Enhancing Women's Sexual Health: Prevention Measures in Diverse Populations of Women

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Introduction

The landscape of interventions to prevent transmission of sexually transmitted infections (STI), including human immunodeficiency virus (HIV), has changed considerably in the last decade. Of particular relevance to women are the licensure and uptake of highly effective immunization against genital human papillomavirus (HPV) and associated prevention against associated consequences, including cervical cancer; encouragement about the use of topical antiretroviral agents as pre-exposure prophylaxis to reduce risk of HIV and genital herpes acquisition; enhanced emphasis on expedited partner management and rescreening for persons infected with *C. trachomatis* and *N. gonorrhoeae*; and the availability of a modified female condom. While these advances are encouraging, effective prevention of HIV and the other STI remains a high priority, both internationally and domestically, and most urgently among women. UNAIDS reported in 2010 that while the rate of new HIV infections has fallen in several countries, these favorable trends are at least partially offset by increases in new infections in others; moreover, the proportion of infections in women is increasing in several countries, and young people ages 15–24 account for 41% of new HIV infections in sub-Saharan Africa [1]. In 2008, the CDC revised its estimates of the annual incidence of new HIV infections in the USA by 40% (an increase from an estimated 40,000 new infections annually to approximately 56,000) [2]. Moreover, a large proportion of new HIV infections continue to be diagnosed in late stages of the disease, and women are not exempt from these trends [3, 4]. As discussed below, rates of reportable non-HIV STI either have not declined or have actually increased in women. This chapter will review the current state of prevention interventions for HIV/STI in diverse populations of women.

It is worth noting from the outset that the complexities that underlie women's vulnerability to many of the infections discussed here serve to highlight that structural interventions with the potential to effect system change are needed. Globally, women's socioeconomic and educational status is by far below that of men, and power dynamics often place women at the lower end of hierarchies within relationships and families, and in the workplace. For many prevention interventions to have a meaningful impact, these inequities will need to be addressed, or at least acknowledged.

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Epidemiologic Trends for High-Impact Infections in Women, with Emphasis on Adverse Impacts on Sexual/Reproductive Health

Chlamydia trachomatis is the most commonly reported infectious disease in the USA, and typically infects the cervix with occasional infection of the urethra in some women. In 2009, >1.2 million diagnoses of *C. trachomatis* were reported to CDC, but approximately 3 million new cases are estimated to occur annually [5]. Most chlamydial infections cause neither signs nor symptoms and thus are able to ascend without notice to the upper reproductive tract. There, chronic infection can elicit immunopathogenesis with consequent scarring of the fallopian tubes, ovaries, endometrial lining, and occasionally, the adjacent peritoneum [6]. Thus, genital chlamydial infection is the leading cause of preventable infertility and ectopic pregnancy [7]. Selective screening of appropriate women is necessary to control this infection and its sequelae, and most experts agree that it has effected widespread declines in reproductive tract sequelae; whether it has effected declines in prevalent infection is a question of debate [8]. The U.S. Preventive Services Task Force and the CDC recommend that all sexually active women age 25 years or younger be screened annually for *C. trachomatis*, with screening of older women based on behavioral risk criteria [9]. Despite this, rates of appropriate screening in young women remain suboptimal, and interventions to enhance screening in target populations are needed [10].

In 2009, the number of reported cases of gonorrhea in the USA remained stable, with the highest attack rates occuring in 15- to 24-year-old women and men; however, after adjustment for sexual experience, the highest rates are seen in sexually active 15- to 19-year-old women [11]. According to the population-based National Health and Nutrition Examination Survey (NHANES), in 1999–2002, the prevalence was higher among non-Hispanic black persons relative to white (1.2%; CI, 0.7–1.9%), and 46% of those infected with gonorrhea also had *C. trachomatis* detected [12]. The Ad Health study of young adults showed similar results in 2001–2002. Among 12,548 persons aged 18–26 years, the prevalence of gonorrhea was 0.43% (95% CI, 0.29–0.63%), and strikingly higher in blacks than whites (2.13%; 95% CI 1.46–3.10%) [13]. Overall, more cases of gonorrhea are reported in men than women, which probably reflects both a greater ease of diagnosis in men and a substantially higher rate of infection in men who have sex with men (MSM) than in heterosexual men and women. The rate of gonorrhea in African American populations in the USA is almost 25 times higher than that in whites or persons of Asian ancestry; Latino populations and Native Americans experience intermediate rates. Only a small portion of these differences can be explained by greater attendance of nonwhite populations at public clinics, where case reporting is more complete than in private health facilities. Race and ethnicity are demographic markers of increased risk, not factors that directly denote a high risk for gonorrhea or other STDs. Differing incidence rates between population subgroups are related less to variations in numbers of sex partners than to complex and poorly understood differences in sex partner networks, as well as access to health care and related societal factors. A detailed analysis of rising gonorrhea incidence in California from 2003 to 2005 raised the importance of contact with a recently incarcerated partner as a major risk, and highlighted the relatively understudied contribution of this infection in corrections settings, especially for women [14].

The major current concern with gonorrhea is advancing antimicrobial resistance. Overall, prevalence of fluoroquinolone-resistant strains, which was <1% during 1990–2001, increased to 4.1% in 2003, and 13.8% in 2006. [15] Such increases prompted CDC to recommend in 2007 that fluoroquinolones no longer be used to treat gonorrhea in the USA [16]. Highlighting this relentless trend, the CDC reported the first case of a clinical isolate of *N. gonorrhoeae* with high-level resistance to azithromycin from a woman evaluated in Hawaii in early 2011 [17]. Of note, the CDC's Gonococcal Isolate Surveillance Project (GISP), the sole national system designed to monitor emergence of antimicrobial resistance

in this pathogen, tests isolates only from men with symptoms of urethritis who are seeking care at selected Sexually Transmitted Disease (STD) Clinics. These data may approximate antimicrobial resistance patterns in women, but the implications of potential differences in the spectrum of gonorrhea in women are worth noting: antibiotic regimens for pelvic inflammatory disease (PID) should retain excellent activity against gonorrhea, and options in the current landscape are quite limited. Infertility resulting from fallopian tube obstruction is the most common serious consequence of PID and occurs in 15–20% of women after a single episode and 50–80% of those who experience three or more episodes [18]. Infertility may be more common after chlamydial than gonococcal PID, perhaps because the more acute inflammatory signs associated with gonorrhea bring women to diagnosis and treatment sooner. Moreover, *N. gonorrhoeae* is a nefarious player in PID. The PID Evaluation and Clinical Health (PEACH) study enrolled over 800 women aged 14–37 with symptomatic PID [19]. Despite clinical cure and apparent microbiologic eradication of gonorrhea, as evidenced by lower tract cultures, infertility rates were 13% for women with *N. gonorrhoeae* identified, 19% for those with *C. trachomatis*, and 22% for those with anaerobic bacteria over 35 median months of follow-up [20]. Rates of chronic pelvic pain were 27% among women with gonococcal infection [21].

The resurgence of syphilis in the USA, and in many other industrialized countries, has largely involved men who have sex with men (MSM) [5]. In 2009, cases of primary and secondary syphilis comprised the highest number of cases reported since 1995, and the majority of these occurred in men [5]. However, some data suggest that an epidemiologic shift of the syphilis resurgence into heterosexual networks may be underway [22]. Congenital syphilis continues to occur in the U.S., largely in situations where prenatal screening was not obtained. For example, high rates of congenital syphilis in Maricopa County, Arizona (U.S.) prompted an analysis of syphilis case report data from state and county health departments [23]. This showed that among 970 women reported to have syphilis, 49% were Hispanic, of whom 49% were non-US citizens. Of the latter group, the majority (64%) reported having a male sex partner who reported drug use or anonymous sex. These data indicate the complex interplay of limitations in successful access to care and sexual networks that are likely needed to sustain outbreaks of this devastating neonatal disease, and the interventions needed to prevent them [24].

Sexually transmitted herpes simplex virus (HSV) infections now cause most genital ulcer disease throughout the world and an increasing proportion of cases of genital herpes in developing countries with generalized HIV epidemics, where the positive feedback loop between HSV and HIV transmission is a growing, intractable problem. Despite this consistent link, randomized trials evaluating the efficacy of suppressive antiviral therapy to suppress HSV in both HIV-uninfected and HIV-infected persons have not demonstrated a protective effect against acquisition or transmission of HIV [25, 26]. In the USA, the prevalence of antibody to HSV-2 began to fall in the late 1990s, especially among adolescents and young adults; the decline is presumably due to delayed sexual debut, increased condom use, and lower rates of multiple (≥4) sex partners, as is well documented in the U.S. Youth Risk Behavior Surveillance System (YRBSS) [27].

Genital human papillomavirus (HPV) remains the most common sexually transmitted pathogen in this country, infecting 60% of a cohort of initially HPV-negative, sexually active Washington state college women within 5 years in a study conducted from 1990 to 2000 [28]. The scale-up of HPV vaccine coverage among young women—discussed in detail in text that follows—promises to lower the incidence of infection with the HPV types included in the vaccines. The available vaccines target the major oncogenic HPV types (16/18), responsible for the majority of cervical cancers; the quadrivalent vaccine targets the two HPV types that cause genital warts (6/11) as well. Uptake of the vaccines has generally been good, with the majority of US pediatricians offering it to older adolescents; however, barriers remain, most significantly, high cost [29]. A great deal of activity in designing post-immunization

surveillance programs to monitor genital HPV infection and related consequences is now underway [30].

Finally, vaginal infections are an under-recognized cause of morbidity in women, and in the case of trichomoniasis and bacterial vaginosis (BV), increase the risk of acquisition of other STI, including HIV [31]. Up to 50% of women of reproductive age in developing countries have bacterial vaginosis (arguably acquired sexually), and trichomoniasis remains a sexually transmitted cause of vaginitis worldwide. Although few nationally representative surveys have been performed, trichomoniasis prevalence measured by culture of vaginal fluid was reported for women in the National Health and Nutrition Survey (NHANES), which uses a complex, stratified, multistage probability sample design with unequal probabilities of selection to obtain a nationally representative sample of the U.S. civilian noninstitutionalized population. Of over 3,754 women in the 2001–2004 NHANES who supplied a self-collected swab of vaginal secretions for *T. vaginalis* PCR assay, prevalence was 3.1% (95% CI, 0.7–2.3%) [32]. Prevalence was 1.3% among non-Hispanic white women, 1.8% among Mexican American women, and 13.3% among non-Hispanic Black women. Independent risks for infection included non-Hispanic black race/ethnicity, being born in the U.S., higher number of lifetime sex partners, increasing age, lower educational level, poverty, and douching. Only 15.2% with trichomoniasis reported vaginal symptoms. Of significant interest is that 49.8% of women with trichomoniasis also had bacterial vaginosis. Using PCR assay applied to 12,449 participants in the National Longitudinal Study of Adolescent Health, overall prevalence was 2.3% (95% CI, 1.8–2.7%), and higher in women (2.8%), especially Black women (10.5%) [33]. In a study of trichomoniasis in over 13,000 women in the second trimester of pregnancy, the prevalence by culture was 13%. Infection by *T. vaginalis* was associated with Black race, being unmarried, a history of gonorrhea, and having multiple sexual partners during pregnancy. The high prevalence of this sexually transmitted pathogen in pregnant women is of concern because data suggest that trichomoniasis is linked with an increased risk of low birth weight. However, treatment of symptomatic trichomoniasis has not been shown to reduce preterm birth [34].

Demographic Trends in Sexual Risk Behaviors

Specific Practices and Associated Risk

Vaginal, Oral, Anal Sex

Several recent reviews have described patterns of sexual behavior across various age groups and populations [35]. Of great interest for populations most susceptible to bacterial STI are surveys of adolescents. The 2009 Youth Risk Behavior Surveillance System (YRBSS) was conducted among students in grades 9–12. Among high school students nationwide, 34.2% were currently sexually active, 38.9% of currently sexually active students had not used a condom during their last sexual intercourse, and 2.1% of students had ever injected an illegal drug [36].

Same- and Opposite-Sex Behavior

According to the 2006–2008 National Survey of Family Growth, 13% of women aged 15–44 and 5.2% of men reported same sex behavior in their lifetime [37]. Women who have sex with women (WSW) represent diverse communities of women who may exclusively have sex with women, or historically (or currently) engage in sexual partnerships with both men and women. Despite the fact that same sex behavior is not infrequent among women in the USA and despite the widespread prevalence of chlamydia, little data at the clinic, community, or population levels are available that describe its prevalence among these sexual minority communities. Numerous studies support that greater than 90% of women who self-identify as lesbian report a sexual history with men [38]. Moreover, recent studies indicate that some communities of WSW, particularly adolescents and young women might be at increased risk for STDs and HIV as a result of certain reported risk behaviors [39–41], including

sex with high risk men. Same-sex sexual behavior is likely underreported to care providers [42]. Moreover, tremendous gaps of knowledge exist in understanding what specific sexual behaviors among WSW place them at risk for STI. Sexual practices involving digital-vaginal or digital-anal contact and those including penetrative sex objects represent plausible means for transmission of cervicovaginal secretions.

Genital Hygiene Measures

Vaginal douching does not protect against acquisition of STD/HIV, and increases the risk of certain vaginal infections, notably BV. Among HIV-uninfected Kenyan female sex workers, increased frequency of vaginal washing was associated with a higher likelihood of BV, as were vaginal lubrication with petroleum jelly (OR 2.8, 95% CI = 1.4–5.6), lubrication with saliva (OR = 2.3, 95% CI = 1.1–4.8), and bathing less than the median for the cohort (14 times/week; OR = 4.6, 95% CI = 1.2–17.5). The authors concluded that modification of intravaginal and general hygiene practices should be evaluated as potential strategies for reducing the risk of BV [43].

Genital hygiene methods for washing after sexual exposure, including vaginal washing and douching, are ineffective in protecting against HIV and STD and may increase the risk of bacterial vaginosis, some STD, and HIV [44].

Hormonal Contraception

While exogenous hormones may modulate mucosal immunity to STD/HIV, data remain insufficient to recommend that women modify their hormonal contraceptive practices to reduce their risk of STD/HIV acquisition. Hormonal contraceptives do not provide protection against STD/HIV acquisition, and need to be used in conjunction with barrier methods of protection (condoms) in women at risk. A systematic review of data from 1966 through early 2005 concluded that studies of combined oral contraceptive and depot medroxyprogesterone use generally reported positive associations with cervical chlamydial infection, although not all associations were statistically significant. For other STI, the findings suggested no association between hormonal contraceptive use and STI acquisition, or the results were too limited to draw any conclusions. Evidence was generally limited in both amount and quality, including inadequate adjustment for confounding, lack of appropriate control groups and small sample sizes. Thus, observed positive associations may be due to a true association or to bias, such as differential exposure to STI by contraceptive use or increased likelihood of STI detection among hormonal contraceptive users [45].

The relationship between hormonal contraception and HIV acquisition was recently examined in two well done observational studies. The largest and most sophisticated cohort investigation prospectively followed 6109 HIV-uninfected women from family planning clinics in Uganda and Zimbabwe to assess risk of HIV acquisition over 15–24 months [46]. Neither combined oral contraceptives (HR, 0.99; 95% CI, 0.69–1.42) nor DMPA (HR, 1.25; 95% CI, 0.89–1.78) was associated with risk of HIV acquisition overall, including among participants with cervical or vaginal infections. However, hormonal contraceptive users who were HSV-2 seronegative had an increased risk of HIV acquisition (for combined oral contraceptive use, HR, 2.85; 95% CI, 1.39–5.82; for DMPA, HR, 3.97; 95% CI, 1.98–8.00).

A second study accounted for HSV-2 serostatus in a prospective cohort study of 1206 HIV seronegative sex workers from Mombasa, Kenya who were followed monthly. 233 women acquired HIV (8.7/100 person-years). HSV-2 prevalence (81%) and incidence (25.4/100 person-years) were high. In multivariate analysis, including adjustment for HSV-2, HIV acquisition was associated with use of oral contraceptive pills (adjusted HR, 1.46; 95% CI, 1.00–2.13) and depot medroxyprogesterone acetate (adjusted HR, 1.73; 95% CI, 1.28–2.34). The effect of contraception on HIV susceptibility did not differ significantly between HSV-2 seronegative and seropositive women. HSV-2 infection was associated with elevated HIV risk (adjusted HR, 3.58; 95% CI, 1.64–7.82). These authors concluded that in this group of high-risk African women,

hormonal contraception and HSV-2 infection were both associated with increased risk for HIV acquisition. HIV risk associated with hormonal contraceptive use was not related to HSV-2 serostatus [47].

A retrospective cohort study at a U.S. university clinic assessed STI incidence among 304 HIV-infected women, 82 of whom received DMPA and 222 who did not. No significant differences in trichomoniasis, chlamydial infection, and gonorrhea occurred between the women receiving or not receiving DMPA [48].

Groups with Specific Concerns

Adolescents

Adolescent females have the highest rates of chlamydia and gonorrhea in the USA. Risk is elevated in this group relative to other age groups likely due to a combination of biological predisposition (cervical ectopy, which exposes more vulnerable columnar epithelium to these pathogens), behavior (participation in sexual networks with high levels of infection) and access to care (inability to independently pay for health care and concerns for confidentiality). In 2009, rates of chlamydia increased in 15–19 year-old women 1.8% from the prior year, to 3,329.3 cases per 100,000 population [5]. While women in this age group continue to have the highest gonorrhea rates (568.8 cases per 100,000 population), this number actually represented a decline of 10.5% from 2008.

Data support the need for adolescents to receive comprehensive, current, and accessible information on prevention of STD/HIV and pregnancy, including condoms. Data from the 1994 to 2002 National Longitudinal Study of Adolescent Health (Add Health) compared subsequent sexual behaviors and risk of STI among adolescents who did and did not use a condom at their sexual debut [49]. Adolescents who reported condom use at sexual debut were more likely to report condom use at most recent intercourse (on average, 6.8 years after sexual debut), and were half as likely to test positive for chlamydia or gonorrhea (adjusted OR 0.50; 95% CI, 0.26–0.95). Reported number of lifetime sexual partners did not differ between the two groups. A separate analysis of Add Health data included teens enrolled in 2001 who were followed 1 and 3 years later; those teens who took a virginity pledge reported a longer time until sexual debut than teens who did not take similar pledges [50]. However, overall sexual behaviors subsequent to pledging, including patterns of condom use, did not differ between these groups. A more recent analysis demonstrated that teens who took the pledge and who did have sex were less likely to use condoms at sexual debut [51].

Pregnant Women

Surprisingly few data are available on STI/HIV incidence in pregnancy, but data suggest that this period is a time of enhanced vulnerability for acquisition of these infections, particularly HIV. Moreover, women who acquire HIV during pregnancy are more likely to transmit the virus to their infants in utero, probably due to a combination of the high plasma HIV viral loads associated with the primary infection period and cell-mediated immunomodulation during pregnancy. Of course, non-HIV STI transmission to the neonate can have devastating consequences as well; the majority of congenital syphilis cases likely result in spontaneous abortion, for example, and both *C. trachomatis* and *N. gonorrhoeae* cause serious ophthalmic and (in the case of chlamydia) respiratory problems.

Sexual Minorities

Prior studies indicate that women who practice same sex behavior, including exclusively same sex behavior, are at risk for STIs, including genital types of human papillomavirus (HPV), HIV, genital herpes, and trichomoniasis [52–58]. Moreover, bacterial vaginosis (BV) occurs commonly among women who report sex with women, and there is a high degree of concordance among monogamous same sex couples, suggesting a potential role for sexual transmission in this group [59]. These observations emphasize the need for healthcare providers and public health advocates to address the sexual and reproductive health care needs of this group of women in a comprehensive

and informed manner. Beyond exploring the sex and number of sex partners of their WSW patients, providers should elicit history of past and current sex with men, history of preventive health examinations (including Papanicolaou smears and STI screens), detailed sexual practices (oral sex, anal sex, penetrative sex with toys/objects, etc.), use of safer sex methods (dental dams, condoms, etc.) and associated drug use.

In the first analysis of its kind, investigators found that women aged 15–24 years attending family planning clinics in the U.S. Pacific Northwest 1997 through 2005 and who also reported same sex behavior had higher positivity of *C. trachomatis* than women who reported exclusively heterosexual behavior [60]. Factors associated with chlamydial infection among WSW in this study included use of nucleic acid amplification tests (NAAT) for diagnosis, testing at a non-"routine visit," report of genitourinary symptoms and report of a sex partner with chlamydial infection. Over the study period, WSW who reported sexual behavioral risks also had the highest chlamydia positivity compared to women reporting sex only with or women who reported sex with men and women who reported similar risks. Interestingly, a greater proportion of women reporting sex with men and women reported sexual risk behaviors compared with both heterosexual women and those reporting sex only with women; despite this, *C. trachomatis* positivity was not highest in this group. Of note, there was relatively high chlamydia positivity among American Indian/Alaska Native WSW, a finding that is consistent with racial/ethnic disparities previously described from the Region X IPP data [61]. The finding of higher chlamydia positivity among WSW relative to women reporting sex exclusively with men was unexpected. Possible explanations for this observation relate to differences in these two groups' use of reproductive health care services (including chlamydia screening), biological susceptibility to lower genital tract infection, infrequent use of barrier methods to prevent STI transmission with female partners, trends towards higher risk behaviors, and differential characteristics of their respective sexual networks.

Several investigators have reported that WSW are less likely to undergo routine Papanicolaou smear screening—and generally, preventive gynecologic care, often sought in the context of obtaining birth control—relative to their exclusively heterosexual counterparts [62, 63]. This would logically reduce the number of health care encounters at which chlamydia testing would likely be performed. Moreover, most women who report same sex behavior often do not believe that they are at risk of acquiring STI from their female partners [64]. This may lead to less frequent use of some preventive measures (for example, washing sex toys between partners) or infrequent use of barrier methods (including gloves, condoms, dental dams) for STI prevention [65]. Further, health care providers do not always obtain a complete sexual history and may thus fail to elicit reports from WSW of higher risk behaviors that would prompt *C. trachomatis* screening and related prevention counseling [66].

Another potential explanation for finding of some STI, including chlamydia, among WSW relates to selection of sex partners. Some women who report same sex behavior may be more likely to select higher risk sex partners and participate in higher risk behaviors, including unprotected vaginal and anal sex with homosexual or bisexual men [38, 67]. One large cross-sectional survey across health care sites in the USA found that women who identified as lesbians reported more male sex partners and higher numbers of male sex partners who reported sex with other men in the past year than either heterosexual or bisexual women [41]. In a Seattle-based study of women reporting sex with at least one woman in the past year, concurrency (overlap between partnerships reported by participant) was common, especially among bisexual women [68]. Bisexual women frequently reported inconsistent condom use with either vaginal or anal intercourse with men. Many of these women (16%) believed their male partner had sex with another man at some point in time. Additional studies have demonstrated other high-risk behaviors among some WSW, including use of injection drugs and crack cocaine, and exchange of sex for drugs or money [38, 69–72].

Taken together, the data cited above emphasize that WSW should undergo routine age-based annual screening for *C. trachomatis* as recommended by current guidelines. No data are available to inform screening for *N. gonorrhoeae* in this group.

In the USA, the National Health and Nutrition Examination Surveys (NHANES) have provided the principal window into population-based trends in HSV seroprevalence in adults since the survey first reported on this outcome in 1989 [73]. Using audio computer assisted self-interview (A-CASI) obtained from women ages 18–59 years who participated in NHANES 2001–2006, Xu and colleagues assessed participants' report of recent and life time same-sex behavior [74]. In addition, a subset of these women, ages 18–49 years, had type-specific serologic testing for HSV that, as they point out, can serve as a valuable surrogate marker for cumulative lifetime sexual risk. The percentage of participants who reported ever having had sex with another woman translates to 5.7 million (95% CI, 4.9–6.6), a number that will serve as a useful denominator for future analyses and that emphasizes the normative aspects of this behavior. Moreover, more than half of all respondents who reported having sex with another woman in their lifetime identified themselves as heterosexual, including 25% who reported having had sex with another woman in the prior year. These findings are very good reminders that equating sexual behavior to sexual identity—a tendency still evident in many clinical interactions and some guidelines—is neither reliable nor advisable, and is essentially scientifically irresponsible.

In the NHANES group, 7.1% of women reported ever having had sex with a woman (95% CI, 6.1–8.2), significantly lower than the 11.2% reported in the 2002 National Survey of Family Growth (another large, U.S. population-based survey) [75], but higher than the 4.9% reported in the U.K.'s National Survey of Sexual Attitudes and Lifestyles (NATSAL 2000, 1999–2001) [63]. It is unlikely that the true prevalence differs greatly between the USA and the U.K., but several factors may have contributed to these discrepancies: interviewing methodology, phrasing of survey questions and the changing sociopolitical climate. Using CASI has been shown to increase the frequency of reporting of potentially stigmatized behaviors; paradoxically, CASI was not used in the NSFG study, but was employed in both NHANES and NATSAL. The phrasing of questions regarding sexual practices differed: the NSFG study asked participants about "a sexual experience," the definition of which could conceivably be open to interpretation, while NHANES and NATSAL asked more specifically about sexual practice. And lastly, timing is everything—particularly in reference to generational attitudinal shifts. Report of any lifetime same-sex behavior in NHANES was considerably higher in younger women, peaking at 9.4% in ages 18–29 years, and in fact, was negatively correlated with increasing age. The higher overall prevalence of lifetime same-sex behavior in this age group has been suggested by other data, and may truly reflect that times really are changing: more open attitudes and evident tolerance for homosexuality has likely created a freer climate for young women to pursue and to report sexual relationships with other women.

Xu and colleagues found strikingly high seroprevalence of HSV-2 in certain subgroups of women who reported ever having had sex with a woman, and identified some intriguing risks as well. The most intriguing finding was that HSV-2 seroprevalence was significantly higher among the groups of women reporting same-sex behavior. The HSV-2 seroprevalence of women who identified as heterosexual and reported no lifetime same-sex behavior was 23.8%, compared to 45.6% of women who identified as heterosexual with some lifetime same-sex behavior, or 35.9% of women who identified as bisexual—although the bisexual group reported a higher number of lifetime male sex partners than the former (median, 17.6 vs. 10.8). HSV-2 seroprevalence was 30.3% for those sexually active with women in the past year and 36.2% for those ever active with women. Interestingly, the seroprevalence of HSV-2 among women who self-identified as "homosexual" (8.2%) was nearly identical to that in a much smaller, clinic-based sample done in Seattle nearly a decade ago [56]. It is worth

noting, though, that even among (the admittedly small number of) self-identified homosexual or lesbian participants in NHANES, most (84%) had had at least one male sex partner, so the authors could not estimate HSV-2 seroprevalence among women who reported no lifetime sex with men. Report of same-sex behavior—whether during the lifetime or more recently—was also associated with earlier sexual debut and higher numbers of total lifetime sex partners; however, self-identification (as homosexual, bisexual, or heterosexual) significantly impacted this association. Again, even these relatively straightforward data collected at the population level emphasize the complex interplay between sexual behavior, identity, and orientation.

Prevention Interventions in Women, with Emphasis on Relevance to and Access for Key Vulnerable Populations

Barrier Methods

Male Condoms

When used consistently and correctly, male latex condoms are effective in preventing sexual transmission of HIV and other STDs, including chlamydia, gonorrhea, syphilis, genital HPV, and trichomoniasis. By limiting lower genital tract infections, male condoms might also reduce the risk of women developing pelvic inflammatory disease (PID) [76]. In heterosexual serodiscordant relationships in which condoms were consistently used, HIV-negative partners were 80% less likely to become HIV-infected compared with persons in similar relationships in which condoms were not used [77]. Condom use may also reduce the risk for transmission of herpes simplex virus-2 (HSV-2), although data for this effect are more limited [78, 79]. Finally, condom use reduces the risk of HPV [80, 81] and HPV-associated diseases (e.g., genital warts and cervical cancer) [82]. Use of condoms has been associated with regression of cervical intraepithelial neoplasia (CIN) [83] and clearance of HPV infection in women, and with regression of HPV-associated penile lesions in men [84]. A prospective study among newly sexually active college women demonstrated that consistent condom use was associated with a 70% reduction in risk for genital HPV transmission. Investigators followed 82 female university students who reported their first intercourse with a male partner either during the study period of within 2 weeks before enrollment [81]. Cervical and vulvovaginal samples for HPV DNA testing and Pap smears were collected every 4 months. Incidence of genital HPV infection was 37.8 per 100 patient-years at risk among women whose partners used condoms for all instances of intercourse during the 8 months before testing, compared with 89.3 per 100 patient-years at risk in women whose partners used condoms less than 5% of the time (adjusted hazard ratio (HR) 0.3, 95% CI, 0.1–0.6). In women reporting 100% condom use by their partners, no cervical squamous intraepithelial lesions (SIL) were detected in 32 patient-years at risk, whereas 14 incident lesions were detected during 97 patient-years at risk among women whose partners did not use condoms or used them less consistently.

In an analysis that pooled data from all published studies that prospectively assessed condom use and HSV-2 incidence, persons who always used condoms had a 30% decreased risk of acquiring HSV-2 compared with those who reported no condom use ($P=0.01$) [85]. Moreover, risk of acquiring HSV-2 decreased by 7% for every additional 25% increment in the time that condoms were used ($P=0.01$). Conversely, HSV-2 acquisition rose steadily with report of increasing frequency of unprotected sex acts. These effects were consistent for men and women.

Two general categories of nonlatex condoms exist. The first type is made of polyurethane or other synthetic material and provides protection against STD/HIV and pregnancy equal to that of latex condoms. These condoms provide an acceptable alternative for persons unable to use latex condoms. A Cochrane review concluded that while one nonlatex condom (eZon) did not protect against pregnancy as well as its latex comparison condom, no differences were found in the typical use efficacy between the Avanti and

the Standard Tactylon and their latex counterparts. The nonlatex condoms had higher rates of clinical breakage than latex comparators (OR for clinical breakage, 2.64 (95% CI, 1.63–4.28) to 4.95 (95% CI, 3.63–6.75)). Contraceptive efficacy of nonlatex condoms could not be estimated, and will require more research [86]. The FDA has published draft guidelines modifying the labeling on male latex condoms to reflect these findings [87].

Female Condoms

Laboratory studies indicated that the original version of the female condom (Reality™) is an effective mechanical barrier to viruses and semen. If used consistently and correctly, the female condom might substantially reduce the risk for STI. Female condoms are safe to use repeatedly if proper care procedures are followed. Two systematic reviews support the potential effectiveness of female condoms. The first reviewed 137 articles and abstracts on various aspects of the female condom and five randomized controlled trials on its effectiveness [88]. The review concluded that while the evidence is limited, "the female condom is effective in increasing protected sex and decreasing STI incidence among women." A second systematic review concluded that "randomised controlled trials provide evidence that female condoms confer as much protection from STIs as male condoms." [89].

The comparative effectiveness of the male condom and female condom was assessed in a randomized controlled trial that assigned women to sequential use of ten male latex condoms, then ten female polyurethane condoms [90]. The association between frequency and types of self-reported mechanical failure and semen exposure were measured by prostate-specific antigen. Moderate to high postcoital prostate-specific antigen (PSA) levels were detected in 3.5% of male condom uses and 4.5% of female condom users (difference 1.4; 95% CI, 1.6–3.7). PSA levels were more frequent with mechanical problems and less frequent with other problems or correct use with no problems. Although mechanical problems were more common with the female condom, the risk of semen exposure was probably similar.

The FDA held an advisory meeting in December 2008 to review evidence in support of a new version of the female condom [91]. The new version has a slightly modified shape, no seam, and is made from nitrile (as opposed to polyurethane, the material of the first version). Modifications to the manufacturing process as a result of this shift have resulted in considerable cost reductions to the product. The advisory panel voted to support FDA approval of the new female condom, and it became available in 2009. The new female condom is already in use in many countries outside of the USA and has been endorsed by the World Health Organization (WHO) after a similar review process. This new design should theoretically afford protection similar to the polyurethane female condom and allows for lower manufacturing cost.

Diaphragms

Observational studies demonstrate that diaphragm use protects against cervical gonorrhea, chlamydia, and trichomoniasis [89]. The MIRA trial examined the effect of a diaphragm plus polycarbophil (Replens) lubricant on HIV acquisition in women in Zimbabwe and South Africa. The authors found no additional protective effect of latex diaphragm, lubricant gel, and condoms on HIV acquisition compared to condoms alone [92]. A subsequent analysis of data from this study evaluated outcomes of chlamydia and gonorrhea [93]. Median follow-up time was 21 months, and the retention rate was over 93%. Four hundred seventy-one first chlamydia infections occurred, 247 in the intervention arm and 224 in the control arm with an overall incidence of 6.2/100 woman-years (relative hazard (RH) 1.11, 95% CI: 0.93–1.33) and 192 first gonococcal infections, 95 in the intervention arm and 97 in the control arm with an overall incidence of 2.4/100 women-years (RH 0.98, 95% CI: 0.74–1.30). Results indicated that when diaphragm adherence was defined as "always use" since the last visit, a significant reduction in gonorrhea incidence occurred among women randomized to the intervention (RH 0.61, 95% CI: 0.41–0.91). The authors concluded that while no difference by study arm was found in the rate of acquisition of chlamydia or gonorrhea,

per-protocol results suggested that consistent use of the diaphragm may reduce acquisition of gonorrhea.

Another analysis from the MIRA trial estimated the diaphragm's effect on HPV incidence and clearance in women in Zimbabwe [94]. No overall difference in HPV incidence occurred at the first post-enrollment visit and at 12 months, or in HPV clearance at 12 months among women HPV-positive at enrollment. However, clearance of HPV type 18 was lower in the diaphragm group at exit visit (RR 0.55; 05% CI: 0.33–0.89) but not at 12 months. Women reporting diaphragm/gel use at 100% of prior sex acts had a lower likelihood of having one or more new HPV types detected at 12 months (RR 0.75; 95% CI: 0.58–0.96). The authors concluded that diaphragms did not reduce HPV incidence or increase clearance.

Diaphragms should not be relied on as the sole source of protection against STI or HIV infection. Diaphragms used with nonoxynol-9 (N-9) spermicides have been associated with an increased risk for bacterial urinary tract infections in women.

Other Methods

Microbicides

In general, results of topical microbicides with nonspecific antimicrobial activity for the prevention of HIV and STD have been disappointing [95, 96]. Although a randomized controlled trial comparing vaginal application of 0.5% PRO 2000 (a synthetic polyanionic polymer that blocks attachment of HIV to the host cell) to BufferGel (a vaginal buffering agent), placebo gel, and condom use only found that PRO 2000 was associated with a 30% reduction in risk of HIV acquisition relative to no gel use (adjusted HR 0.70 (95% CI, 0.46–1.08; $P=0.10$)) or to placebo gel use (adjusted HR 0.67 (05% CI, 0.44–1.02; $P=0.06$)), and that women randomized to the PRO2000 arm who had high adherence to gel and used condoms infrequently experienced a 78% reduction in risk [97], a considerably larger study (the MDP301 trial, conducted in four sub-Saharan African countries) assessing 0.5% PRO2000 relative to placebo gel found no protective effect [98]. Taken together, these studies do not support further testing of polyanion-type compounds with nonspecific activity against STD and HIV.

Other microbicide products have not fared well either. A randomized controlled trial compared coitally dependent use of Carraguard (a carrageenan derivative with in vitro activity against HIV) to methylcellulose gel placebo among South African women at high risk for HIV infection. After 2 years follow-up, HIV incidence in the Carraguard group ($N=3{,}011$) was 3.3 per 100 woman-years, and 3.8 per 100 woman-years in the placebo group ($N=2{,}994$) (adjusted HR 0.87 (95% CI: 0.69–1.09)). Applicator dye testing—one means of measuring actual vaginal insertion of the product—indicated that adherence to product was low (42% of sex acts overall). Self-reported product use was substantially higher than the estimate obtained from applicator testing, and some investigators have reported low accuracy for applicator dye testing [99, 100].

Two randomized controlled trials compared daily 6% cellulose sulfate (an HIV entry inhibitor) vaginal gel to corresponding placebo. A multicountry trial enrolled 1398 African women at high risk for HIV. Twenty-five newly acquired HIV infections occurred in the cellulose sulfate group and 16 in the placebo group, with an estimated hazard ratio of infection for the cellulose sulfate group of 1.61 ($P=0.13$). This result, which is not significant, is in contrast to the interim finding that led to the trial being stopped prematurely (hazard ratio, 2.23; $P=0.02$) and the suggestive result of a preplanned secondary (adherence-based) analysis (hazard ratio, 2.02; $P=0.05$). No significant effect of cellulose sulfate as compared with placebo was found on the risk of gonorrhea (HR, 1.10; 95% confidence interval [CI], 0.74–1.62) or chlamydia (hazard ratio, 0.71; 95% CI, 0.47–1.08). The authors concluded that cellulose sulfate did not prevent and may have increased risk of HIV acquisition [101]. A second randomized, placebo-controlled trial of cellulose sulfate in Nigeria was stopped prematurely after the data safety monitoring board of the multicountry trial concluded that cellulose sulfate might be increasing the risk of HIV [101, 102].

With the limited data available, cellulose sulfate gel appeared not to prevent transmission of HIV, gonorrhea, or chlamydial infection.

Two trials of the effectiveness of 1.0% C31G (Savvy; a surfactant) in preventing HIV acquisition were similarly disappointing. In the first, more women in the SAVVY group reported reproductive tract adverse events than placebo [103]. In the second, 33 seroconversions (21 in the SAVVY group and 12 in the placebo group) occurred in the 2,153 participants. The cumulative probability of HIV seroconversion was 2.8% in the SAVVY group and 1.5% in the placebo group ($P=0.121$) with a hazard ratio of 1.7 for SAVVY versus placebo (95% CI: 0.9, 3.5) [104]. The trials indicated that SAVVY did not reduce the incidence of HIV infection, and may have been associated with increased risks.

Pre-exposure Prophylaxis for HIV and STD

In the last 2 years, the field of pre-exposure prophylaxis (PrEP) has been galvanized by the results from clinical trials of antiretroviral medications (ART) to impact transmission and acquisition of HIV. In HIV-infected persons, ART reduces viral load and presumably reduces infectiousness. A recent trial, HPTN 052, provided more optimism about the use of ARVs for prevention [105]. Focusing on the HIV infected partner of discordant couples, HPTN 052 was a randomized, multicenter, clinical trial to evaluate the effectiveness of ARV in preventing sexual transmission. To be eligible, the HIV-infected partner needed to have a CD4 cell count of 350–550 cells/mm^3, above the level of current WHO recommendations to initiate therapy. Couples were randomized to one of two study arms: (1) immediate initiation of ARVs in the index case upon enrollment, or (2) delayed initiation of ARVs until two consecutive CD4 cell counts were below 250 cells/mm^3 or with an AIDS defining illness. The HPTN 052 results were striking, and validated findings from seven previous observational studies [106]. Participants in the immediate ARV initiation arm had a 96% lower risk of acquiring HIV than those in the delayed arm. Moreover, the HIV-infected partner in the immediate arm also suffered fewer HIV-related complications than those in the delayed arm.

In HIV-uninfected persons, ART reduces susceptibility to infection, a concept supported by animal studies and by a study of safety and acceptability in West African women. Most recently the results of the CAPRISA 004 and the iPrEX studies have provided proof of concept for both topical and oral PrEP [107–109]. CAPRISA 004 randomized 889 women in South Africa to coitally dependent use (up to 12 h before and within 2 h after intercourse, not to exceed two administrations in 1 day) of 1% tenofovir gel inserted vaginally, or to corresponding placebo gel, for a median of 30 months. Women randomized to the tenofovir gel group had a significantly reduced rate of HIV acquisition: 5.6 per 100 women-years, compared to 9.1 per 100 women-years (incidence rate ratio 0.61; 95% CI = 6–60). The risk of HSV-2 acquisition was also reduced in the tenofovir group (by 51%; $P=0.003$).

In the first clinical trial reporting on the efficacy of oral PrEP (iPrEx), nearly 3,000 men at high risk for HIV acquisition through sex with other men were randomized to daily oral tenofovir-emtricitabine (TDF-FTC) or placebo and followed for a median of 1.2 years [110]. Men in the TDF-FTC arm experienced a 42% reduction in incidence of HIV (95% CI = 18–60) [111]. A nested case-control analysis compared drug levels in men randomized to the TDF-FTC group. Among men with detectable drug level, as compared with those without a detectable level, the odds of HIV infection were lower by nearly 13-fold (O.R. 12.9; 95% CI, 1.7–99.3), corresponding to a relative reduction in HIV acquisition risk of 92% (95% CI, 40–99). Of note, adherence among men randomized to the active study product as estimated by TDF or FTC levels in peripheral blood mononuclear cells (PBMC) was approximately 50%. More recently, the iPrEx investigators reported that daily oral TDF-FTC use for 2 years in HIV-uninfected men was associated with small but significant loss of bone mineral density at the femoral neck (net effect, −1.1% (95% CI, −0.4 to −1.9)) [112]. The encouraging findings from the iPrEx study prompted CDC to publish interim guidance on the use of TDF-FTC for PrEP in MSM [113]. Planning is underway to issue full guidelines, expected sometime in 2011.

While the results of iPrEx and CAPRISA 004 are extremely encouraging, a Phase III, double-blind, randomized, placebo-controlled trial of daily oral TDF-FTC among African women at high risk for HIV acquisition was stopped early when its Independent Data and Monitoring Committee concluded that the study would be unable to determine if oral Truvada is effective in preventing HIV infection in high-risk women [114]. An equal number of HIV infections ($n=28$) were observed in each arm among the 1,951 women enrolled to that point. The study had planned to enroll 3,900 women and follow them for 1 year. Complete analysis of the final data set must occur before a plausible explanation for this disappointing result can be offered, and is anticipated in the next several months. In the interim, other randomized controlled trials of PrEP are underway which examine different dosing strategies (daily vaginal use of 1% tenofovir gel in the VOICE study (MTN 003)) [115], risk behavior (heterosexual acquisition in reproductive age women in the VOICE study and in HIV serodiscordant couples in the Partners in Prevention Study), and geographic locale. Information on these studies is available at http://www.avac.org.

Two studies examined suppression of HSV as a means of reducing acquisition or transmission of HIV. Infection with herpes simplex virus type-2 (HSV-2) is a significant risk for acquisition and transmission of HIV [116]. A meta-analysis of 19 prospective observational studies reported that infection with HSV-2 increased risk of HIV acquisition 2.7-fold in men and 4.4-fold in women [117]. However, two studies of daily suppressive acyclovir therapy in HIV-uninfected adults in Africa did not show a reduction in risk of HIV acquisition, despite high rates of reported adherence and excellent retention in one [25, 118]. A similar study among HIV-infected persons showed that although acyclovir treatment reduced the frequency of genital ulcers by 73% and HIV plasma viral load by 40% (0.25 $\log_{10}$ copies/ml) compared to placebo, it did not effect a reduction in risk of HIV acquisition [26, 119]. Notably, participants treated with acyclovir had a small but significant reduction in risk of progression to HIV-related disease including decline of CD4 cells to <200 cells/mm^3, initiation of antiretroviral medication, or death.

Regarding PrEP for other STD prevention, as described earlier, an unexpected finding from the CAPRISA 004 trial was the protective effect of 1% tenofovir gel on HSV-2 acquisition [120]. Earlier work had shown that oral tenofovir did not produce drug levels in the vagina necessary to reach the EC50 against herpes. However, topical tenofovir allows local drug concentrations nearly 1,000 times higher than oral dosing. In CAPRISA 004, the higher level of tenofovir in cervicovaginal fluid was associated with significantly reduced rates of HSV-2 acquisition. The relationship between vaginal tenofovir gel use and HSV-2 acquisition will also be assessed in heterosexual women participating in the ongoing VOICE study, with results expected in early 2013.

Another randomized trial of STI pre-exposure prophylaxis evaluated other vaginal infections. It assessed the effect of directly observed oral treatment with 2 g of metronidazole plus 150 mg of fluconazole compared with metronidazole placebo plus fluconazole placebo administered monthly in reducing vaginal infections among Kenyan women at risk for HIV-1 acquisition. Of 310 HIV-1-seronegative female sex workers enrolled (155 per arm), 303 were included in the primary end points analysis. Compared with control subjects, women receiving the intervention had fewer episodes of BV (HR, 0.55; 95% CI, 0.49–0.63) and more frequent vaginal colonization with any *Lactobacillus* species (HR, 1.47; 95% CI, 1.19–1.80) and hydrogen peroxide-producing *Lactobacillus* species (HR, 1.63; 95% CI, 1.16–2.27). The incidences of vaginal candidiasis (HR, 0.84; 95% CI, 0.67–1.04) and trichomoniasis (HR, 0.55; 95% CI, 0.27–1.12) among treated women were less than those among control subjects, but the differences were not statistically significant. The authors concluded that periodic presumptive treatment reduced the incidence of BV and promoted colonization with normal vaginal flora [121]. Another trial randomized women with asymptomatic BV to observation or treatment and prophylaxis with twice weekly intravaginal metronidazole gel. Women in the metronidazole gel arm had fewer chlamydial infections over the subsequent 6 months [122].

Postexposure Prophylaxis for STI/HIV, and Unintended Pregnancy

In the USA, an emergency contraception (EC) pill with the brand name Plan B is available over the counter to women aged 17 years and older and by prescription to younger women. Plan B contains two tablets of 0.75 mg levonorgestrel, which may be taken 12 h apart as labeled or together as a single dose. If Plan B is not readily accessible, oral EC also may be provided using many commonly available brands of oral contraceptive pills by instructing the woman to take a specified number of tablets at once. Emergency insertion of an IUD up to 7 days after sex can reduce pregnancy risk by more than 99%. However, this method is not advisable for a woman who may have untreated cervical gonorrhea or chlamydia, who is already pregnant, or who has other contraindications to IUD use. All oral EC regimens are most efficacious when initiated as soon as possible after unprotected sex but have some efficacy as long as 5 days later. EC is ineffective (but is also not harmful) if the woman is already pregnant [123]. More information about EC is available in the 19th edition of *Contraceptive Technology* [124], or at http://www.arhp.org/healthcareproviders/resources/contraceptionresources.

A Cochrane review summarized the efficacy, safety, and convenience of various methods of emergency contraception. The review concluded that mifepristone middle dose (25–50 mg) was superior to other hormonal regimens. Mifepristone low dose (<25 mg) could be more effective than levonorgestrel 0.75 mg (two doses) but this was not conclusive. Levonorgestrel proved more effective than the Yuzpe regimen. The copper IUD was another effective emergency contraceptive that can provide ongoing contraception [123].

CDC guidelines for the use of postexposure prophylaxis with antiretroviral therapy aimed at preventing HIV acquisition as a result of sexual exposure are available [125], as are recommendations for STI prophylaxis after sexual assault.

Immunization

Preexposure vaccination is one of the most effective methods for preventing transmission of two main STDs: HPV and hepatitis B. In March 2007, the Advisory Committee on Immunization Practices (ACIP) issued guidelines for administration of the quadrivalent HPV vaccine to females aged 25 years and younger [126]. Specific details are available at http://www.cdc.gov/std/hpv. This vaccine confers protection against HPV types 6/11 (responsible for 90% of genital warts) and 16/18 (responsible for 70% of cervical cancers). In published clinical trials, the quadrivalent HPV vaccine has demonstrated efficacy for prevention of vaccine HPV type-related cervical, vaginal, and vulvar cancer precursor and dysplastic lesions, and external genital warts [127]. Universal vaccination of females aged 11–12 years is recommended, as is catch-up vaccination for females aged 13–26 years. The vaccine is also efficacious in preventing infection in women aged 24–45 years not already infected with the relevant HPV types [128]. Data on the efficacy of the quadrivalent HPV vaccines in protecting young men from vaccine-type HPV acquisition indicates similarly high levels of protection [129, 130], and the ACIP issued permissive guidance for immunization to prevent genital warts in young men in 2010. Both men and women are also likely to benefit from protection against anal intraepithelial neoplasia afforded by the quadrivalent vaccine. A bivalent vaccine that is effective in preventing cervical neoplasia associated with HPV types 16/18 has also been approved for use in the USA, and is recommended by ACIP [131, 132].

Immunization against hepatitis B has been routinely recommended for infants since 1991 and was subsequently recommended for adolescents. While this has been temporally associated with marked declines in HBV incidence in the USA [133], sexual transmission still accounts for the majority of new infections, which are especially common among unvaccinated MSM. Consequently, hepatitis B vaccination is recommended for all adults who are at risk for sexual infection, including sex partners of hepatitis B surface antigen (HBsAg)-positive persons, sexually active persons who are not in a long-term, mutually monogamous relationship, persons seeking evaluation or treatment for a STD, and

MSM [134]. Moreover, all HIV-infected persons should be immunized against hepatitis B, as the natural history of hepatitis B is accelerated in the setting of HIV, and coinfection imposes specific considerations in selection of antiretroviral agents. Hepatitis A vaccine is licensed and is recommended for MSM and illicit drug users (both injecting and noninjecting) [135]. Specific details are available at http://www.cdc.gov/hepatitis.

Prospects for an effective HIV vaccine remain on the distant horizon. Recent disappointing results from human trials have stimulated a renewed focus on the basic biology of HIV pathogenesis. Two phase III trials of a vaccine aimed at eliciting neutralizing antibodies against the envelope glycoprotein 120 did not find protection against HIV infection [136, 137]. A phase IIB trial of the first T-cell vaccine (Merck's MRKAd5 HIV-1 gag/pol/nef trivalent product, using a replication-defective adenovirus type-5 vector with three HIV genes) was stopped in September 2007. Interim analysis revealed no protective effect against HIV acquisition, and no reduction in initial viral loads among participants infected with HIV [138, 139]. Further analysis showed that pre-existing immunity to adenovirus type-5 was directly associated with a significantly higher risk of acquiring HIV, and that this untoward effect was further augmented among uncircumcised men. A community-based, randomized, double-blind, placebo-controlled trial performed in over 16,000 Thai adults evaluated four priming injections of a recombinant canary pox vector vaccine (ALVAC-HIV) plus two booster injections of a recombinant glycoprotein 120 subunit vaccine (AIDSVAX B/E) [140]. There was a trend toward HIV prevention in the intention-to-treat analysis (vaccine efficacy 26.4% (95% CI -4.0 – 4.79)), but not in the per protocol analysis (vaccine efficacy 26.2% (95% CI -13.3 – 51.9)). Vaccination did not affect HIV viral load or CD4 count in participants who acquired HIV during the trial.

Circumcision in Male Sex Partners

Three randomized controlled trials performed in healthy African men showed that male circumcision was effective in preventing HIV acquisition. In studies performed in Uganda, South Africa, and Kenya, men were randomized to be offered immediate or delayed (24 months) circumcision, and followed over 2 years for acquisition of HIV and other STDs [141–144]. The summary rate ratio for reduction of HIV acquisition in the men who underwent immediate circumcision for the three trials was 0.42 (95% CI 0.31, 0.57), identical to that obtained from observational studies, which translates into a protective effect of male circumcision of 58% [142]. On the basis of these findings, a WHO and UNAIDS consultation in March 2007 recommended that circumcision be recognized as an effective intervention for HIV prevention of heterosexual HIV acquisition in men [145]. WHO and UNAIDS also recommended that male circumcision be offered to HIV-negative men in addition, but not as a substitute, to other HIV risk-reduction strategies.

Circumcision also affords a similar level of protection against acquisition of other STI, particularly nonulcerative pathogens, including high-risk genital HPV and genital herpes [146–148]. In South Africa, after 21 months of follow-up, circumcision protected against high-risk HPV (OR 0.57; 95% CI, 0.43–0.75), but not gonorrhea [146]. The association between trichomoniasis and male circumcision remained borderline when controlling for age, ethnic group, number of lifetime partners, marital status, condom use and HIV status (adjusted OR, 0.48, $p=0.069$). In the as-treated analysis, this association became significant (OR, 0.49, $p=0.030$ and adjusted OR, 0.41, $p=0.03$). The authors concluded that male circumcision reduces incident trichomoniasis among men. Men in Uganda were also followed for acquisition of STD for 2 years. At 24 months, the cumulative probability of HSV-2 seroconversion was 7.8% in men randomized to circumcision (1,684 men who were initially HSV2-seronegative) and 10.3% in the control group (1,709 men initially HSV2-seronegative) (adjusted HR 0.72 (95% CI, 0.56–0.92; $P=0.008$)) [148]. The prevalence of high-risk HPV genotypes was 18.0% in the intervention group and 27.9% in the control group (adjusted risk ratio, 0.65; 95% CI, 0.46–0.90; $P=0.009$). However, no significant difference between the two study

groups was observed in the incidence of syphilis (adjusted HR, 1.10; 95% CI, 0.75–1.65; $P=0.44$). Among men enrolled in the Kenya study, circumcision afforded no protection against incident gonorrhea, chlamydia, or trichomoniasis [149].

No randomized controlled trials of circumcision have been performed among men in the USA. However, a cross-sectional analysis reported that among 394 heterosexual African-American men attending a Baltimore STD clinic who reported known HIV exposure, circumcision was significantly associated with lower HIV prevalence (10.2% vs. 22.0%); adjusted prevalence rate ratio (PRR) 0.49 (95% CI, 0.26–0.93). No such association was seen for men with unknown HIV exposure [150]. The benefits of circumcision to MSM are unproven. A meta-analysis of studies reported that overall, circumcised MSM had lower odds of being infected with HIV (OR, 0.86; 95% CI, 0.65–1.10), an association that did not reach statistical significance and that was similar among men who reported primarily engaging in insertive anal sex [151].

Unfortunately, the benefits of male circumcision in reducing HIV acquisition in men do not extend to women; however, other benefits may occur. Female sex partners of men who participated in the Uganda circumcision trial were followed to assess effects on their genital symptoms and vaginal infections [152]. Among women with normal vaginal flora scores at enrollment, rates of BV at follow-up were significantly lower in wives of men who had been circumcised compared to men who had not (prevalence risk ratio (PRR) 0.80; 95% CI, 0.65–0.97). In women with BV at enrollment, persistent BV at 1 year was significantly lower in the intervention arm than control arm women (PRR 0.83; 95% CI, 0.72–0.96). The adjusted prevalence risk ratio of GUD among wives of circumcised men compared with uncircumcised men was 0.78 (95% CI, 0.61–0.99), consistent with circumcision efficacy of 22%. The adjusted prevalence risk ratio for trichomoniasis in intervention arm wives relative to controls was 0.55 (95% CI, 0.34–0.89; efficacy 45%). The authors concluded that male circumcision may have direct benefits for prevention of genital ulceration, trichomoniasis, and BV in female partners and that this should be considered when planning scale-up of male circumcision programs for HIV prevention.

Implementation of male circumcision as a HIV prevention strategy remains to be fully defined. Concerns include possible disinhibitory effects on sexual risk behaviors, complications from unsafe or inexperienced providers, and acceptability by substantial numbers of men at highest risk for HIV [96]. Male circumcision is a compliment to, not a substitute for, other HIV risk-reduction strategies. WHO and UNAIDS recommend that countries with hyperendemic and generalized HIV epidemics and low prevalence of male circumcision expand access to safe male circumcision services within the context of ensuring universal access to comprehensive HIV prevention, treatment, care, and support.

Interactive Counseling Strategies

New data continue to support the use of individual client-centered counseling to reduce recipients' risk of acquiring HIV/STD. The U.S. Preventive Services Task Force (USPSTF) recently reviewed the evidence base on this topic [153, 154], and concluded with the following summary statement:

> The USPSTF recommends high-intensity behavioral counseling to prevent sexually transmitted infections (STIs) for all sexually active adolescents and for adults at increased risk for STIs. This is a grade B recommendation. The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of behavioral counseling to prevent STIs in non-sexually active adolescents and in adults not at increased risk for STIs [153].

Training modules are available to help providers develop skills in this area; one consolidated resource is at http://www.stdhivpreventiontraining.org. Patient-centered counseling can have a beneficial impact on the likelihood of patients' assuming new or enhancing current risk-reduction practices. All providers should routinely obtain a sexual history from their patients, and address management of risk reduction as indicated [155, 156]. This is particularly important

for routine care of HIV-infected persons, and for adults and adolescents at risk for acquisition of STI.

Systems-Based Approaches for Improving Women's Sexual Health: Priorities

Because women — and their infants — are uniquely vulnerable to the consequences of the infections discussed above, structural interventions that can effect wide-scale system change have the most potential to promote positive change. Examples include the adoption of chlamydia screening as a standard of care that is linked to provider (or health plan) performance and the provision of antimicrobial therapy for sex partners without requiring that they be examined (expedited partner management).

Optimization of selective screening for chlamydial infection remains a cornerstone of the interventions available to promote and protect women's health [157]. Randomized controlled trials have evaluated the effect of rescreening for chlamydia or gonorrhea in preventing repeat infection, and have uniformly provided support. The largest study randomly assigned women and heterosexual men with gonorrhea or chlamydial infection to have their partners receive expedited treatment or standard referral. The expedited-treatment group was offered medication to give to their partners, or if they preferred, study staff contacted partners and provided them with medication without examination. Persons assigned to standard partner referral were advised to refer partners for treatment and offered assistance notifying partners. Persistent or recurrent gonorrhea or chlamydia occurred in 13% assigned to standard partner referral and 10% assigned to expedited treatment of sexual partners (relative risk, 0.76; 95% CI, 0.59–0.98). Expedited treatment was more effective than standard referral of partners in reducing persistent or recurrent infection among patients with gonorrhea (3% vs. 11%, $P=0.01$) than in those with chlamydia (11% vs. 13%, $P=0.17$) ($P=0.05$ for comparison of treatment effects) and remained independently associated with a reduced risk of persistent or recurrent infection after adjustment for other predictors of infection at follow-up (relative risk, 0.75; 95% CI, 0.57–0.97). Patients assigned to expedited treatment of sexual partners were significantly more likely than those assigned to standard referral of partners to report that all of their partners were treated and significantly less likely to report having sex with an untreated partner [158].

Additional observational studies support that this strategy should continue to be emphasized. Among 897 female adolescents attending school-based health centers, 236 had one or more subsequent positive tests for a cumulative incidence of reinfection in one year of 26.3% (95% CI, 23.4–29.2) [159]. Project RESPECT data were used to determine the incidence of new infections during the year after a visit to a STD clinic. Among 1,236 women, 25.8% had one or more new infections (11.9% acquired *C. trachomatis*, 6.3% *N. gonorrhoeae*, and 12.8% *T. vaginalis*); among 1,183 men, 14.7% had 1 or more new infections (9.4% acquired *C. trachomatis*, and 7.1% *N. gonorrhoeae*). The authors concluded that individuals who receive diagnoses of any of these STI should return in 3 months for rescreening [160]. This approach has also been used successfully for trichomoniasis [161]. Rescreening several months after a diagnosis of chlamydia, gonorrhea, or trichomoniasis detects substantial numbers of new infections, and can be recommended as a population-level prevention method. Community-level behavioral interventions since these have been extensively reviewed elsewhere [162].

Conclusion

A range of preventive interventions is needed to reduce the risks of acquiring STI and HIV among sexually active people. A flexible approach targeted to specific populations should integrate combinations of biomedical, behavioral, and structural interventions. These would ideally involve an array of prevention contexts, including (1) communications and practices among sexual partners, (2) transactions between individual clients and

their health care providers and (3) comprehensive population-level strategies for prioritizing prevention research, ensuring accurate outcome assessment, and formulating health policy.

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