine and vaginal swabs in diagnosis has enabled providers to supply diagnostic and screening services outside traditional clinical facilities and has greatly enhanced the coverage of outreach activities (Schachter 2001). Unfortunately, many of these tests are currently too expensive for routine use in developing countries. Single-dose oral azithromycin has improved the treatment of several bacterial STIs (Lau and Qureshi 2002), but quinolones are apparently becoming ineffective for gonorrhea in some locations (Donovan 2004).

A major recent advance in STI prevention is the early success of a prophylactic, monovalent human papillomavirus (HPV) type 16 vaccine (Koutsky and others 2002); HPV

vaccines may be able to help prevent genital and anal cancers in the foreseeable future. Researchers are evaluating multivalent vaccines for preventing moderate to severe cervical dysplasia as well. Other advances include easier episodic treatment of genital herpes (Strand and others 2002) and the use of suppressive therapy to reduce the transmission of genital herpes to regular partners (Corey and others 2004). In a related development, a prophylactic vaccine against herpes simplex virus type 2 (HSV-2) has shown limited efficacy in that it has proved partly effective for HSV-seronegative women, but not for men or herpes simplex virus type 1 (HSV-1) seropositive women (Stanberry and others 2002). Prevention successes of the recent past include STI sequelae, such as pelvic inflammatory disease and cervical cancer. A randomized controlled trial showed that selective screening of women for *Chlamydia trachomatis* significantly reduced the incidence of pelvic inflammatory disease (Scholes and others 1996).

Widespread implementation of syndromic management as an approach to STI case management has apparently had a considerable effect on the epidemiology of STIs, particularly in resource-poor settings (King Holmes and Michael Alary, personal communication, May 15, 2003).

In some developing countries, including Cambodia, the Dominican Republic, and Thailand, sexual risk behaviors have been changing over the past decade. In Uganda, for example, the age of sexual debut has increased, the frequency of sex with casual partners has decreased, and the use of condoms has increased (Stoneburner and Low-Beer 2004). During the 1990s, demographic and health surveys in 29 developing countries asked individuals if they had done anything to avoid AIDS (Low-Beer and Stoneburner 2003): almost 80 percent of men and 50 percent of women surveyed reported that they had. Specific behavior changes reported included increased monogamy, reduced number of partners, avoidance of sex workers, and increased condom use.

By contrast, in developed countries, recent years have seen behavior changes in the opposite direction; for example, in many European countries and in the United States, risk behaviors among men who have sex with men have increased significantly (CDC 2004; L. Doherty and others 2002). In addition, Grémy and Beltzer (2004) report declines in condom use among heterosexual adult populations in Europe. Investigators attribute increases in risk behaviors to the introduction and availability of antiretroviral therapy for HIV infection and the difficulties in sustaining preventive behaviors in the long term, referred to as *prevention fatigue*. Some researchers speculate that the widespread introduction of antiretroviral therapy in developing countries may have a similar disinhibitory effect on sexual behaviors and that changes in sexual behavior may offset the beneficial effect of antiretroviral therapy (Blower and others 2001; Blower and Farmer 2003; Blower and Volberding 2002; Over and others 2004).

Advances in STI prevention in recent decades have enhanced understanding of transmission dynamics and the role of interventions. Investigators have articulated the following five emergent insights about STI epidemiology and prevention over the past two decades:

- Populations consist of many diverse subpopulations, and each population-level epidemic trajectory consists of many distinct subpopulation epidemic trajectories (Pisani and others 2003). The epidemic trajectories of specific STIs differ depending on when and where the infection was introduced; the natural history and transmissibility of the infection; the structure of sexual networks; the demographic, economic, social, and epidemiological context; and the state of the health system (Aral and others 2005).
- Temporal dimensions are important in relation to STI epidemiology (Aral and Blanchard 2002). At the individual level, concurrency of partnerships and gaps between partnerships are risk factors for the acquisition and transmission of STIs (Adimora and others 2002; Agrawal, Gillespie, and Foxman 2001; Kraut and Aral 2001). At the population level, investigators have described the evolution of STI epidemics through sometimes predictable phases, characterized by changing patterns in the distribution and transmission of STI pathogens within and between subpopulations (UNAIDS and WHO 2000; Wasserheit and Aral 1996).
- Sexual networks are important in the transmission dynamics of STIs at the population level, and position in a sexual network is important in the transmission and acquisition of STIs at the individual level (Morris 2004).
- Trajectories whereby STI epidemics evolve differ for different types of population-pathogen interactions (Aral 2002a; Blanchard 2002; Garnett 2002). Whereas highly infectious, short-duration bacterial STIs—for instance, gonorrhea—depend on the presence of core groups marked by multiple sex partnerships of short duration for their spread, less infectious, long-duration viral STIs—for example, HSV—depend on the presence of multiple partnerships of longer duration.
- Interactions among sexually transmitted pathogens affect STI epidemic trajectories at the population level (Wasserheit 1991). The inconsistent findings of three landmark randomized community trials evaluating the effect of STI treatment on HIV transmission (Grosskurth and others 1995; Kamali and others 2003; Wawer and others 1999) can be accounted for by the complex, multifactorial, multilevel, and phase-specific nature of STI epidemics (Orroth 2003).

Epidemiology and Control

The epidemiology of STI pathogens, the local prevention and care infrastructure, and the cultural and sociopolitical context

vary considerably within and across developing countries. At the same time, health care delivery for STIs varies by type of institution and location, although inadequate resources are universal in the developing world, as are recordkeeping, data management, and data analysis. The limited data that are available suggest that STIs are a major public health burden in the developing world. Although the prevalence and incidence of bacterial STIs have apparently declined because of expanded syndromic management, changes in sexual behavior, and death of high-risk populations, the prevalence and incidence of viral STIs seem to have increased over the past decade.

Syndromic Management. Health systems can use three different approaches to manage patients presenting with symptoms suggestive of an STI. First, etiology-based management relies on identifying causative micro-organisms or detecting specific antibodies. It requires costly and often technically complex laboratory diagnosis, trained personnel, quality assurance programs, and infrastructure. Second, clinical diagnosis-based management is rapid, inexpensive, and requires less infrastructure than etiology-based management; however, clinical diagnosis is often inaccurate, may miss multiple infections, and may result in undertreatment or overtreatment. Third, syndromic management, which is based on the recognition of a constellation of clinical signs and symptoms, is inexpensive, can be standardized, and can be used by both physicians and paramedical personnel, though it often results in some overtreatment. Nevertheless, syndromic management has been recommended as a realistic approach for managing symptomatic patients in developing countries (Over and Piot 1993). Implementation issues associated with the syndromic management approach involve inadequate local evaluation of treatment algorithms because of a lack of local data, inconsistencies in implementation, and inadequate monitoring (Dallabetta, Gerbase, and Holmes 1998; Hawkes and Santhya 2002; WHO 2001b).

Limitations of the syndromic management approach include the inability to directly target the subclinical STI pool, the variability of STI symptoms and signs, the potential for wasting antibiotics, the risk of promoting drug resistance, and the unintended consequence of decreasing the skill levels of health care providers (Dallabetta Gerbase, and Holmes 1998; Donovan 2004). Moreover, syndromic management tends to undermine STI surveillance efforts because cases are managed and treated in the absence of a specific clinical or laboratory diagnosis (O'Farrell 2002).

Role of Core Groups and Bridge Populations. Core groups—that is, groups of individuals who have large numbers of sex partners who themselves have large numbers of sex partners—play an important role in the spread and persistence of STIs and are characterized by a high prevalence of STIs. Examples of

core groups include sex workers, drug users, truck drivers, and bar girls. Because a case treated or prevented in a core group member tends to prevent that person from infecting several others, interventions that target core groups tend to be more effective and more cost-effective than interventions that target the general population (Ainsworth and Over 1997; Over 1999; Over and Piot 1993). In situations in which a high prevalence of STIs is concentrated in core groups, so-called bridge populations (individuals who have sexual links with members of both high- and low-prevalence subpopulations) may play an important role in disseminating infection from core groups to the general population (Aral 2000; Aral and others 1999; Gorbach and others 2000; Morris and others 1996).

Several variables influence the relative importance of core groups in the spread of STIs, including the characteristics of the specific pathogen, such as its transmissibility and duration of infectiousness; the phase of a particular epidemic; and the duration of sexual partnerships among those involved in multipartner sexual activity (Aral 2002a, 2002b; Blanchard 2002; Garnett 2002; Wasserheit and Aral 1996). The role of core groups in STI dissemination tends to be greater during the initial and later phases of epidemics, when infection is highly concentrated in small, high-risk subpopulations, than during the middle phases of epidemics, when infection tends to be widely spread across subpopulations. The importance of core groups appears to be greater in populations in which most people are involved in sexual activity with a single partner and only a small minority of people engage in short-term sexual partnerships with a large number of sex partners (Laumann and Youm 1999).

Antibiotic Use and Drug Resistance. Antibiotic use is unregulated in many developing countries, and antibiotics are frequently misused and overused, which results in drug resistance. Resistance to antimicrobial drugs is increasing mortality and morbidity from infectious diseases (Hart and Kariuki 1998). STIs are among the most frequently occurring infections worldwide, with more than 76 percent estimated to occur in the developing world (WHO 2001a). *Neisseria gonorrhoeae* has shown great versatility in developing resistance to antimicrobial drugs, including sulfonamides, penicillins, and tetracycline. Fluoroquinolones such as ciprofloxacin and ofloxacin have proved highly effective in treating gonorrhea, but after widespread and often inappropriate use of fluoroquinolones, resistant *N. gonorrhoeae* has emerged. In some areas, such resistance leaves third-generation cephalosporins as the only predictably effective antibiotic treatment for gonorrhea.

STIs and HIV/AIDS. Because HIV is a sexually transmitted infection, people who are infected with another STI also tend to be at increased risk of HIV infection and vice versa. However, beyond this correlation resulting from common risk

behaviors, STIs and HIV may facilitate each other's transmission.

BACTERIAL AND VIRAL STIs AND THEIR SEQUELAE

Both bacterial and viral STIs are widespread in developing countries; recently, incidence of bacterial STIs has declined while that of viral STIs has been increasing.

Natural History of Bacterial STIs and Their Sequelae

Chancroid is a genital ulcer disease caused by *Haemophilus ducreyi*. Its incidence has declined greatly in both developed and developing countries. This decline has been associated with the provision of STI diagnostic and therapeutic services to sex workers (Steen 2001) and with improved syndromic management of genital ulcers. Like other genital ulcer diseases, chancroid is associated with increased acquisition and transmission of HIV (Donovan 2004).

Syphilis is a genital ulcer disease caused by *Treponema pallidum*. In 1999, the World Health Organization (WHO) estimated the global prevalence of syphilis at 12 million (WHO 2001a), with high prevalence rates in South and Southeast Asia and Sub-Saharan Africa. Those most likely to be affected are populations in developing countries and disadvantaged subpopulations in developed countries. Since 1999, syphilis outbreaks have reemerged in many developed countries among men who have sex with men (CDC 2004; L. Doherty and others 2002). Among heterosexuals, sexual contact with sex workers is an important risk factor. If untreated, syphilis during pregnancy may lead to stillbirth and congenital syphilis (Genc and Ledger 2000).

Gonorrhea is a discharge disease caused by *N. gonorrhoeae*. In 1999, WHO estimated its global prevalence at 62.4 million (WHO 2001a). Like syphilis, its prevalence is high in South and Southeast Asia and Sub-Saharan Africa, in many developing countries elsewhere, and among high-risk groups and disadvantaged subpopulations in developed countries. Community surveys reveal a substantial pool of asymptomatic gonococcal infections (Chandeying and others 2000; Turner and others 2002). Following the emergence of AIDS, gonorrhea cases declined among men having sex with men, sex workers, and the general population in the developed world and among sex workers in many developing countries (Donovan 2004).

In most populations tested, infection with *Chlamydia trachomatis* is the most common bacterial STI. In 1999, WHO estimated the global prevalence of chlamydial infection to be 92 million (WHO 2001a). Chlamydial infection is common in most countries, especially among young people. Key risk

factors are being younger than 25 and having a new sex partner. Many women with uncomplicated infection are asymptomatic or have mild symptoms. Like untreated gonococcal infection, untreated chlamydial infection can cause pelvic inflammatory disease, chronic pelvic pain, and ectopic pregnancy. Chlamydial infection is an important acquired cause of infertility in women (Simms and Stephenson 2000). Roughly half of men with urethral chlamydial infection develop symptomatic urethritis, chlamydial infection is the most common cause of epididymitis in young men, and both men and women may develop chlamydial conjunctivitis or reactive arthritis (Stamm 1999). Research also suggests that chlamydial infection in men may be associated with reduced fecundity among couples (Idahl and others 2004). In addition, chlamydial infection can affect neonates: many delivered vaginally become infected, developing conjunctivitis or, less often, chlamydia pneumonia (Donovan 2004). The role of *C. trachomatis* in preterm births and in cervical cancer awaits further clarification through research (Samoff and others 2004; Wallin and others 2002).

In the absence of control programs, the prevalence of *Trichomonas vaginalis* varies greatly across countries, ranging from less than 1 percent among urban women to more than 20 percent in underserved populations in the same country (Brown and Brown 2000), and may increase with age. WHO estimated the global prevalence of *T. vaginalis* at 174 million in 1999. The introduction of nucleic acid amplification tests highlighted the poor sensitivity of microscopy in the detection of *T. vaginalis*. Even though most infected people are asymptomatic, *T. vaginalis* can cause vaginitis with vaginal discharge in women and urethritis in men. *T. vaginalis* has been associated with preterm birth and may promote the sexual transmission of HIV (Laga and others 1993). However, a randomized controlled trial did not show that screening and treatment for *T. vaginalis* to prevent preterm birth were effective (Klebanoff and others 2001).

Like *T. vaginalis*, bacterial vaginosis and vulvovaginal candidiasis cause vaginal symptoms in women, are extremely prevalent in developing countries, and in one or more studies have been associated with HIV acquisition or HIV genital shedding by women (Donovan 2004). Although often referred to as reproductive tract infections rather than STIs, they are managed in conjunction with STIs, and bacterial vaginosis is associated with some of the same risk factors as other STIs.

Viral STIs and Their Sequelae

Both HSV-1 and HSV-2 infect the genital and anal areas, but HSV-2 causes the most clinical recurrences in the genital tract. Symptoms are mild in most of those infected and tend to go unrecognized and undiagnosed (Corey 2000; Scoular 2002). Genital herpes establishes a lifelong infection that in some people is associated with significant morbidity. Complications of

HSV-2 include severe primary disease, meningitis, hepatitis, erythema multiforme, and neonatal herpes (Donovan 2004). Infected neonates may die or develop severe neurological sequelae despite antiviral therapy. In contrast to bacterial STIs, HSV-2 may be transmitted to sex partners many years after initial infection and during periods when the infected individual may be asymptomatic. Infection with HSV-2 is now one of the most common STIs worldwide and is the most frequent cause of genital ulcers in almost all areas; however, this observation may be related to better diagnostic technologies rather than a genuine alteration in the spectrum of genital ulcer disease (Corey and Handsfield 2000). Improved control of chancroid and syphilis as well as actual increases in the sexual transmission of HSV-2 in areas with advanced HIV epidemics, where HIV-related immunosuppression causes more frequent and more severe HSV-2 disease, may also play a role. Estimates indicate that 10 to 30 percent of adults worldwide are infected with HSV-2 (Brugha and others 1997). Prevalence increases with age and is higher in women and high-risk populations.

HPV types are grouped into low-risk (nononcogenic) and high-risk (oncogenic) types. Low-risk types, including types 6 and 11, cause benign anogenital warts, whereas high-risk types, including HPV 16, 18, 31, and 45, occasionally lead to genital and anal squamous cell cancers. The introduction of nucleic acid amplification tests revealed that genital and anal HPV infection is common even among relatively sexually inexperienced individuals (Giuliano and others 2002; Stone and others 2002). Investigators believe that most adults become infected with HPV but that only a few develop warts or genital or anal cancer. Infection with a high-risk HPV type is implicated in nearly all cases of invasive cervical cancer (Walboomers and others 1999) and with vaginal, vulvar, and anal cancers.

In developed countries, hepatitis B virus is spread predominantly by sexual and injecting drug-use transmission. Indeed, the first three trials of hepatitis B vaccine successfully demonstrated prevention of sexual transmission of hepatitis B virus in men who have sex with men (Manhart and Holmes 2005). In developing countries, hepatitis B is more often acquired perinatally or during childhood, but a rise in seroincidence in adolescence and young adulthood in some countries probably reflects sexual or injecting drug-use transmission. Hepatitis B virus causes acute hepatitis and in some people causes chronic hepatitis that can lead to cirrhosis and liver cancer.

Human T cell lymphotropic virus type I (and perhaps in more cases type II) is, like hepatitis B virus, transmitted perinatally and sexually. In some high-risk populations, for example, female sex workers in Latin America, human T cell lymphotropic virus type I infection is substantially more common than HIV infection. This infection causes a serious form of spastic paralysis or human T cell lymphotropic-associated myelopathy, as well as T cell lymphoma or leukemia.

Coinfection with Sexually Transmitted Pathogens

The epidemiology and natural history of coinfection with more than one sexually transmitted pathogen may have important intervention and economic implications. Coverage by clinical services, outreach, access, partner management, and treatment may be different with coinfection than with independent infections. Although coinfections with HIV and other STIs have received a great deal of attention in recent years, researchers have not focused on overlaps among non-HIV STIs in a similar systematic manner. A number of biological mechanisms may lead to coinfection with STIs: infection with one pathogen may increase the probability of acquiring or transmitting another pathogen; infection with one pathogen may increase or decrease the frequency, the severity, or both of symptoms associated with another sexually transmitted pathogen; and presence of one STI may affect the natural history of another STI. High-risk behaviors and networks often lead to coinfection.

Empirical data on coinfection are limited. Most studies have been conducted in developed countries and have focused on co-occurrences of chlamydial and gonococcal infection. Earlier studies of coinfection assessed the proportion of gonorrhea cases with concurrent chlamydial infection in a variety of clinical settings. Reported levels of coinfection were 4 to 64 percent among attendees at STI clinics, 46 percent among prenatal clinic attendees, and 4 to 25 percent at primary health care facilities (Creighton and others 2003). The proportion of those with chlamydia who also have gonorrhea has been assessed less well, and estimates have ranged between 3 and 4 percent (Creighton and others 2003).

Sexual Behavior and Sexual Health Care

Unprotected sex with an infected partner is the most important risk factor for acquiring an STI. This risk is influenced by the behaviors of the individual and the probability that the partner is infected, which is determined by the prevalence and distribution of infection in the population as well as the partner's behaviors. Current approaches to STI epidemiology recognize at least three distinct components of transmission dynamics at the population level: likelihood of sexual exposure between infected and uninfected individuals, transmissibility of infection upon exposure between an infected and an uninfected person, and duration of infection among those infected (Aral and Holmes 1999; Over and Piot 1993). The first of these components is entirely behavioral, and behavior plays an important role in the last two—for example, condom use, sexual practices, and health care-seeking behaviors.

Demographic and Social Risk Markers. The prevalence and incidence of STIs vary across societies and subpopulations defined by age, gender, race and ethnicity, and socioeconomic

status (Fenton, Johnson, and Nicoll 1997). In all societies, adolescents and young people are at greater risk for acquiring most STIs. Women tend to have a higher prevalence and incidence of all STIs (except for men who have sex with men) and suffer more of the serious complications, such as pelvic inflammatory disease, ectopic pregnancy, infertility, and chronic abdominal pain. For many STIs, the probability of transmission from an infected man to a susceptible woman is higher than from an infected woman to a susceptible man. Social and behavioral patterns also increase women's vulnerability to STIs; for instance, many men have concurrent sex partnerships, which increase their risk for transmitting infection to their female sex partners. In addition, many young women have sex with older male partners, who expose them to the higher STI prevalence rates in older age groups.

In most societies, minority racial ethnic groups have higher STI rates than other groups. Both in the United Kingdom (Fenton, Johnson, and Nicoll 1997) and in the United States (Laumann and Youm 1999), assortative sexual mixing and higher rates of sexual mixing with members of core groups emerge as determinants of ethnicity differentials in STI rates. The prevalence of concurrent partnerships is also higher among racial ethnic minorities (Kraut-Becher and Aral 2003). The relative inadequacy of STI health services and of health care-seeking behaviors among minority racial ethnic groups may also contribute to their higher prevalence of STIs (Aral and Wasserheit 1999).

Socioeconomic status differentials in STI prevalence and incidence are similar to ethnicity differentials. However, the multicollinearity between the two factors makes delineating the independent contributions of either variable to differentials in STI prevalence and incidence difficult.

Behavioral Risk Factors for Exposure to Infected Sex Partners. Most sexual behaviors of individuals are associated with exposure to sex partners infected with sexually transmitted pathogens and, consequently, with acquisition of STI. These behavioral factors include number of sex partners over the individual's lifetime, over the past year, and over a short term (Fenton and others 2001; Laumann and Youm 1999); frequency or number of sexual encounters (Garnett and Rottingen 2001); having sex with members of groups with high STI prevalence, such as core groups and sex workers (Fenton and others 2001; Laumann and Youm 1999) or older age groups (Service and Blower 1996); and position in a sexual network (I. A. Doherty and others 2005). Some sexual behaviors of individuals are associated with transmission of STIs, and for those infected the behaviors increase the probability that people will transmit their infections to susceptible sex partners. These behaviors include having concurrent partnerships (Koumans and others 2001; Kraut-Becher and Aral 2003; Morris and Kretzchmar 1995) and having short

gaps between sex partners in serial monogamous partnerships (Kraut-Becher and Aral 2003).

Sex partners' behaviors are also critical determinants of exposure to infection. Investigators use many behavioral and epidemiological indicators to assess partners' risk of having infection, including existence and number of new sex partners; presence of concurrent partnerships; gap between sex partners; partners' number of partners; and risk status of partners' partners—for example, if they have sex with sex workers or men who have sex with men (Aral 2002b).

Behavioral Risk Factors Associated with STI Acquisition and Transmission on Exposure to Infected Partners. Certain behaviors influence the likelihood of an infected person's transmitting infection to a susceptible partner, including condom use, sexual practices such as anal intercourse, vaginal douching, and use of drying agents in the vagina (Bailey, Plummer, and Moses 2001; Donovan 2000a, 2000b). The probability of transmission varies depending on the pathogen and is much higher for bacterial STIs, such as gonorrhea, syphilis, and chlamydia, than for other STIs, such as HIV infection. Thus, preventive behaviors such as condom use may be more effective in preventing the latter than the former (National Institute for Allergy and Infectious Diseases 2001). In addition, the probability of both acquisition and transmission is significantly affected by such nonbehavioral cofactors as circumcision status (Aral and Holmes 1999).

Overall, oral sex and anal sex tend to be practiced less often in the developing world than in the developed world (Vos 1994). Insertion of herbs to tighten or dry the vagina and other practices of vaginal clearing and wiping are widespread (Brown and Brown 2000). Condom use is increasing in some countries—for example, India, Thailand, and Uganda—especially during high-risk encounters.

Behaviors Associated with the Duration of Infectiousness. The duration of infectiousness is an important component of transmission dynamics. Because effective treatment curtails the duration of curable STIs, the speed with which infected individuals seek treatment and the speed and effectiveness with which health care providers supply effective treatment together determine duration. To the extent that suppressive therapies truncate the period of infectiousness of viral STIs, as they do for HSV-2 and HIV infection, duration is also important in the transmission dynamics of incurable viral STIs.

Behaviors that can reduce the average duration of infectiousness include timely and appropriate health care seeking, effective participation in risk assessment, and compliance with therapy and prevention recommendations on the part of those infected and at risk (Aral and Wasserheit 1999). Health care seeking depends on perceived seriousness and causality of symptoms, availability and accessibility of health care, costs

(including opportunity costs) of treatment, perceived and actual quality of care, and beliefs about the appropriate provider to consult. The proportion of those infected seeking care is highly variable, and delays in seeking treatment can be substantial. In many places, the proportion of people seeking timely care from appropriately trained providers is limited (Hawkes and Santhya 2002; Moses and others 2002; Rekart 2002).

Behaviors on the part of health care providers that ensure timely and accurate diagnosis, appropriate treatment, and non-judgmental attitudes toward those infected would also help reduce the duration of infectiousness of STIs. However, establishing effective, accessible, affordable, and decentralized services is difficult (Over 2004; World Bank 2003). The major barriers Moses and others (2002) identified in Nairobi reflect the situation in many developing countries. Those barriers include inadequate basic training and inefficient deployment of health workers; attitudes of health workers toward marginalized groups (for instance, female sex workers); high patient loads at health centers; lack of supportive supervision; inadequate referral systems; chronic shortages of supplies and drugs; and inadequate recording of health information. User fees can be a substantial additional barrier, though they may contribute to the sustainability of the treatment program and improve the provider's incentives.

Behavioral Interactions. Both at the individual and the population levels, people's risk behaviors respond to changing circumstances. In many developing countries where HIV incidence has been high, people have adopted compensatory behavior changes, such as delayed age of sexual debut, reduced number of sex partners, and increased use of condoms (Shelton and others 2004; Stoneburner and Low-Beer 2004), especially with high-risk partners (Peterman and others 2000). Some people now seek health care when they suspect they have been exposed to an STI.

At the same time, risk behaviors can overlap: people who initiate sexual activity early in life tend to have many partners, and people who engage in risky sex tend to also use drugs and alcohol. A history of sexual abuse or of being an abuser is also positively associated with high-risk sexual behaviors and drug use (Aral 2004). The adoption of preventive behaviors raises the possibility that people will compensate by changing other behaviors in response; for example, many believe that the widespread adoption of antiviral therapy or condom use may lead to increases in the numbers of sex partners (Blower and others 2001; Blower and Farmer 2003; Over and others 2004). Although constructing mathematical models to explore the effects of such changes in behavior is helpful, empirical research in varied contexts is urgently needed to identify the variables that determine patterns of interaction among risky and preventive behaviors. Two such variables may be individual autonomy and awareness of the epidemiological context.

Societal Determinants of STIs. Sexual networks and patterns of sexual partnership formation and dissolution constitute a major mechanism through which the political economy and the sociolegal system influence the rate of spread of STIs in a population. Sexual networks that are highly critical to the rate of spread of STIs include those involving sex work; exchange of sex for drugs, gifts, or material needs; and anonymous sex. The frequency of sex in exchange for money or other goods appears to be highly sensitive to changes in the political economy and the sociolegal system. Internal conflicts, war, economic crises, and social collapse are accompanied by the establishment of major sex markets or the expansion of existing ones. For example, following the collapse of the former Soviet Union, the number and size of commercial sex and sex-drug networks expanded significantly (Aral and St. Lawrence 2002; Aral and others 2005). The availability and use of condoms also influence the rate of spread of STIs.

Many developing countries continuously face political conflict, war, economic deterioration, mass migration, and increasing inequality plus the effect of globalization. In addition, in most developing societies, gender power relationships are marked by great inequality. Those contextual factors lead to sexual networks and sexual mixing patterns that are highly conducive to the spread of STIs. Sexual partnerships are often not stable, and in the long-term absence of a spouse, both men and women (but especially men) have other partners.

In addition, as economic needs rise, the number of women who exchange sex for material needs increases. Wilson and others (1989) estimate that approximately 10 percent of the female population in Bulawayo, Zimbabwe, had engaged in full- or part-time sex work at some time in their lives, whereas Aral and St. Lawrence's (2002) estimates for Saratov, Russian Federation, are closer to 25 percent. As the supply of sex workers increases, the demand for their services often increases in parallel. Economic need also affects sexual mixing patterns. In most developing countries, young girls commonly have "sugar daddies"—that is, older, often married men who provide them with material goods in return for sex while also exposing them to chronic STIs typical of relatively older cohorts (Gregson and others 2002).

Gender inequalities put women in a highly vulnerable position in many ways. For example, Decosas and Padian (2002) find that, among women attending family-planning and primary health care clinics in Zimbabwe, 17 percent had at some time received a gift in exchange for sex, 22 percent had been forced to have sex with a steady partner, 5 percent had been forced to have sex with a nonsteady partner, 35 percent were certain their steady partner had other partners, 27 percent said their partners had STI symptoms, 24 percent said their partner was intoxicated during sexual intercourse more than half the time, and only 10 percent had used a condom in the previous three months.

Income and Inequality. A cross-country database (George Schmid, personal communication, September 15, 2004) enables us to analyze the association between national STI prevalence rates and two important economic variables: gross national income per capita and the degree of income inequality as measured by the Gini coefficient.¹ As table 17.1 shows, these two variables explain 45 percent of the variation in STI prevalence in low-risk groups and 16 percent of STI prevalence in high-risk groups. Figure 17.1 illustrates the relationship between each of these two economic variables and STI prevalence.

Poor countries' higher prevalence rates of STIs are unsurprising and could be explained by the fact that people in richer countries are likely to seek and find care for STIs more quickly. More notable is that income inequality is such a strong predictor of STI prevalence even after controlling for gross national income per capita. Furthermore, income inequality is a strong predictor of STI prevalence among high-risk groups, where income per capita performs less well. A possible explanation for this finding is that greater inequality creates more active markets for commercial and casual sex as higher-income men negotiate for the sexual services of lower-income sex workers (Aral 2002b; Over 1998).

Table 17.1 Cross-Country Regressions of Average STI Prevalence on Per Capita Income and the Gini Coefficient of Inequality for Low- and High-Risk Groups, Selected Countries

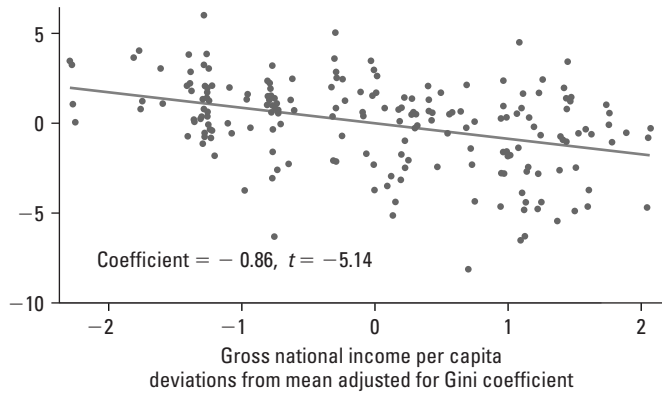
Category	Average prevalence of STIs in low-risk groups	Average prevalence of STIs in high-risk groups
Gross national income purchasing power parity per capita, log, 19–2001	−0.862**	−0.194+
Gini index, 1990s	7.731**	2.73*
Dummy for syphilis	0.093	−0.051
Dummy for chlamydia	1.992**	0.308
Dummy for herpes	3.611**	1.507**
Constant	−0.515	−1.751
R ²	0.45	0.16
Number of countries	204	147

Source: Authors' calculations from Schmid and others 2004.

Note: * = probability of less than 0.05 percent; ** = probability of less than 0.01 percent. Positive numbers indicate a probability of 0.1 to 0.2 percent. Both regressions pool data across these STIs: syphilis, chlamydia, and herpes. The coefficients of the dummies show that the estimated prevalence rates are significantly higher for herpes than for the other diseases. Among low-risk groups, the prevalence of chlamydia is higher than that of syphilis. Standard errors (not shown) are estimated using the White correction for heteroskedasticity under the assumption that the observations for a single country are comparable to a cluster of data. Other explanatory variables that were unsuccessful in explaining a significant proportion of the variance included percentage of the population foreign born, percentage of the population that is Muslim, male-to-female literacy gap, urban male-to-female population ratio, and military personnel per 1,000 urban population.

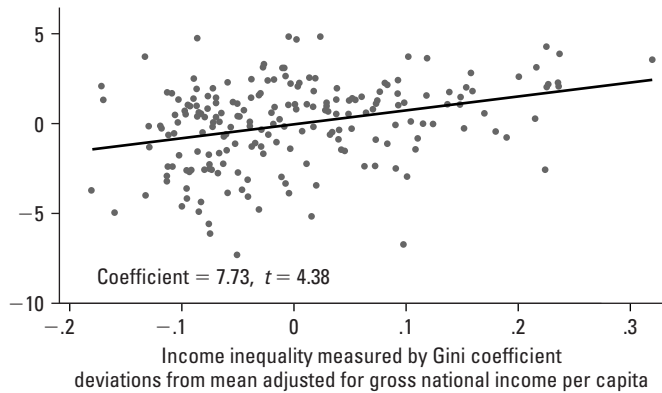
a. Gross national income per capita

Average national prevalence of STIs among low-risk groups (deviations from mean)



b. Income inequality

Average national prevalence of STIs among low-risk groups (deviations from mean)



Source: Authors' calculations based on personal communication with George Schmid (April 5, 2004).

Figure 17.1 Association between Per Capita Income and Income Inequality with STI Prevalence for Low-Risk Groups, Selected Countries

BURDEN OF STIs AND BENEFITS OF CONTROL

On the basis of an independent analysis of cross-country data on STI prevalence, we believe that WHO may have underestimated the burden of STIs relative to that of HIV and other diseases (www.fic.nih.gov/dcpp/gbd.html). Adjusting the WHO estimates on the basis of our calculations increases the estimate of years of life lost burden by about 18.1 percent and the overall estimate of disability-adjusted life years (DALYs) lost by about 8.2 percent.

DALYs Gained from Effectively Preventing or Treating STIs

In the first edition of this volume, chapter 20 presented estimates of the so-called static and dynamic burdens of preventing or curing a single case of an STI and of HIV (Over and Piot 1993). We reproduce those estimates in table 17.2 for four of the STIs.² The static benefit column estimates the average number of DALYs saved for a single person by curing or preventing his or her own case of each disease. These estimates are based on specific assumptions regarding the distribution of incidence, case-fatality rates, and severity across age ranges. Although updating these estimates to 2004 and varying them by region would ideally be possible, we have not found any more recent data. If the person who is cured of an STI ceases to be sexually active, the static benefit would be the only benefit of curing or preventing his or her case; however, most individuals who have contracted an STI remain sexually active and are therefore likely to communicate that STI to others. An STI prevented or cured in a sexually active person will prevent additional cases in that person's sex partners, in the sex partners' partners, and so on. Thus, the dynamic benefit columns indicate the magnitude of those additional benefits.

The key finding is that preventing or curing a case of any of the STIs in a core group member generates approximately

Table 17.2 Discounted DALYs Saved Per Case Prevented or Cured

STI	Static benefits	Dynamic benefits		Total benefits	
		Member of noncore group	Member of core group	Member of noncore group	Member of core group
Chancroid	0.2	0.2	1.6	0.4	1.8
Chlamydia	1.1	4.4	43.0	5.5	44.1
Gonorrhea	0.9	3.6	36.4	4.5	37.3
Syphilis	3.8	16.0	157.0	19.8	160.8
<i>For comparison</i>					
HIV without ulcers	19.5	35.1	340.1	54.6	359.6
HIV with ulcers	19.5	39.2	410.7	58.7	430.2

Source: Over and Piot 1993, table 20-16, appendix 20B.

10 times the dynamic benefits of the same intervention in a person in a noncore group. This result is driven by the assumption that a member of a noncore group has a new sexual contact every 50 days, or about seven new contacts per year, whereas a member of a core group has 10 times as many contacts. Within this model, the results are proportional to the frequency of partner change, so that the dynamic benefits of curing or preventing a case in a sex worker who has two partners a day would be approximately 10 times as great as for a member of the core group in table 17.2. The implication is that preventing or curing a case of syphilis in a sex worker can result in up to 1,600 DALYs of benefit, a health effect that is likely to be competitive with any discussed in the other chapters in this volume.

Impact of STIs on HIV

The preceding discussion does not address the possibility that STI infections increase HIV transmission. On this point the evidence is mixed, with a study in Mwanza, Tanzania (Grosskurth and others 1995), demonstrating a statistically significant 40 percent reduction in HIV incidence attributable to an STI intervention, while two studies (Kamali and others 2003; Wawer and others 1999) in Uganda failed to show any such effect. Recent reanalyses (Orroth 2003) of the data from these studies suggest that the effect of an STI intervention on an HIV epidemic will vary depending on the sexual activity and resulting prevalence of STIs among those being treated.

None of the randomized controlled trials of the effect of STI treatment on HIV prevention exclusively targeted the most sexually active people in the community. In Mwanza, Tanzania, and Masaka, Uganda, treatment was provided to those who sought it at health care clinics. In Rakai, Uganda, treatment was given to all adults in all households, regardless of whether the individual complained of STI symptoms. Data on the prevalence of HIV infection in the three communities suggest that the HIV and STI epidemics were both at an earlier stage in Mwanza and were therefore more concentrated among those more sexually active. Thus, the people who became symptomatic and sought treatment were among the most sexually active people in Mwanza, and treating them would therefore have had a greater effect on HIV incidence than would treating an average person in the two Ugandan sites. Conversely, in the more generalized epidemics in Uganda, a larger proportion of new infections occurred within stable HIV-1 serodiscordant couples.

An alternative, less rigorous way to test for the effect of STI prevalence on HIV infection is to study the cross-sectional correlation in ecological data. In a replication of an earlier study (Over 1998), we have attempted to explain urban HIV prevalence in a cross-country sample by the prevalence of syphilis and gonorrhea seven years earlier after controlling for six other potentially confounding variables. The results of these cross-

country regressions are presented in table 17.3.³ Columns (1) and (2) of table 17.3 present the results of regressions estimated on the subsets of countries for which data are available on all eight explanatory variables and on the dependent variable (2002 urban HIV prevalence). Their specifications differ only by the replacement of the prevalence of syphilis as an explanatory variable in column (1) with the prevalence of gonorrhea in column (2). Columns (3) and (4) repeat the same two regressions by replacing missing values of the two prevalence rates with estimates that are based on a regression of these rates on the other variables in the regression. This procedure expands the samples dramatically from 56 and 38 to 181 and 180, respectively.⁴

In interpreting these regressions, note first that all four specifications explain more than half of the variance in 2002 urban HIV prevalence, a remarkably good fit for cross-sectional regressions. In all these specifications, the lagged value of an STI prevalence is a statistically significant predictor of HIV prevalence approximately seven years later. The coefficient for gonorrhea is larger than the coefficient for syphilis and is more statistically significant in the augmented sample, though less so in the basic sample.

After the age of the epidemic is controlled for, several other variables contribute to explaining the variation in HIV prevalence. These variables include national income per capita (richer countries have lower infection rates), the percentage of the population that is Muslim (a higher percentage is associated with lower infection rates), and the ratio of males to females in the sexually active age range (higher ratios are associated with higher infection rates).

The major difference between the regressions using the augmented sample and those using the basic sample is in the statistical significance of the estimated coefficient of income inequality as measured by the Gini coefficient. When the sample is expanded to take advantage of the available data, the coefficient stabilizes at about 5.3 and is statistically significant at the 0.01 probability value, suggesting that an increased degree of income inequality is associated with increased HIV infection even after controlling for STI prevalence. This result lends support to the idea that income inequality is just as important as poverty in setting the stage for HIV transmission.

As with the results of any ecological or cross-sectional analysis, questions of attribution and interpretation arise. Is the statistically significant coefficient of syphilis or gonorrhea capturing a biological effect of an STI on increasing the transmission probability during sexual intercourse? Or is the coefficient instead simply reflecting the fact that greater sexual activity spreads all STIs, including gonorrhea, syphilis, and HIV? Is the coefficient of the percentage of the population that is Muslim capturing differential sexual activity or the prevalence of male circumcision, which is increasingly recognized as biologically protective? A biological interpretation of both the STI and the Muslim coefficients is suggested by the fact that the variable

Table 17.3 Multiple Regression of circa 2002 Urban HIV Prevalence on circa 1995 STI Prevalence and Other Socioeconomic Variables

Category	(1)	(2)	(3)	(4)
	Basic sample with syphilis	Basic sample with gonorrhea	Augmented sample with syphilis	Augmented sample with gonorrhea
Age of epidemic (urban low) in 2002 ^a	0.177 (4.07)***	0.131 (2.00)*	0.12 (2.90)***	0.08 (1.70)*
Per capita national income, median 1996–2001	−1.344 (2.82)***	−1.177 (2.30)**	−0.929 (3.63)***	−0.949 (4.45)***
Income equality, Gini index, 1990s	0.125 (0.04)	3.186 (0.83)	5.349 (2.77)***	5.258 (2.79)***
Percentage of the population that is Muslim, 1999	−0.026 (4.05)***	−0.031 (3.50)***	−0.015 (3.45)***	−0.02 (4.10)***
Urban male-to-female ratio for those age 20–39, 1999	6.178 (2.03)**	6.199 (1.40)	3.27 (1.29)	3.038 (1.19)
Urban high-risk population dummy (1 if yes, 0 is no)	1.17 (2.83)***	0.564 (0.85)	0.894 (2.64)***	0.37 (0.71)
Logit syphilis in low-risk group, 1995 ^b	0.31 (2.46)**		0.233 (1.78)*	
Logit gonorrhea in low-risk group, 1995 ^b		0.502 (1.92)*		0.479 (1.86)*
Constant	0.297 (0.05)	−0.791 (0.11)	−2.117 (0.63)	0.054 (0.02)
Number of observations	56	38	181	180
Number of countries	40	29	101	100
R ²	0.57	0.56	0.5	0.51

Source: Authors' calculations. Syphilis and gonorrhea prevalence in 1995 (George Schmid, personal communication, April 5, 2004). HIV prevalence circa 2002 is from the urban low-risk tables in the U.S. Bureau of Census database on HIV prevalence. Other variables are from World Bank data.

* = significant at 10 percent; ** = significant at 5 percent; *** = significant at 1 percent.

Note: The figures in parentheses are robust *t*-statistics.

a. Age of epidemic is defined as the number of years since the first case of HIV/AIDS was reported.

b. The logarithm of the ratio of the prevalence to 1 minus the prevalence of the given STI for the low risk population in 1995.

urban male-to-female ratio is probably already capturing much of the variation in the most risky sexual behavior: the practice of prostitution.

Increasing the availability of treatment for STIs and for HIV infection reduces the prevalence of the former and increases the prevalence of the latter. Thus, this statistical relationship between STI prevalence and HIV prevalence, even if once valid, will no longer obtain. Under current conditions, estimating the effect of a change in the prevalence rate of an STI on the incidence rate of HIV would be more relevant.

If we assume that in 2002 the HIV epidemic was approaching equilibrium in many urban settings and that prior to anti-retroviral treatment the median duration of the illness was about 10 years, the prevalence of HIV infection is approximately equal to 10 times the incidence rate. Thus, a 10 percentage point increase in the prevalence of syphilis or gonorrhea is estimated to increase the incidence of HIV by 0.27 percentage points for syphilis and 0.57 for gonorrhea. For comparisons,

the Mwanza trial found that a reduction in the prevalence of male urethritis of 0.6 percent was associated with a decrease of 0.7 percent in the incidence of HIV (Grosskurth and others 1995). Thus, the present study suggests an effect about one-fourth as strong as that of the Mwanza study.

EFFECTIVENESS OF THE PRINCIPAL INTERVENTIONS

Unlike HIV interventions, STI interventions benefit from a large body of rigorous evaluations. STI interventions that have been rigorously evaluated for effectiveness can be organized by intervention level (that is, individual, group, or community); by the outcomes measured; and by the intervention modality used (for example, behavior change, vaccination, topical microbicide use, screening, or treatment). Prevention outcomes may measure the prevention of acquisition, of

transmission, and of complications of STIs (Manhart and Holmes 2005). This section reviews the interventions for which the strongest evidence exists.

Individual-Level Interventions

A large number of STI interventions that have been rigorously evaluated are individual-level interventions.

Preventing Acquisition. The following have been the main means of preventing STI acquisition:

- *Behavior change.* Counseling on risk reduction was the most frequently used behavior-change approach. Most studies showed a reduction in risk behaviors as a result of counseling, and some showed decreases in STI outcomes (Kamb and others 1998).
- *Antimicrobial prophylaxis.* Two studies (Harrison and others 1979; Kaul and others 2004) showed reductions in the incidence of gonococcal, chlamydial, or trichomonal infections following antimicrobial prophylaxis.
- *Vaccines and passive immunization.* A yeast-derived HPV type 16 vaccine was 100 percent efficacious in preventing persistent HPV-16 infection in young college women (Koutsky and others 2002), and a bivalent HPV type 16 and type 18 vaccine was also highly efficacious in preventing those infections. An HSV-2 glycoprotein D-adjuvant vaccine among those with no serological evidence of prior HSV-1 infection partially protected women, but not men, from experiencing genital herpes disease, with 73 percent efficacy for such women in one trial and 74 percent in another (Stanberry and others 2002).
- *Microbicides.* To date, studies have not identified any efficacious topical microbicides.
- *Male circumcision.* Even though cross-sectional evidence suggesting that male circumcision decreases the risk of acquiring chancroid and HIV is strong, outcome data are not yet available from ongoing randomized trials in Kenya, South Africa, and Uganda.

Preventing Transmission. All individual-level interventions aimed at preventing transmission have involved curative or suppressive therapy. Giving tinidazole to male partners of females treated for vaginal trichomoniasis infections significantly reduced recurrences in the females; administering valacyclovir to positive members of HSV-2 serodiscordant couples reduced the incidence of symptomatic genital herpes and HSV-2 seroconversion in the uninfected partners; patient-delivered therapy to partners of women with chlamydial infection demonstrated a nonsignificant trend toward reduced risk of reinfection with *C. trachomatis*; and expedited partner therapy (usually patient delivered) significantly reduced persistent

or recurrent gonococcal or chlamydial infection in the index patient (Golden and others 2005).

Preventing Complications. Risk-based screening for *C. trachomatis* infection resulted in a 56 percent reduction in the subsequent risk of incident pelvic inflammatory disease (Scholes and others 1996). Several trials have shown that antiviral suppression decreases clinical and virological recurrences of genital herpes (Corey and Handsfield 2000).

Group-Level Interventions

Studies of behavior-change methods in small-group settings to reduce the acquisition of STIs had mixed outcomes. Behavior-change approaches resulted in significant reduction in incident STIs; antimicrobial prophylaxis and provision of female condoms did not.

Community-Level Interventions

Four community-level randomized trials have sought to reduce the prevalence and transmission of STIs by shortening the duration of infectiousness within the general population (Manhart and Holmes 2005).

The “Mema Kwa Vigara” study in Mwanza, Tanzania, randomized 20 communities to intervention and control communities. The intervention consisted of school-based sexual and reproductive health education, enhanced reproductive health services for youths, condom distribution, and community activities. Knowledge and reported behaviors improved; however, no differences were apparent between the intervention and control communities in relation to HIV or HSV-2 seroincidence, incidence of other STIs, or pregnancy outcomes (Hayes and others 2003).

A second study in Mwanza, Tanzania, randomized communities to intervention and control conditions. The intervention consisted of syndromic treatment of STIs. The results showed a 40 percent reduction in HIV incidence and reductions in symptomatic urethritis in men and prevalence of syphilis seroreactivity; the prevalence of gonorrheal or chlamydial infection in prenatal women did not change (Grosskurth and others 1995; Mayaud and others 1997).

In a community randomized trial in Masaka, Uganda, one community received information, education, and communication; a second community received information, education, and communication plus syndromic management of STIs; and the control received community development assistance. The results showed no differences in HIV-1 incidence. The incidence of HSV-2 seroconversion declined in the community receiving information, education, and communication only; the incidence of syphilis and of gonorrhea decreased in the community receiving information, education, and communication plus

STI syndromic management; and condom use increased in all three communities (Kamali and others 2003).

In Rakai, Uganda, a community randomized trial evaluated the efficacy of repeated mass treatment of STIs. Relative to control communities, in intervention communities the prevalence of *T. vaginalis* in women was reduced significantly, but no significant reduction was apparent in prevalence of gonorrhea, chlamydial infection, new syphilis seroreactivity, and bacterial vaginosis; in HIV incidence; or in history of urethral or vaginal discharge or genital ulcer disease (Wawer and others 1999). A subanalysis of pregnant participants showed a reduction in the prevalence of several STIs in women tested near delivery and in potentially STI-related pregnancy, puerperal, and neonatal morbidity (Gray and others 2001).

Conclusions on Interventions

The review of STI intervention research suggests several, perhaps counterintuitive, insights:

- First, most evidence is on individual-level interventions aimed at reducing STI acquisition, even though individual-level interventions may be costly and difficult to sustain.
- Second, behavior change is the most commonly evaluated modality, followed by treatment.
- Third, theory-based behavioral interventions failed to show an effect as often as behavioral interventions not based on theory.
- Fourth, behavioral interventions delivered in small group settings were as effective as those delivered to individuals (Manhart and Holmes 2005).
- Fifth, the effect of a particular behavior change on STI risk depended on the type of STI; however, the number of partners may be more predictive of risk for highly infectious STIs than for HIV, and unprotected sex acts may be more predictive of risk for HIV than for highly infectious STIs (Semaan and others 2002). Thus, behavioral interventions may have different effects on STIs of differing infectiousness.
- Finally, the number of intervention trials that demonstrate declines in risk behaviors combined with either no effect on STIs or increases in STIs is increasing. This observation calls into question the use of behavioral outcome measures as indicators of biomedical outcomes (Aral and Peterman 2002).

INTERVENTION COSTS AND COST-EFFECTIVENESS

Widespread implementation of effective interventions depends on cost and cost-effectiveness considerations.

Organization of STI Control Activities in Poor Countries

In poor countries, patients can typically obtain treatment for an STI in a public sector health care facility. Many countries have publicly funded, stand-alone STI clinics, but the typical pattern is for health care personnel to provide care for STIs as part of their regular practice in general outpatient clinics. Despite the availability of such publicly funded care, or perhaps because of concerns about anonymity, many STI patients in poor countries avoid public facilities in favor of traditional healers and private pharmacies. A recent study of the cost-effectiveness of delivering STI treatment through trained pharmacists in Peruvian cities included reports of the popularity of self-treatment in Brazil, Cameroon, Ghana, Nepal, South Africa, Thailand, Vietnam, and Zambia (Adams and others 2003). After reviewing this literature, Adams and others selected the point estimate of 0.4 as their best guess for the proportion of STI patients seeking treatment from a pharmacy in Lima.

Determinants of the Costs of Interventions

We adopt a government perspective in analyzing the costs and cost-effectiveness of interventions. Thus, we define the costs of an activity as the total budgetary expenditure attributable to that activity—that is, the total budget for buildings, equipment, personnel, and supplies, with adjustments made when buildings are used for multiple purposes.

We define the unit costs of an activity as the total budgetary expenditure during a stated time period divided by the number of units of output during that same period. Because the same activity can have several outputs, this definition necessarily entails some ambiguity. For example, an intermediate output of the delivery of STI treatment services is the patient treated, whereas a more final output is the patient cured. An even more complete measure of output would include the secondary infections averted as a result of the cure.

One of the reasons that many economists prefer cost-benefit analysis to cost-effectiveness analysis is that the former attaches a dollar value to each of the outputs of an activity and then aggregates across the outputs to construct a summary measure of the total benefit of the activity. However, this simple result hides many arbitrary assumptions that are required to value the separate outputs. One of the most arbitrary of these assumptions is the assignment of a dollar value to a healthy life year. So instead we present costs and cost-effectiveness denominated in the outputs for which we have data. We then go as far as we can toward aggregation by adopting the conventions of the healthy life year and the disability-adjusted healthy life year.

Kumaranayake and others' (2004) background study for this chapter reviews the literature on the unit costs of STI treatment. They identify 35 studies on this topic that provide a total of 77 unit cost estimates. These are grouped in table 17.4 by the disease or syndrome being treated and by the output that was

Table 17.4 Average Estimated Costs per Unit of Output, by Disease or Syndrome and Type of Output (2001 US\$)

Disease or syndrome	Treatment	Cure	Average
Syphilis	36.04 (5.91)	n.a. n.a.	36.04 (5.91)
Urethral discharge	14.29 (20.68)	89.07 (0)	29.25 (37.94)
Genital ulcer	23.16 (21.73)	100.60 (83.74)	48.97 (59.56)
Venereal disease	25.47 (18.56)	82.65 (111.55)	31.83 (37.12)
Pelvic inflammatory disease	7.12 (3.09)	n.a. n.a.	7.12 (3.09)
Vaginal discharge	48.23 (0)	102.92 (89.63)	81.04 (70.10)
Total	24.05 (19.04)	96.10 (73.44)	39.49 (47.23)

Source: Authors' calculations based on a literature review done as a background study for this chapter by Kumaranayake and others 2004.

n.a. = not applicable.

Note: The figures in parentheses are standard deviations. The 42 observations in the table are individual unit cost estimates distributed across separate studies.

costed. Of the 46 estimates of the unit cost of treatment, only 33 could be interpreted as, or converted to, 2001 U.S. dollars, and the same applied to 9 of the 10 estimates of the unit cost of a cure. Table 17.4 summarizes the results of these studies by the disease or syndrome that occasioned the treatment.

The most notable thing about the summary statistics is their variability: the cost per unit of output can vary by a factor of 100 or more. Even though the mean dollar cost per cure could plausibly be almost four times that of treatment alone, the standard errors are so large as to make the difference statistically insignificant.

The same point—that is, that unit costs vary enormously from one site to another—is made by the preliminary results of a study by Dandona and others (2005). The cost per case treated in the study varies by a factor of 10 across the 14 sites. Furthermore, the two sites that treat the fewest and the most cases per year also display the highest costs, a finding that suggests the existence of both economies and diseconomies of scale.

The variables that determine the costs—and therefore the cost-effectiveness—of STI treatment include the following:

- delivery by the public or private sector
- economies of scale
- economies of scope
- prevalence and incidence
- epidemic phase
- transmission efficiency
- health system characteristics

- population composition and concentration
- resource combinations and input prices
- incentives to providers for high quality and quantity of service delivery
- willingness to pay for treatment as a function of price, income, and distance
- stigmatization
- disutility of condom use.

SCALING UP CONTROL STRATEGIES

Throughout the history of STI control, tension has been apparent between those who support prioritizing resources for the small proportion of people with the most sexual contacts and those who advocate spreading prevention, screening, and treatment resources more thinly over the entire population. Opponents of prioritization argue that most of the people who practice the riskiest behavior are hard to find and that attempts to find them would expose those individuals to stigmatization and repressive measures.

A group of researchers at the University of North Carolina has developed and applied a novel approach to STI interventions that has demonstrated in several countries that finding the people who practice the riskiest sexual behavior without targeting them as individuals is possible (Weir and others 2003). As an example of this approach, consider its application to Madagascar, a country where risky sexual behavior had previously been thought to be too common to be identified or to be distinguished from less risky behavior.

In May 2003, the Malagasy Steering Committee, which consisted of representatives of the Ministry of Health, local government officials, and other knowledgeable experts, selected five towns judged to be at high risk for STIs for a pilot study. The Priorities for Local AIDS Control Effort (PLACE) method applied in these towns was, first, to interview adults at random on the streets of the city to find out where people go to meet and socialize and, second, to visit and collect data on these locations and the people who frequent them.

In each of the five cities, the informants tended to agree on the most frequented sites. They identified between 70 and 267 unique socialization sites of various types, ranging from bars and restaurants to beaches and brothels. Interviews with people frequenting the sites revealed them to be much more sexually active than the average Malagasy adult. According to the 1997 demographic and health survey, 13 percent of women outside the capital city, Antananarivo, had two or more sexual partners in the previous year. In contrast, the percentage of women at the socialization sites who had had more than two partners ranged from 46 to 68 percent. According to the demographic and health survey, only about 3 percent of women outside Antananarivo had four or more partners in the previous year, but the percentage of women at the study sites

having this many partners was 10 times larger. The men interviewed at these sites were even more sexually active than the women.

The pilot study also investigated whether information on or products for prevention of STIs, HIV, or both were available at the socialization sites. In the five towns, the proportion of sites where condoms were available on the day of the visit varied from 27 to 54 percent. These percentages are not negligible and are undoubtedly much higher than they were 10 years ago, and the availability of condoms at so many of these sites is a tribute to the success of the condom social-marketing campaign. However, the statistics also indicate substantial room for improvement, for example, by distributing condoms in 100 percent of identified socialization sites. The feasibility of such a program is enhanced by information from the PLACE study that more than 80 percent of the owners or managers of these sites expressed their willingness to host STI and HIV prevention programs, and more than half were willing to sell condoms.

Researchers have carried out similar PLACE studies in Burkina Faso, Ghana, South Africa, and elsewhere. Unfortunately, in none of these countries has this extensive risk mapping been followed by the implementation of prevention programs at all the identified locations. Until such programs are implemented and evaluated, no African country will be able to claim that it has scaled up the most effective type of STI prevention to population levels.

RESEARCH AND DEVELOPMENT AGENDA

Priorities for global STI research include the following:

- The development and evaluation of therapeutic (drug treatment or vaccines), behavioral, and structural interventions to prevent or reduce STIs and their sequelae. Given the spread of drug-resistant strains of gonorrhea and other STIs, new pharmaceutical products and new combination therapies are needed to prevent and treat STIs.
- The development and evaluation of mechanisms to accurately quantify the disease burden in order to prioritize activities.
- The development and evaluation of inexpensive and practical rapid diagnostic tests to permit early detection and treatment of STIs.
- The conducting of studies to evaluate effective prevention modalities for persons at highest risk for STIs.
- The undertaking of health services research to gain an understanding of practical and cost-effective STI prevention strategies or systems that ideally can be integrated into existing public health infrastructure. When an individual is treated for an STI, this treatment has both positive and neg-

ative spillover effects (externalities). The right combination of patient and provider incentives needs to be found that will maximize the beneficial spillovers while minimizing the harmful ones.

- The implementation of studies in support of global elimination programs.

Because of the clandestine nature of most sexual behavior, STIs are probably massively underreported, which in turn leads to an underestimation of their importance. New survey and measurement tools have been developed. They now need to be applied to populations in poor countries to improve these estimates.

In addition, randomized controlled trials need to be conducted in different settings to test the hypothesis that treating or preventing STIs in high-risk individuals has beneficial spillover effects by preventing infections among low-risk individuals. An improved understanding of the determinants of high-risk sexual behavior and the role that such behavior can sometimes play in helping women to escape from poverty and helping men to cope with it is also needed, as is a better understanding of the full range of benefits of effective STI interventions for high-risk individuals and their dependents.

As concerns disease modeling and surveillance, further improvements are needed in understanding the implications for interventions of different kinds of local, regional, and international sex networks.

Tools

Because of the difficulty of persuading patients to adhere to a course of medication for the prescribed period, single-dose therapy would be valuable. Rapid, point-of-care diagnostics are also a high priority, so that drugs can be targeted at pathogens more accurately. New approaches for treating chronic STIs should be incorporated into prevention strategies, and blister packs of antibiotics that can be sold over the counter for syndromic management of STIs should be available.

Vaccines would be particularly valuable, both for preventing and for potentially treating chronic viral STIs and chlamydial infection, which is often asymptomatic but is responsible for considerable morbidity.

Diagnostics tests that could be used at home or at social meeting spots may help people decide whether to engage in risky sex. Packages of diagnostic tests that change color when the contents expire would also be useful.

Intervention Methods

Syndromic management algorithms have now existed for more than a decade. However, treatment algorithms are sensitive to changes in the relative prices of pharmaceuticals and diagnostic

reagents, in the prevalence of the various STIs, in pathogens' resistance, and so on. Thus, every country needs some ability to respond to local changes by developing or modifying algorithms as needed.

As concerns intervention packaging, many policy makers continue to believe that the most sexually active people are hard to find. This belief hampers efforts to target these people with STI prevention programs. The PLACE methods developed at the University of North Carolina offer an opportunity to correct that impression and should be packaged with other urban public health functions. Packaging sex education into school curricula is a challenge in most of the world. As enrollment rates for poor children, especially girls, rise, the presence of a strong, culturally appropriate, sex education curriculum will lay the foundation for strong STI prevention and treatment campaigns.

As this chapter has argued, the determinants of the unit costs of STI treatment and prevention are largely unknown. We recommend health services and operations research to study the determinants of the unit costs of STI prevention and treatment services. The purpose of this research would be to learn not only how to deliver care in the most cost-effective ways, but also how to build systems that achieve that technological frontier in a high percentage of public and private facilities and pass those cost savings on to the government and to patients. Given the beneficial spillover effects from effective STI prevention and treatment among those who are most sexually active, research is needed to learn how the PLACE approach to targeting can be implemented most cost-effectively in different cultural contexts.

Finally, improved understanding of the best way to design an STI treatment system, including the rewards and penalties that best motivate providers (to be polite, discrete, prompt, efficient, and accurate in following best practice, evidence-based treatment protocols) and patients (to seek and then to adhere to treatment) is a priority. Improved data on the costs of each STI intervention at the pilot stage and after scaling up to the national level are also necessary.

CONCLUSIONS

Regarding the cost-effectiveness of STI control, the position this chapter takes is "it depends." The health benefit in terms of numbers of disability-adjusted, discounted, healthy life years saved by curing or preventing a case of syphilis varies from 3 years in a person who has ceased all sexual activity to as many as 161 years in a sex worker with two partners a day. The cost of treating that prostitute for syphilis varies from US\$5 to US\$100. Thus, the cost per DALY of syphilis treatment can range from 100/3 or US\$33 per DALY to 5/161 or less than US\$0.05 per DALY.

As we learn more about the complexities of delivering STI treatment services and take into account the diversity of risk behavior, the ease with which STI interventions can be ascribed a simple cost-effectiveness ratio has declined. If no easy way to summarize experience to date with a simple cost-effectiveness ratio is available, how should we analyze economic investments in STI treatment? We believe that the way forward is a better understanding of why STI treatment and other health services vary so much in terms of their efficiency and effectiveness from one setting to another. By studying the determinants of this variation, we should gain an improved understanding of the full costs of high-quality STI service delivery and its place in the health sector investment picture.

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NOTES

1. The Gini coefficient is a measure of inequality that here we apply to income. If income is distributed equally in the population, the coefficient is equal to 0, and if a few individuals hold almost all the wealth, the coefficient is close to 1.

2. Given that WHO has expended enormous efforts to estimate discounted years of life lost, disability years lost, and DALYs lost as a result of STIs, the simplest and most direct approach for computing the DALY benefits of preventing or curing an STI in a single patient would be to use WHO's years of life lost, disability years lost, or DALY per case assumptions. Alternatively, one could simply divide WHO's aggregate values of these indicators by the incidence rate of each disease in each region to obtain the estimated burden per incident case. Unfortunately, neither the case-specific burden numbers nor the incidence rates that correspond to the DALY aggregates are available from WHO.

3. In contemporaneous data, STIs can either affect or be affected by HIV prevalence. To focus on the effects of an STI on HIV infection, we lag infection by an STI by seven years. Though partially correcting for simultaneity bias, this strategy does not allow us to identify whether lagged STI prevalence is directly affecting HIV infection or only serving as a proxy for the risky sexual behavior that drives both epidemics.

4. The samples include two measures of HIV prevalence (low- and high-risk groups) for some countries. These measures enable us to expand the sample used in the column (1) regression from 40 countries to 56 separate observations. Equations are estimated with Stata's cluster option to correct the standard errors of the coefficients for the correlation between the errors on separate observations from the same country. The variable urban high-risk dummy is used to shift the intercept coefficient for the high-risk sample in comparison with the low-risk one.

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