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CME

LEARNING OBJECTIVES

Upon completion of this article, participants will be able to:

- Describe the differences in prevalence and epidemiologic data for STDs in research-poor countries.
- Review the evidence of the amplifying effect of STDs on HIV infection.
- Discuss various prevention strategies targeting a combined approach to HIV and STDs and the potential impact of these approaches on both STD and HIV dissemination rates.

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Treating STDs to help control HIV infection

By Willard Cates, Jr., MD, MPH

Only by combining several preventative strategies can we hope to make a dent in controlling the skyrocketing levels of sexually transmitted disease worldwide—and reducing the HIV pandemic.

With more than 36 million adults and children worldwide living with HIV or AIDS alone, high rates of sexually transmitted diseases are clearly a huge reproductive-health issue—yet one that hits close to home, as well.[1] What's more, scientific studies continue to suggest a synergistic relationship between HIV and STDs.[2] Studies imply that STDs make it easier to sexually transmit HIV—and the interaction seems to go both ways.

Analogous to syphilis at the beginning of the 20th century, a range of STDs remains the major international public health problem of the 21st century.[3-5] More and more, trends in prototype STDs are becoming important indicators of unsafe sexual behavior in both developed and developing countries. Thus, by keeping abreast of these variations in the STD profile, we can monitor the effectiveness of our prevention programs, including—most importantly—those aimed at controlling the spread of HIV.

But, of course, what most affects the average obstetrician/gynecologist is dealing with the major reproductive health consequences of STDs: infertility, ectopic pregnancy, chronic pelvic pain, genital neoplasia, and enhanced HIV transmission. (For example, in the United States, women make up 30% of new HIV infections and most new cases are heterosexually transmitted.[4])

Unfortunately, the goal of infection-free reproductive health seems as far away today as it did 100 years ago. In this article, I will examine the magnitude and dimensions of the daunting global STD challenge—one that will demand myriad preventative strategies if we are to keep it from escalating out of control. I will focus on the two-way interactions between HIV and STDs, with their disturbing potential for mutual reinforcement, and discuss results of the best interventional strategies to date for reducing HIV transmission.

Epidemiology of STDs in resource-rich countries

In recent decades, most STDs have shown consistent patterns in developed countries (Figure 1). In North America and Europe, rates of genital chlamydial infections and viral STDs steadily climbed during the 1970s and 1980s, as gonorrhea rates were generally declining.[6,7]

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Faculty Disclosures

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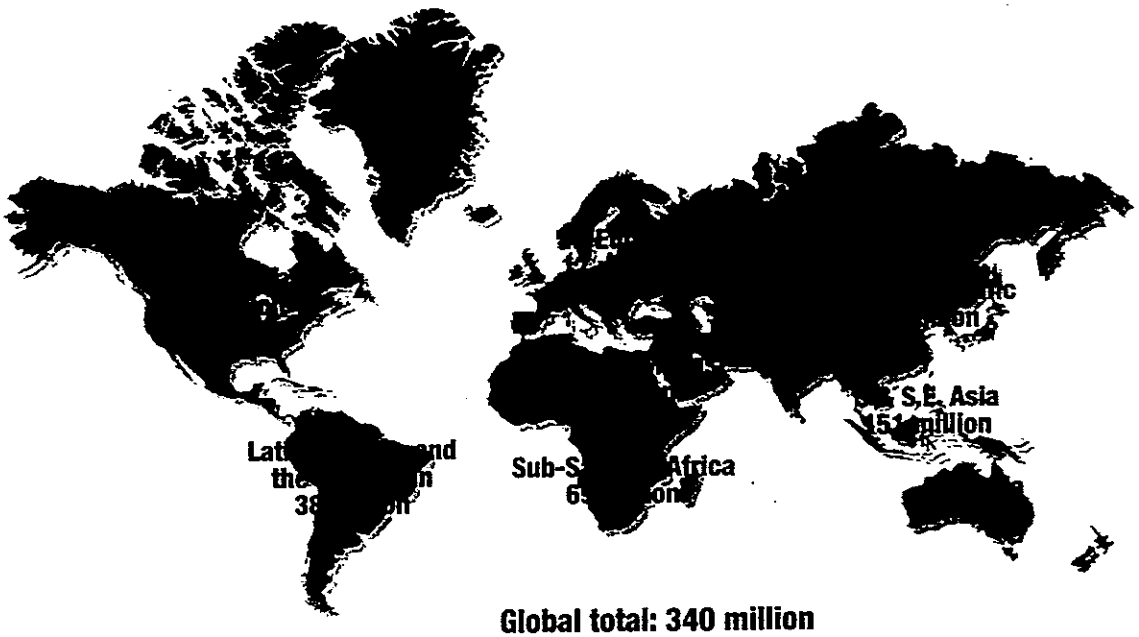
FIGURE 1

Estimated new cases of curable STDs* among adults, 1999



* gonorrhea, chlamydia, syphilis, and trichomoniasis

Source: WHO, 2001.[11]

Depending on the country, however, syphilis rates varied by population subgroups. Although not strictly sexually transmitted, endogenous vaginal infections such as bacterial vaginosis (BV) and candidiasis are categorized as genital infections frequently seen by ob/gyns. These remained high, accounting for up to 5% of primary care visits.[6]

Rise and fall of syphilis. In industrialized countries, the incidence of syphilis rose during World War II, but fell thereafter, coinciding with the introduction of penicillin. Soon after reaching its lowest levels in the late 1950s, the disease bounced back, increasing from the 1960s on. A rapidly rising male-to-female ratio coincided with its spread among men having sex with men (MSM) throughout the 1970s. In the 1980s, however, syphilis rates in gay males dropped precipitously, reflecting safer sexual behaviors credited to HIV prevention messages.[7,8] These positive overall trends, however, were offset in the US and other developed countries, where syphilis rates climbed during the late 1980s among heterosexuals of minority races, fueled by the crack cocaine epidemic.[8] But by the mid-1990s, falling syphilis levels in most developed countries led to programs aimed at eliminating the disease altogether.[8]

Steadier gonorrhea rates. Gonorrhea generally declined in the 1970s and thereafter, with US rates remaining high only chiefly among minority races and adolescents.[6] In addition, reported cases of gonorrhea are associated with a younger average age than syphilis among all gender and race categories.

Rising chlamydia rates. During the 1970s, chlamydial infections became the most prevalent bacterial STD in the developed world.

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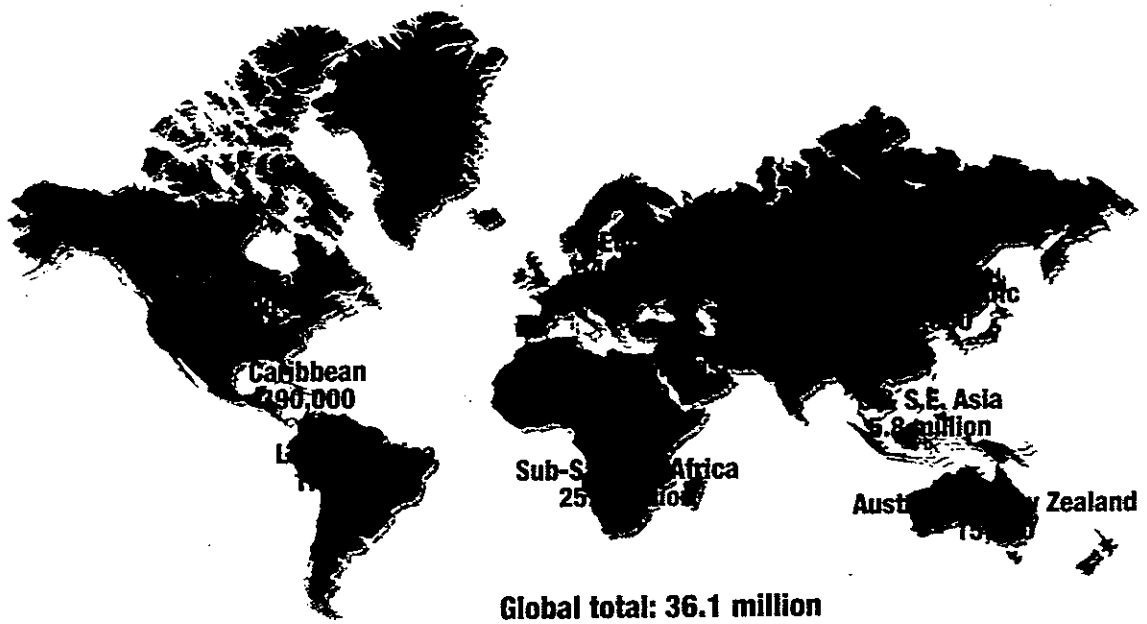
FIGURE 2

Adults and children estimated to be living with HIV/AIDS at the end of 2000



Source: UNAIDS/WHO, 2000.[1]

Because the disease is not universally reported, syndromes have been used as proxies to monitor trends. In England and the US, nongonococcal urethritis diagnoses outpaced those of gonorrhea in the early 1970s, with the gap widening in recent years.[6,7] In all industrialized countries, women have more chlamydial infections than do men—and prevalence of the disease is strongly correlated with younger age and heterosexual behaviors.

Herpes. Viral STDs are widespread within developed countries. In the United Kingdom and the US, symptomatic genital herpes and genital warts cases increased five- to 15-fold during the 1970s and 1980s.[6] In the developed world, symptomatic genital herpes causes over 10 times more genital ulcer cases than does syphilis. Moreover, recent investigations show that symptomatic infections with herpes simplex viruses (HSV) are just the tip of the iceberg.[9] Even though an estimated 45 million Americans have been infected with HSV-2, fewer than one-quarter perceive themselves ever to have had genital herpes.

Human papilloma virus infections. Likewise, diagnoses of symptomatic genital warts caused by the human papilloma virus (HPV)—along with its asymptomatic counterpart—have skyrocketed in the developed world during the last two decades.[6] Cervical and vaginal HPV infections are now the most common STDs among sexually active adolescents—and HPV is now present in most sexually active young women. In 1996, 5.5 million of the estimated 20 million people in the US infected with HPV were *newly* infected.[7]

HIV in industrialized nations. The epidemiologic pattern of HIV infection in the developed world differs dramatically from that in resource-poor countries (Figure 2).[1,10] Beginning in the mid-1970s, HIV was transmitted initially among MSM and flared as end-

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stage HIV infection in this group by the early- to mid-1980s. After entering the injection drug-using (IDU) populations in the early 1980s, the virus rapidly spread in Western Europe and North America. Limited heterosexual transmission occurred in these regions until the late 1980s.[1]

Ob/gyns need to be especially aware that over the past 5 years, the greatest proportionate increase of reported AIDS cases in the US has occurred among heterosexuals. Even so, recent increases of HIV (and other STDs) among MSM have raised public health concerns. By the end of 2000, an estimated 920,000 North Americans and 540,000 Western Europeans were infected with HIV.[1]

Differing epidemiology of STDs in resource-poor countries

Overall, STDs are a more frequent health problem in developing countries. The World Health Organization (WHO) estimates that in 1999 at least 340 million new cases of curable STDs occurred globally, the bulk of which were in developing countries (Figure 1).[11] In many African countries, STDs are among the top five causes of consultation at health services—and they are the leading diagnosis among adults.[12] Even though intensive studies of women in India, Egypt, Turkey, and elsewhere found STD rates ranging from 52% to 92%, fewer than half of the women recognized their symptoms as abnormal.[13-16]

Syphilis rates a throwback to the '50s? Syphilis rates in developing countries remain at levels seen half a century ago in industrialized nations. Although it's technically difficult to interpret serological tests for syphilis, past syphilis infections among prenatal populations in developing countries have ranged from 1% in Saudi Arabia to 33% in Swaziland.[17]

Widespread gonorrhea. Also more prevalent in the developing world is gonorrhea, with very rough estimates for large African cities suggesting an annual rate of between 3,000 and 10,000 cases per 100,000 inhabitants.[17] Gonorrhea rates in surveys of pregnant women vary from below 1% to 40%, but are lower among women attending family planning clinics (2% to 17%).[17]

Chlamydia. Genital chlamydial infections occur at similarly high rates throughout the world. Among pregnant women, chlamydial infections are more frequent than gonorrhea (ranging from 6% in Nigeria to 29 % in Kenya).[17] But among men with symptoms of urethritis, rates of chlamydial infection appear at least to be lower than in the developed world.

In 1999, WHO estimated that about 12 million new cases of adult syphilis, some 62 million new cases of gonorrhea, and approximately 92 million new cases of chlamydia occurred among adults worldwide, all mostly in South Asia and Sub-Saharan Africa.[11]

Chancroid. Fueled by the crucial role sex workers and their clients play in its spread, this disease is highly endemic in many tropical countries, particularly Southeast Asia and Eastern/Southern Africa.[18] The availability of new detection methods for its causative organism, *Haemophilus ducreyi*, have sparked interest in chancroid, whose incidence around the globe probably equals that of syphilis.

Trichomoniasis. Of all curable STDs, WHO estimates that trichomoniasis is the most widespread.[11] Prevalence rates among women at antenatal clinics range from 12% in Kenya to 47% in Botswana. Though trichomonal infection is frequently asymptomatic in men, cross-sectional screening has found this infection in nearly one quarter of Nigerian male and female adolescents. WHO estimates that in 1999, 174 million new cases of trichomoniasis occurred among adults worldwide, especially in resource-poor countries.[11]

Viral STDs. The level of viral STDs is also high in poor countries, with serologic documentation of asymp-

One trial documented that fewer people acquired HIV infection when improved STD services were continually provided.

tomatic herpes simplex type 2 infections more common than evidence of past syphilis.[18] Moreover, HSV-2 was found to be a main cause of genital ulcers.[19] Likewise, some studies found HPV to be the most prevalent STD, surpassing even vaginal bacterial infections.[15] Finally, in Asia and elsewhere, hepatitis B virus is widely transmitted, not only among sexual partners, but also from mothers to their newborns.

Asia catching up with Africa in HIV cases. HIV infection in the developing world has been predominantly transmitted through heterosexual contact.[20] By the end of 2000, an estimated 36 million persons were infected worldwide, with 25 million in sub-Saharan Africa alone (Figure 2).[1] Although the HIV epidemic was slower to emerge in Asia, it's rapidly increasing in both South and Southeast Asia. By 2010, the estimated number of infections on this continent will rival that in Africa.[1]

The level of endogenous STDs among women in developing countries is typically even higher than the traditional STDs; for example, they were found in up to 92% of women in rural India.[13] The type of dominant endogenous infection varied among the populations studied, although BV and candidiasis—again, not STDs in the strictest sense—were both common.

Interactions between STDs and HIV infection

As touched upon earlier, current theoretical and applied research has underscored the reciprocal relationships—referred to as "epidemiologic synergy"—between HIV infection and other STDs.[22] Each may alter the transmission or manifestations of the other, resulting in a potentially explosive, mutually reinforcing spiral of infection. The evidence implies that STDs facilitate sexual HIV transmission; simultaneously HIV-induced alterations in the natural history, diagnosis, or response to therapy of other STDs create bi-directional interactions between these effects. Thus, the other STDs are biologically, behaviorally, and epidemiologically inextricably linked to HIV.[21]

The scientific evidence supporting a role for STDs in facilitating sexual HIV transmission has come from three types of investigations.[22-24] First, clinical studies have suggested potential biological mechanisms for this association. Second, cohort studies of HIV incidence have estimated the increased risk of HIV infection associated with either specific STDs, or STD syndromes. Finally, community-level randomized controlled trials (RCT) have begun to evaluate the effect that STD treatment can have on HIV incidence.

Biologic plausibility

Several biologic mechanisms exist by which other STDs can facilitate sexual transmission of HIV infection by increasing infectiousness or susceptibility.[23] HIV is detected routinely in the exudate of genital ulcers from HIV-infected men and women.[25-27] Ulcers bleed easily and can come in contact with vaginal, cervical, oral, urethral, and rectal mucosa during sex. In men and women, both inflammatory STDs (such as gonococcal, chlamydial, and trichomonal infections) and ulcers appear to augment the prevalence of HIV shedding and the HIV RNA "viral load" in genital secretions.[28-31] Thus, these STDs are likely indicators of HIV infectiousness.[20] In HIV-infected men, gonococcal infection increases shedding of HIV RNA in semen tenfold, but effective treatment of gonorrhea rapidly reduces HIV shedding to background levels.[31] Although treatment of STDs reduces HIV genital viral load, in most cases it does not abolish genital tract shedding.

In addition to infectiousness, STDs can affect susceptibility. Both ulcerative (herpes, syphilis, and chancroid) and nonulcerative STDs (gonorrhea, chlamydia, and trichomoniasis) attract CD4+ lymphocytes to either the ulcer surface, the endocervix, or the vagina.[32,33] This in turn disrupts epithelial and mucosal barriers to infections and establishes a potential mechanism to increase susceptibility to HIV infection. Also, inflammatory changes associated with ulcers or discharge may upregulate HIV receptors and increase receptor density on target cells.

Observational studies

Since the mid-1980s, studies have consistently noted a strong epidemiologic association between HIV/AIDS and other STDs in both resource-rich and poor countries.[2,23] Multiple observational

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TABLE 1

Summary of STD control interventions in observational studies

Author and location	Study design/analysis	STD intervention
Crabbé, Cameroon[46]	Observational, pre- and post	Prepackaged urethritis treatment
Laga, Kinshasa, Zaire[47]	Prospective cohort	Intensive condom promotion and regular STD screening
Jenniskens, Nairobi, Kenya[48]	Observational, pre- and post	Improved syphilis screening and treatment in antenatal clinics
Hanenberg, Bangkok, Thailand[49]	Analysis of existing surveillance data	100% condom policy in brothels
Jana, Sonagachi, India[50]	Observational, pre- and post	STD services and education in clinics serving brothels
Tuladhar, Nepal[51]	Observational, pre- and post	Training pharmacy workers in STD treatment
Sánchez, Lima, Peru[52]	Cross-sectional	STD services to sex workers
Vuylsteke, São Paulo and Rio de Janeiro, Brazil[53]	Observational	STD training for primary care clinicians
Steen, Welcom, South Africa[54]	Prospective cohort	Periodic presumptive STD treatment and education of sex workers
Levine, LaPaz, Bolivia[55]	Cross-sectional	Improved STD services for sex workers

Source: Adapted from Dallabetta G, et al.[22]

studies, including cross-sectional, case–control, and cohort studies of persons infected with HIV, have indicated a twofold to fivefold increased risk for HIV infection among persons who have other STDs.

Both genital ulcer diseases and nonulcerative, inflammatory STDs have been implicated.[34-44] These "STD cofactor effects" were corroborated microbiologically for each of the major specific genital ulcer pathogens—*T pallidum* (syphilis), *H ducreyi* (chancroid), and herpes simplex virus type 2 (HSV-2, genital herpes), as well as for those organisms whose symptoms were genital discharge—*N gonorrhoeae*, *C trachomatis*, and *T vaginalis*.[2] Evidence has also suggested that BV is linked to an increased risk for HIV infection.[43,44]

Most observational studies have examined HIV acquisition in HIV-uninfected persons with STD symptoms.[2,23] Studies of HIV transmission associated with STD symptoms or diagnoses in HIV-infected individuals are limited. Data from HIV discordant couples in Uganda suggest that such enhanced transmission may be important in the spread of HIV in populations.[45]

A variety of pilot STD control interventions, using observational designs, have evaluated a range of service-delivery issues and strategies (Table 1).[46-55] Observational findings from these evaluation approaches have often helped generate hypotheses for future research.[6] Spanning the three major regions of the world, the investigations involved such diverse popula-

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tions as antenatal clinic attendees, sex workers, and the general public.[46-55] They were aimed at a cascading variety of "sub-interventions," including targeting high-risk groups for education about STD symptoms, training health providers in STD services, providing more accessible, prepackaged treatment in pharmacies, and providing presumptive STD treatment on a monthly basis to sex workers. Moreover, the usual end points of these studies were not HIV incidence per se, but rather some surrogate measure of the STD control intervention, including reported sexual behaviors, changes in STD prevalence, or differences in STD incidence.

Epidemiologic modeling

Attempts to model the biologic effects of other STDs on HIV infectiousness and susceptibility have documented that typical epidemiologic measures of effect (for example, odds ratios or relative risks) probably underestimate the impact of STDs on overall HIV spread.[56,57] This occurs because standard measures do not consider the amplifying effect of STDs on ongoing HIV transmission, namely that levels of STDs can simultaneously affect both susceptibility of HIV-uninfected persons and the infectiousness of those already infected. Moreover, models suggest that STD incidence and prevalence could be critical determinants of whether sustained heterosexual HIV epidemics can persist in subpopulations with different levels of risky sexual behavior.[58]

Modeling also suggests other findings relevant to the role of STD treatment in a comprehensive approach to HIV prevention. First, STD control has a substantially greater effectiveness and cost-effectiveness when it is implemented early in an HIV epidemic, before widespread dissemination of infection.[59] Appearing to corroborate this prediction is the greater impact measured in one of the two community randomized trials of STD control (discussed in detail below).

Second, the practice of directing STD interventions toward persons at highest risk for acquiring and transmitting STDs, including HIV, may generate a greater impact on the subsequent course of an epidemic.[60,61] Empiric evidence supports these models, namely that lower HIV incidence was associated with the widespread provision of condoms and improved STD services for female sex workers in countries such as Thailand and Zaire (where HIV transmission is strongly associated with commercial sex).[47,49,62]

Randomized interventions

To test these biologic and observational findings, and to assess the population-level impact on HIV incidence, two major community-level interventional RCTs were conducted.

The Tanzania trial. One unblinded trial, in the Mwanza district of Tanzania, documented that fewer people acquired HIV infection when improved STD services were continually provided.[63] That study involved an aggregate of coordinated STD interventions: (1) educating communities to recognize STD symptoms; (2) providing effective drugs for STDs; and (3) training and monitoring health-care providers to improve treatment of symptomatic STDs. These efforts lowered HIV incidence by 38% in six intervention communities compared with six matched comparison communities and reduced the prevalence of symptomatic urethritis and incident syphilis. This lower HIV incidence was not accompanied by differential changes in sexual behavior or by condom use: factors that might otherwise confound the direct association between improved STD treatment and lowered HIV incidence.

The Mwanza study—using improved treatment for the symptomatic curable STDs—was the first documented intervention at the population level that successfully reduced HIV incidence at that level. The Mwanza data suggest that treating symptomatic STDs through a strong clinical infrastructure is an effective, community-level strategy for HIV prevention in settings where other STDs are prevalent. The program's estimated cost-effectiveness of $217 per HIV infection averted and $10 per disability-adjusted life-year (DALY) saved compared favorably with other highly effective public health interventions.[64]

Uganda RCT. The second trial, undertaken in the Rakai District of Uganda, used an alternative approach: intermittent mass STD treatment of the general population,

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administered every 10 months.[65] Unlike the Mwanza trial, the Rakai study found no difference in the incidence of HIV infection between the intervention and the comparison communities, despite significant reductions in curable STDs in the intervention areas.

After 20 months of intervention, which covered three mass treatment rounds, the rate of HIV was similar in the five intervention and five comparison communities overall (adjusted rate ratio 0.97, 95% CI 0.81–1.16) and in each of the five randomized pairs. At the end of the second follow-up period, the prevalence of serologically diagnosed syphilis and culture-documented trichomoniasis was significantly reduced in the intervention communities. The incidence of trichomoniasis also dropped (adjusted rate ratio 0.52, 95% CI 0.35–0.79), but the incidence of syphilis did not. Finally, although BV prevalence was lowered, it was only of borderline statistical significance.

Thus, the two best studies to date produced divergent results: In Mwanza, HIV incidence in the intervention communities was significantly lower, as were the rates of urethritis and syphilis; in Rakai, the incidence of some STDs was lower, but this had no measurable impact on HIV incidence. But since each study was addressing different approaches to STD control, it is not surprising that differing answers were obtained.

Lessons learned. Nevertheless, the two studies taught us important lessons.[66-68] First, a clinical infrastructure providing continuous STD treatment appeared more important than intermittent or episodic STD service delivery, even when the latter is highly intensive. Second, the stage of an HIV epidemic may be crucial: at the time of the first trial, Mwanza was experiencing a relatively early HIV epidemic, which affected only 4% of the community, whereas the Rakai study took place in one of the world's most mature epidemics, with approximately 16% of the community infected with HIV.[63,65] Third, HIV incidence could be disproportionately affected by levels of symptomatic STD in which shedding is increased, whereas STD incidence may be most closely related to the prevalence of the asymptomatic STDs among the population. Analyses of the population attributable fraction of incident HIV in Rakai, however, suggest that most HIV acquisition and transmission occurs among persons with no recognized or reportable STD symptoms.

Conclusion

Controlling the high levels of STDs will be crucial to both improving global reproductive health and reducing the HIV pandemic. A combination of strategies will be necessary to make any inroads into the STD problem: more available diagnostic techniques, wider STD treatment, safer sexual behaviors, and STD prophylactic vaccines. In the meantime, practicing ob/gyns can do their part by initiating conversations about the sensitive topic of sexual health and screening for STDs, as necessary. ☐

A lengthier version of this article was first presented at the Workshop on "Sexually Transmitted Diseases (STDs) and Reproductive Tract Infections (RTIs): Diagnosis, Antecedents, Outcomes, Prevention and Treatment," November 8-10, 2000, in New Delhi, India.

FREE GUIDE

A new free manual "A Guide to the Clinical Care of Women with HIV" is now available from the federal government. Published by the HIV/AIDS Bureau of the Health Resources and Services Administration, it can be viewed or downloaded by visiting http://hab.hrsa.gov/womencare.htm

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