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Prevention of sexually transmitted infections

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INTRODUCTION — Sexually transmitted infections (STIs) are common and preventable causes of morbidity and serious complications. Untreated chlamydial and gonococcal infection may result in pelvic inflammatory disease, which can lead to infertility, ectopic pregnancy, and chronic pelvic pain in 10 to 20 percent of cases [1]. STIs can also result in adverse outcomes in pregnancy, including spontaneous abortion, still birth, premature birth, and congenital infection [2]. Finally, the presence of STIs can facilitate HIV transmission [3-5]. Thus, primary prevention of STIs needs to be given high priority.

This topic addresses issues related to the prevention of sexually transmitted infections. Screening for sexually transmitted infections is discussed elsewhere. (See "Screening for sexually transmitted infections".)

EPIDEMIOLOGY — A key strategy in the prevention of STIs involves the screening, diagnosis, and treatment of patients, as well as their sexual partners, to interrupt transmission. Routine sexual histories are critical to allow targeted STI screening and prevention counseling. Assessment of any history of substance abuse, which can lead to disinhibition and risk-taking behaviors, is also important. Risk factors are listed below:

- Unmarried status
- Residence in an urban area
- New sex partner(s)
- Multiple sexual partners (concurrent)
- History of a prior STI
- Illicit drug use
- Contact with sex workers
- Intimate partner violence

All patients who have a history of, or risk factors for, an STI should be offered HIV counseling and testing as well as screening for other STIs. Conversely, anyone who is identified as HIV-seropositive should undergo testing for other STIs [6]. This topic is discussed in detail elsewhere. (See "Screening and diagnostic testing for HIV infection".)

Risk groups — The United States Preventive Services Task Force (USPSTF) and the Centers for Disease Control and Prevention recommend periodic sexual risk assessment to determine which patients are most likely to benefit from STI screening or risk reduction counseling.

All sexually active adolescents are at increased risk for STIs and should be offered counseling. Adults should be considered at increased risk if they have a current or past history of a sexually transmitted infection or a history of multiple sex partners. In areas of high prevalence for STIs, all sexually active patients in nonmonogamous relationships may be considered at increased risk. (See 'Counseling and other prevention modalities' below.)

Adolescents — The Centers for Disease Control and Prevention (CDC) created a national surveillance system to monitor risk-taking behaviors in adolescents, which may increase their risk of acquiring an STI. In 2013, an estimated 47 percent of US high school students had a history of sexual intercourse, 15 percent reported four or more lifetime sexual partners, and 41 percent of sexually active students reported not using a condom at their last sexual encounter [7]. Furthermore, each year approximately one half of the estimated 19

million incident STI infections in the United States occur in young people ages 15 to 24 [8].

Despite the prevalence of STIs among adolescents, providers frequently fail to inquire about sexual behavior or counsel about risk reduction [9]. The American Academy of Pediatrics recommends asking adolescents about sexual activity at annual clinic visits, and offering STI screening to all sexually active adolescents [10]. (See "Screening for sexually transmitted infections", section on 'Taking a sexual history'.)

Men who have sex with men — Men who have sex with men (MSM) are at high risk for HIV infection and other viral and bacterial STIs due to unsafe sexual practices [9]. Increased rates of syphilis, gonorrhoeae, and chlamydial infections, mostly in HIV-infected MSM, have been reported in many cities in the United States and Europe. (See "Pathogenesis, clinical manifestations, and treatment of early syphilis" and "Epidemiology, clinical presentation, and diagnosis of syphilis in the HIV-infected patient" and "Clinical manifestations and diagnosis of Neisseria gonorrhoeae infection in adults and adolescents" and "Treatment of uncomplicated gonococcal infections" and "Epidemiology of Chlamydia trachomatis infections".)

In the fall of 2012, an outbreak of invasive meningococcal disease was detected among MSM in New York City. Although not an STI per se, Neisseria meningitidis can be transmitted through close contact, including kissing and sexual contact. Meningococcal vaccination is recommended for MSM who may be exposed to this outbreak. (See "Meningococcal vaccines", section on 'In adults'.)

Clinicians need to assess sexual risk for all male patients through careful sexual history-taking and counseling on risk reduction at regular clinic visits [11,12]. Clinicians should also routinely ask patients about symptoms consistent with common STIs, including urethral discharge, dysuria, ulcers, or anorectal symptoms. (See "Screening for sexually transmitted infections", section on 'Taking a sexual history'.)

HIV-infected patients — A substantial number of HIV-infected individuals remain sexually active and acquire STIs [13]. Concurrent or recurrent STI infections (eg, herpes simplex virus) are particularly important as they increase HIV shedding, and increase the risk of HIV transmission to sexual partners. Accordingly, routine screening and treatment of STIs in HIV-infected persons is recommended [9]. Patients with repeated STIs need enhanced behavioral counseling. (See "Screening for sexually transmitted infections", section on 'Screening special populations'.)

Community-based trials to assess the effect of either improved individual-focused clinical care or mass community treatment of STIs on HIV transmission have been conducted in East Africa; a meta-analysis of four trials found no overall reduction in HIV incidence, although clinically significant reductions in syphilis and gonorrhea were noted [14].

Sexual transmission of HCV can occur, particularly among HIV-infected patients. Common practices associated with clusters of acute HCV infection that have been reported in the United States and Europe include serosorting (ie, HIV-infected men having sex with one another), group sex, and the use of cocaine and other non-intravenous drugs during sex [9].

VACCINES — Immunizations are available for the prevention of several infections that are sexually transmitted or associated with sexual activity; these include hepatitis A, hepatitis B, human papillomavirus (HPV), and Neisseria meningitidis. Individuals with advanced immunodeficiency may have an impaired response to vaccination. For HIV infected patients, vaccines that had been administered at a CD4 count <200/microL should be repeated after the CD4 count has risen to >200 cells/microL. (See "Immunizations in HIV-infected patients".)

Hepatitis A — Vaccination against hepatitis A is recommended by the CDC for MSM, injection drug users, and patients with chronic liver disease [9]. In 2006, hepatitis A vaccination was incorporated into the routine childhood vaccination schedule in the United States. Postvaccination serologic testing is not recommended in immunocompetent individuals because most persons respond to the vaccine. In persons with advanced immunodeficiency and a likelihood of an impaired humoral response, postvaccination serologic testing after one month is indicated to assess the need for supplemental doses [15].

Hepatitis A virus replicates in the liver and is shed in high concentrations in feces from two weeks before to one week after the onset of clinical illness. Since sexual transmission of hepatitis A probably occurs because of fecal-oral contact, barrier measures, such as condoms, are ineffective in preventing acquisition of this disease. (See "Hepatitis A virus vaccination and postexposure prophylaxis".)

Immunization is also recommended for HIV-infected patients who have chronic liver disease or are at risk for hepatitis A (MSM, injection drug users, or patients with a history of hemophilia). Hepatitis A vaccine is safe and effective in HIV-infected patients, particularly when administered before onset of advanced immunosuppression. (See "Immunizations in HIV-infected patients".)

Hepatitis B — The primary risk factors that have been associated with hepatitis B infection among adolescents and adults are unprotected sex with an infected partner, unprotected sex with more than one partner, and history of other STIs. MSM and injection drug users are considered high risk groups for HBV acquisition [9].

The Advisory Committee on Immunization Practices (ACIP) recommends universal hepatitis B immunization for all unvaccinated adults presenting to an STI clinic, including those who did not complete their immunization series [16]. Patients with a history of HBV vaccination should have either documentation of immunization or serologic testing for hepatitis B surface antibody. Appropriate screening tests and the vaccine administration schedule are discussed elsewhere. (See "Hepatitis B virus vaccination".)

Although this vaccine is quite effective and safe, studies indicate that many high risk patients are not immunized. In a cross-sectional study of 682 STI clients, 23 percent had antibody to hepatitis B core antigen, indicating previous infection, and 9 percent had antibody to hepatitis B surface antigen, indicating past vaccination; however, the vast majority were still susceptible to hepatitis B infection [17].

All pregnant women receiving STI services should be tested for HBsAg, regardless of whether they have been previously tested or vaccinated [9] (see "Initial prenatal assessment and first trimester prenatal care"). The Global Advisory Group of the Expanded Program on Immunization and the WHO recommend routine hepatitis B vaccination among neonates as part of national immunization programs. Adoption in the US is expected to alter the epidemiology of carrier rates and complications of chronic hepatitis B infection as shown in other countries with early adoption of the recommendation [18-20].

All HIV-infected patients should receive HBV immunization. Although the vaccine is safe, efficacy can be affected by the presence of HIV RNA and advanced immunosuppression. Accordingly, antibody to hepatitis B surface antigen should be checked at least one month after completion of the vaccine series, and patients with titer levels ≤10 IU/mL should be revaccinated [15]. (See "Immunizations in HIV-infected patients" and "Treatment of chronic hepatitis B in the HIV-infected patient".)

Human papillomavirus — Two human papillomavirus (HPV) vaccines are available for the prevention of HPV infection in women: a bivalent vaccine (Cervarix), which protects against HPV types 16 and 18 and a quadrivalent vaccine (Gardasil), which protects against types 6, 11, 16 and 18. Both vaccines offer protection against the HPV types that cause 70 percent of cervical cancers (eg, types 16 and 18) and the quadrivalent HPV vaccine also protects against HPV types that are associated with genital warts (eg, types 6 and 11). Only the quadrivalent vaccine (Gardasil) is approved in the US for use in males.

Immunization with HPV vaccine is recommended by the CDC's Advisory Committee on Immunization Practices (ACIP) in girls and women 9 to 26 years of age [21,22]. The quadrivalent vaccine can also be used in males aged 9 to 26 years to prevent genital warts [9]. Clinical trial data, dosing and administration of the vaccines, and side effects are discussed elsewhere. (See "Recommendations for the use of human papillomavirus vaccines" and "Clinical trials of human papillomavirus vaccines".)

Neisseria meningitidis — Although not an STI per se, N. meningitidis can be transmitted through close contact, including kissing and sexual contact. Outbreaks and clusters of meningococcal meningitis have been reported among MSM in the United States (New York City) and Europe [23,24]. Meningococcal vaccination is indicated for MSM who may have close contact with other MSM from the sites of those outbreaks. (See "Meningococcal

vaccines", section on 'In adults'.)

Vaccines in development

Human immunodeficiency virus — No vaccine is currently available for HIV prevention, although new technologies and approaches to vaccine development hold promise [25] (see "Immunology of HIV-1 infection"). After disappointing results from prior studies, results from an HIV vaccine trial in 2009 suggested the first, albeit moderate, protection from heterosexual HIV transmission; intention to treat analysis excluding HIV-infected patients at baseline showed vaccine efficacy was 31.2 percent (95% CI 1.1-52.1; p = 0.04) [26].

Hepatitis C — Several prophylactic vaccines for hepatitis C virus (HCV) are under study, although they remain in the relatively early stages of development [27].

CONDOM USE — One of the most important means of preventing STIs is through condom use [28]. The amount of protection provided by condom use for the prevention of HIV and other STIs is difficult to establish given the ethical limitations of conducting randomized controlled trials. Both the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) assert the protective value of condoms in preventing STIs, and the WHO has incorporated condoms as an essential component in public health strategies to prevent STIs [9,29].

In 2000, the National Institutes of Health convened an expert panel to critically review available scientific literature on the effectiveness of condoms to prevent STIs, including HIV, chlamydia, gonorrhoeae, syphilis, human papillomavirus, chancroid, trichomonas, and genital herpes simplex virus. The panel concluded that condom use prevented HIV transmission in both men and women during vaginal intercourse and prevented gonorrhoeae in men [30]. The panel felt there was insufficient data to draw conclusions on the ability of condoms to prevent other STIs [30]. Of note, most data on the efficacy of condoms are related to male condom use rather than female condom use [30].

Studies on the efficacy of condom use are subject to a number of limitations [31]. Assessment of condom use is generally by self-report, which may be unreliable, incorrect use of condoms that would reduce their efficacy is rarely evaluated, and frequency of condom use is usually recorded as a static measure, when it may change over time. All these would underestimate the efficacy of appropriate condom use. Nevertheless, since publication of the expert panel's findings in 2000, multiple other prospective studies have been reported that have contributed substantially to understanding the protective role of condoms in other STIs, including chlamydia, gonorrhoea, herpes simplex type 2, trichomoniasis, and human papillomavirus [32].

Human immunodeficiency virus (HIV)

Transmission — HIV can be transmitted through anal, penile-vaginal, and oral intercourse, but the far greatest risk is with anal intercourse. The presence of ulcerative genital lesions also increases the risk of HIV transmission. (See "Nonoccupational exposure to HIV in adults".)

Effectiveness of condoms — In vitro studies of latex and polyurethane condoms have demonstrated that they are impenetrable to HIV viral particles [33]; however the majority of evidence for condom effectiveness derives from observational studies. In a meta-analysis of 12 studies of HIV heterosexual serodiscordant couples, condom usage was classified in three categories: always, sometimes, or none. HIV seroconversion rates were much higher in those who never used condoms versus those who always did (0.9 seroconversions versus 6.7 seroconversions per 100 person years) [34]. The authors estimated that condoms provided an 85 percent reduction in transmission risk. Based on these data, the National Institutes of Health's expert panel concluded that condoms are effective for preventing HIV infection in women and men when used consistently and correctly [30]. A similar Cochrane review estimated that the consistent use of male latex condoms, defined as using a condom for all acts of penetrative vaginal intercourse, reduces HIV incidence by 80 percent, based on several longitudinal female-to-male and male-to-female serodiscordant couples [35]. In 2009, a collaborative statement from the American College of Physicians and the HIV Medicine Association also called for wider availability of condoms and education about their proper use to minimize the risk of HIV transmission [36].

Barrier methods are strongly emphasized in Uganda's "ABC strategy" of abstinence, being faithful, and condom use, which is credited for making a significant impact on transmission rates in that country [37]. However, in order for condom use to be effective in decreasing HIV prevalence, they need to be used consistently, with ongoing exposures, particularly in areas of high prevalence. To increase the effectiveness of condoms in reducing HIV transmission, others have argued that partner reduction should be emphasized as well, particularly in highly endemic areas [38].

Since women are often unable to convince their partners to use a condom, there is a need to assess other barrier methods that women can initiate. Female condoms are impervious to viruses, including HIV; however, there are few data regarding efficacy in prevention of HIV transmission [39] and no randomized controlled trials have been conducted on the protective effect of female condoms against HIV infection.

Gonorrhea, chlamydia, and trichomonas — Gonorrhoeae, Chlamydia, and trichomonas cause the vast majority of sexually transmitted infections worldwide.

- Although the infectious dose of N. gonorrhoeae is not known, one ejaculate from an infected male contains approximately six million bacteria [40]. Data suggest an average transmission of one infection for every two exposures. Transmission from male to female is approximately fourfold more efficient than female to male [30].
- Chlamydia infection is the most common bacterial STI in the United States, with approximately three million cases per year. Like gonorrhoeae, chlamydia is more efficiently transmitted from males to females. Although easily treated, many patients are undiagnosed due to lack of symptoms. Asymptomatic disease contributes to spread of infection.
- Trichomonas is a protozoan that is responsible for approximately 160 million cases of vaginitis worldwide. Transmission rates have not been measured, but are thought to be high; the infectious dose is not known [30].

The NIH expert panel concluded in 2000 that epidemiologic studies suggested that consistent condom use may reduce the risk of gonorrhoeae in men; data were lacking for conclusion regarding chlamydia and trichomoniasis [32]. Subsequently, several studies suggest a protective effect of condoms against gonorrhoeae, chlamydia, and trichomoniasis infection, as illustrated below:

- Studies of regular STI evaluation and treatment and provision of condoms in female sex workers in Peru showed that condom use promotion was associated with a significantly decreased risk of gonorrhoeae, chlamydia and trichomonas infections among female sex workers [32,41,42].
- A significant reduction in the combined incidence of gonorrhoea, chlamydial infection, or trichomoniasis was also observed in a study of adolescent African-American females [43]. In this study, 17.8 percent of females reporting 100 percent condom use developed a recurrent STI compared with 30 percent of females who did not use condoms consistently.
- A study of mass treatment for STIs in Uganda revealed a significant reduction in the prevalence of syphilis, gonorrhoea, and chlamydia, or both, in men and women reporting consistent condom use, compared to the nonuse of condoms [44].
- A 30 percent reduction in trichomonas infection was reported among women attending an STI clinic who reported using condoms as a method of contraception (106 of 1021 patients) compared with those who did not use barrier methods (525 of 4660 patients) [45].

In a subsequent review of all studies published from 1966 to 2004 that evaluated the effectiveness of condom use in preventing gonorrhoeae and chlamydia, most have demonstrated a reduced risk of infection [46].

Genital herpes — Both herpes simplex viruses type 1 and type 2 can cause painful genital ulcerations. Transmission can occur during symptomatic and asymptomatic periods due to intermittent viral shedding.

The effect of condom use on transmission of HSV infection has been evaluated in two large studies of heterosexual discordant couples. Both trials demonstrated that condoms were effective in preventing HSV transmission, although only one of the studies demonstrated a protective effect in women. (See "Treatment of genital herpes simplex virus infection".)

HSV acquisition is also associated with an increased risk of HIV acquisition. (See "Epidemiology, clinical manifestations, and diagnosis of genital herpes simplex virus infection", section on 'HSV-2 and risk of HIV transmission'.)

Human papillomavirus — Condom use has been associated with a reduction in the risk of acquiring HPV infection, clearance of infection, and higher rates of regression of cervical intraepithelial neoplasia in women and penile lesions in men [47-53].

The efficacy of condom use in preventing HPV infection has been studied in women and men:

- In a study of 82 women who reported their first sexual encounter after study entry or two weeks before enrollment, the risk of developing HPV infection was 70 percent lower among women whose partners consistently used condoms compared with women whose partners used condoms less than 5 percent of the time [47]. Condom use was also effective in preventing cervical intraepithelial lesions. (See "Epidemiology of human papillomavirus infections", section on 'Risk factors for infection'.)
- In a study of 3323 men who reported sexual intercourse with at least one female partner in the prior six months and had no baseline HPV infection, self-reported consistent condom use was associated with a decreased 12-month incidence of anogenital HPV infection among the 554 men who reported having no steady sexual partner (HR 0.54, 95% CI 0.3-0.95, compared with no condom use) [52]. There was no detected association between condom use and HPV infection among men who had a steady sexual partner, regardless of whether they were monogamous or non-monogamous.

Chancroid — Chancroid causes genital ulcer disease and is primarily found in resource-limited settings. In experimental models, the infectious dose is only a few Hemophilus ducreyi organisms [54]. Transmission occurs in approximately 70 percent of sexual exposures. (See "Chancroid".)

Epidemiologic data suggest a protective effect of condoms, but the lack of microbiologic confirmation in the few studies that have been performed has prevented firm conclusions [30].

Syphilis — Treponema pallidum is transmitted by direct contact with syphilis sores, which may be present on the external genitals, vagina, anus, rectum, lips, and mouth; only a few organisms are required to infect a person through abraded skin. The primary chancre is often painless, but teeming with spirochetes. (See "Pathogenesis, clinical manifestations, and treatment of early syphilis".)

In a study of women considered to be at high risk for STIs, the consistent and correct use of male condoms or female condoms was associated with a statistically significant reduction in the combined incidence of gonorrhoeae, chlamydia, and syphilis when compared to women who used condoms less than 50 percent of the time [32].

A subsequent meta-analysis of condom use and risk of STIs determined that only two studies were rigorously designed as longitudinal assessments of incident syphilis; one study suggested a significantly reduced risk of syphilis among condom users [55].

Pelvic inflammatory disease — In a study of 684 women diagnosed with pelvic inflammatory disease (PID), consistent use of condoms led to lower rates of recurrent PID, chronic pelvic pain, and infertility [56].

Condom regulations — Condoms are regulated as medical devices. Each latex condom manufactured in the United States is tested electronically for holes before packaging. Failure of condoms usually results from inconsistent or incorrect use rather than condom breakage [9].

Patient education — Patients should be advised that condoms must be used consistently and correctly to be effective in preventing STIs. Advice should be given regarding proper use of condoms and water-based lubricants; oil-based lubricants (petroleum jelly, mineral oil) can weaken latex [9].

Women also need to be counseled that contraceptive methods that are not mechanical barriers offer no protection against HIV or other STIs.

Spermicide use — Condoms lubricated with spermicides are no more effective than other lubricated condoms in protecting against the transmission of HIV and other STIs. Studies of spermicides containing nonoxynol-9 (N-9) have produced conflicting results on the ability to prevent STIs other than HIV [57,58]. However, two randomized controlled trials reported an increased risk of HIV acquisition with the use of N-9, possibly due to disruption of the genital epithelium [58].

Other physical barrier methods — Male condoms were superior in the prevention of new STIs compared with other barrier methods in four randomized controlled trials; one study in Kenya and another in Thailand reported very low uptake of the female condom [58].

MALE CIRCUMCISION — Numerous studies suggest a decreased risk of STI acquisition in males who have been circumcised; this is particularly evident for HIV infection [59]. Three randomized controlled trials in Africa demonstrated that circumcision reduces the likelihood of female-to-male HIV transmission by 50 to 60 percent [60].

Nonsurgical circumcision measures appear to be safe and effective but have not yet been studied for their effect on HIV or STI prevention [61].

HIV infection in men — Based on encouraging observational studies, which demonstrated that male circumcision may provide protection against HIV infection, three randomized controlled trials were conducted in Africa. In these trials, men were randomly assigned to an intervention group, in which immediate circumcision was offered, or a control group, in which circumcision was delayed until the end of the study. In all cases, circumcisions were performed by clinicians experienced in the procedure and were rarely associated with moderate or severe adverse effects. These three trials were all ended early because of evidence of reduced HIV incidence in the intervention groups:

- In a trial in Orange Farm, South Africa, circumcision reduced the risk of HIV infection by 60 percent among 3274 men aged 18 to 24 years (20 versus 48 new infections in the circumcision and control groups, respectively, after a mean follow-up of 18 months) [62]. The investigators controlled for behavioral factors, condom use, and health-seeking behaviors.
- In a trial in Kisumu, Kenya, circumcision reduced the risk of HIV infection by 53 percent among 2784 men aged 18 to 24 years (22 versus 47 new infections in the circumcision and control groups, respectively, after a median follow-up of 24 months) [63].
- In a trial in Rakai, Uganda, circumcision reduced the risk of HIV infection by 51 percent among 4996 men aged 15 to 49 years (0.66 versus 1.33 new infections per 100 person years in the circumcision and control groups, respectively, over 24 months) [64]. Following trial closure, the majority of uncircumcised men underwent circumcision. After five years, circumcision remained associated with a lower HIV risk (0.5 versus 1.93 new infections per 100 person years in circumcised and uncircumcised men, respectively) [65].

Population studies in Africa following wider availability and encouragement of voluntary medical male circumcision have also suggested an association between circumcision and reduced incidence of HIV infection and have continued to demonstrate safety of the practice [66,67].

Data from the United States are limited. One study examined visit records of heterosexual African-American men who underwent HIV testing while attending STI clinics in Baltimore from 1993 to 2000 and analyzed the association between circumcision and the risk of HIV infection [68]. "Known" HIV risk was defined as patient notification by either their sexual partner or by an intervention specialist from the partner notification system of

recent HIV exposure. Among 394 visits by patients with known exposure, circumcision was significantly associated with lower HIV prevalence (10.2 percent versus 22 percent; adjusted prevalence rate ratio, 0.49 [95% CI 0.26-0.93]).

These results demonstrate that male circumcision reduces the risk of heterosexual men becoming infected with HIV. The biologic basis for this observation may be related to a high density of HIV target cells in foreskin, including Langerhans cells and macrophages [69]. The potential beneficial effect of male circumcision in MSM has not been studied in countries where the predominant mode of HIV transmission is through male-to-male sexual contact [70].

In light of these data, various professional societies in resource-rich countries have re-examined their guideline recommendations [71]. The WHO has published documents on operational guidance and several countries have integrated this strategy into HIV prevention programs [72].

Any policy to promote circumcision to protect against HIV infection needs to take into account cultural and human rights considerations, the risk of complications from the procedure performed in various settings, the prevalence of infection, and the potential to undermine existing protective behaviors and prevention strategies that reduce the risk of HIV infection [63,73]. Results from observational studies of men who underwent circumcision suggest that this prevention intervention is not necessarily offset by an adverse behavioral impact [74,75]. One study compared sexual behaviors of 324 recently circumcised and 324 uncircumcised Kenyan men at 1, 3, 6, 9, and 12 months after study enrollment [74]. Circumcised men did not engage in more risky behaviors.

HIV infection in women — HIV transmission from men to their sexual partners correlates best with the concentration of HIV in semen [76]; it is feasible that HIV in the foreskin of an infected man could also represent a risk for transmission. However, although male circumcision reduces HIV acquisition in men, studies have not demonstrated a reduction in HIV acquisition among female sexual partners of HIV-infected men who undergo circumcision.

In Uganda, 922 HIV-seropositive men (aged 15 to 49 years) with CD4 cell counts ≥350 cells were randomly assigned to immediate (n = 474) versus delayed circumcision for 24 months (control arm; n = 448) [77]. HIV-seronegative female partners of the men were concurrently enrolled and followed for onset of HIV acquisition at 6, 12, and 24 months by male treatment assignment.

Circumcision did not reduce HIV transmission to female partners; over a 24-month period, the cumulative probability of female acquisition of HIV was 22 percent in the intervention group and 13 percent in the control group (adjusted HR 1.49; 0.52-3.57). In addition, excess HIV transmission occurred within the first six months in the male circumcision arm, particularly among those who resumed intercourse prior to wound healing. These findings suggest sexual abstinence or condom use should be strongly advised until surgical recovery (estimated at six weeks).

The Ugandan male circumcision study also evaluated the effect of male circumcision on STIs in female partners of circumcised men and those randomized to no intervention [78]. At one year, female partners assigned to the circumcision intervention group reported lower rates of genital ulcers and reduced risk of trichomonas and bacterial vaginosis.

HIV infection in MSM — To date, no randomized controlled studies of male circumcision have been conducted among men who have sex with men.

A meta-analysis was performed of 15 observational studies among 53,567 MSM (52 percent of whom were circumcised) to determine the strength of the association between circumcision and the risk of HIV infection [79]. The odds of being HIV-seropositive were 14 percent lower among circumcised versus uncircumcised MSM, but the difference was not statistically significant.

Other sexually transmitted infections — The effect of male circumcision on acquisition of other STIs, such as

herpes simplex virus, human papillomavirus, and syphilis, has also been examined [64,77,80,81]. Results suggest that male circumcision is associated with a reduced risk of viral STIs including HSV-2 and HPV, but not of gonorrhea or chlamydia. This variation may result from the site of infection since gonorrhea and chlamydia infect the urethra, while viral infections tend to involve the foreskin where dendritic cells play a prominent role.

The relationship between circumcision and chancroid and lymphogranuloma venereum (LGV) is unclear, but the best available data suggest a protective effect on chancroid [82] and possibly LGV [83,84]. A randomized trial in Kenya reported genital ulcer disease incidence was halved among circumcised men (RR 0.52, 95% CI 0.37-0.73) [85]. A reduction in any infection associated with genital ulcers is important because the presence of these ulcers facilitates acquisition/transmission of HIV.

There is also evidence that urethral Mycoplasma genitalium infection is less prevalent in circumcised men [86].

Herpes simplex virus — Male circumcision may decrease the risk of transmission of HSV as illustrated by the following:

- In an analysis of two Ugandan trials of circumcision for the prevention of HIV, among the 3393 men who were both HIV and HSV-2 seronegative at baseline, immediate compared with delayed circumcision was associated with a lower risk of HSV-2 seroconversion after 24 months (7.8 versus 10.3 percent probability of seroconversion, respectively; adjusted HR 0.72; 95% CI 0.56-0.92) [81].
- In a trial of 2787 HIV-infected men in Uganda who were randomly assigned to immediate versus delayed circumcision, HSV-2 acquisition after two years was lower in the immediate circumcision arm (7.6 versus 10.1 percent, RR 0.75) [87]. The female partners of the men in the immediate intervention arm also had significantly lower rates of symptomatic GUD, trichomonas and bacterial vaginosis.
- In a study of 3274 males who had been recruited for a circumcision trial, the presence of HSV-2 infection in either partner increased the risk of female-to-male transmission of HIV infection [80]. Conversely, HIV in either partner increased the risk of female-to-male transmission of HSV-2. However, male circumcision was associated with a decreased probability of either event (RR of 0.24, 95% CI 0.11-0.44; and RR of 0.59, 95% CI 0.36-0.91, respectively).

In contrast, in a trial of 2784 men in Kenya, although circumcision reduced the incidence of genital ulcer disease overall, it did not reduce the incidence of HSV-2 infection specifically [85,88]. The reasons for these discrepant results are unclear.

Syphilis — A systematic review and meta-analysis of 26 articles related to genital ulcer disease found that circumcised men are at lower risk of syphilis and chancroid [82]. However, the large prospective trial of male circumcision in Uganda noted above did not demonstrate any difference between the intervention and control arms on the incidence of syphilis, possibly due to low rates of syphilis among the study population [81]. (See 'Herpes simplex virus' above.)

Gonorrhea, chlamydia, and trichomonas — The effect of male circumcision on incident nonulcerative STIs was also examined among 2655 Kenyan males participating in the HIV prevention trial noted above [63]. Circumcision did not reduce risk of gonorrhea, chlamydia, and trichomonas during two years of follow-up [89].

Human papillomavirus — Randomized controlled trials in both HIV-seronegative and HIV-seropositive men have demonstrated that male circumcision reduces acquisition and increases clearance of high-risk HPV types among men who were circumcised compared with no intervention [90-92]. The Rakai circumcision trials for the prevention of HIV infection (discussed above) also demonstrated effectiveness in preventing HPV transmission to female sex partners [93]. At 24 months of follow-up, the incidence of high risk HPV infection in the 1,032 female partners who were enrolled in the circumcision trials was lower in the intervention group than in the control group (21 infections versus 27 infections per 100 person-years; incidence rate ratio = 0.77, 0.63-0.93). Despite these findings, these studies did not address whether circumcision prevents HPV acquisition or decreases the duration of HPV infection or shedding [71,81].

ANTIMICROBIAL-BASED PREVENTION STRATEGIES

Post-exposure prophylaxis for victims of sexual assault — The CDC and others recommend empiric antibiotic prophylaxis since many assault victims will not return for a follow-up visit, and treatment based upon culture results is therefore problematic. In addition, patients often prefer immediate treatment.

Empiric therapy for gonorrhea and chlamydia includes ceftriaxone 250 mg IM and either azithromycin 1 gram PO (single dose) or doxycycline 100 mg PO twice daily for seven days. Metronidazole 2 grams PO (single dose) is also recommended to treat trichomoniasis. (See "Evaluation and management of adult sexual assault victims" and "Patient information: Care after sexual assault (Beyond the Basics)".)

Antiretroviral prophylaxis against HIV

Post-exposure prophylaxis — Although data are limited, observational studies have suggested a possible benefit of antiretroviral prophylaxis in reducing the risk of HIV infection following sexual or other nonoccupational exposure to HIV [94-99]. This topic is discussed in detail elsewhere. (See "Nonoccupational exposure to HIV in adults".)

Pre-exposure prophylaxis — For HIV-uninfected patients who are at high risk for sexually-acquired HIV and are committed to medication adherence and close follow-up, pre-exposure antiretroviral prophylaxis may be an effective strategy for prevention of HIV infection. This issue is discussed in detail elsewhere. (See "Pre-exposure prophylaxis against HIV infection".)

Suppressive therapy for HSV — Suppressive therapy for HSV has been evaluated for both prevention of HSV transmission and HIV infection.

Prevention of HSV transmission — Suppressive therapy with valacyclovir (500 mg once daily) for genital HSV is effective in decreasing the risk of transmission of HSV to an uninfected sex partner. This is discussed in detail elsewhere. (See "Treatment of genital herpes simplex virus infection", section on 'Chronic suppressive therapy for discordant couples'.)

Prevention of HIV infection — Epidemiologic and biologic studies have suggested that genital HSV infection facilitates transmission and acquisition of HIV. However, antiviral suppression of HSV does not reduce the risk of HIV transmission from a HIV/HSV co-infected individual nor does it reduce the risk of HIV acquisition in a HSV-infected individual. This is discussed in more detail elsewhere. (See "Effect of herpes simplex virus on HIV infection: Implications for HIV prevention".)

Topical microbicides — Topical microbicides have been proposed as STI preventive agents by providing chemical, biological, and physical barriers to infection at the mucosal surface (eg, vagina or rectum) [100]. Classes of microbicides include surfactants, membrane disruptors, vaginal milieu protectors, viral entry inhibitors, and reverse transcriptase inhibitors [101]. Delivery systems include gel formulations and vaginal rings, which are engineered for sustained drug release [102].

Clinical trials of microbicides — For approximately two decades, clinical trials of several candidate microbicide agents failed to demonstrate effectiveness in the prevention of HIV transmission [103-105]. One of the largest studies was of PRO2000 vaginal gel, which had been shown to be efficacious in macaques; however, a clinical trial among 5747 sexually active women in Africa did not show a decreased incidence of HIV infection among those who were randomly assigned to the intervention compared with placebo [106].

However, in 2010, a double-blind, randomized controlled trial (CAPRISA 004) demonstrated significant effectiveness of a 1 percent vaginal gel formulation of tenofovir, a nucleotide reverse transcriptase inhibitor (NRTI), for the prevention of HIV acquisition in women [107]. Women assigned to use the tenofovir gel within 12 hours before and after sex had a 39 percent reduction in the risk of HIV acquisition (5.6 versus 9.1 infections per 1000 person years in women assigned to placebo). Additionally, tenofovir gel reduced acquisition of HSV-2, presumably because of antiviral activity achieved with the very high tissue concentrations associated with gel use [108]. Further data on the use of tenofovir vaginal gel for chemoprophylaxis against HIV infection in women

are discussed in detail elsewhere. (See "Pre-exposure prophylaxis against HIV infection", section on 'Vaginal chemoprophylaxis'.)

Clinical trials of microbicides for the prevention of other STIs, including gonorrhea, chlamydia, and syphilis, have not demonstrated substantial efficacy [109].

Effect of seminal plasma on efficacy — Studies of a few microbicidal agents in vitro and in a murine model of herpes simplex virus (HSV) infection suggest that efficacy may also be compromised by exogenous factors [110]. In vitro, seminal plasma competitively inhibited binding of these microbicides to the HSV-2 envelope protein; this observation translated into a loss of protection in the mouse model. These data suggest that seminal plasma may compromise the antiviral effects of microbicides on HSV transmission, and by extension, to HIV transmission as well [111].

The healthy human vagina has an acidic environment, with a pH ranging from 3.5 to 4.5, due to lactic acid and hydrogen peroxide production by lactobacilli. When semen enters the vagina, the pH increases to approximately 7.0 because of the buffering activity of ejaculate. Thus women are exposed to various sexually transmitted pathogens under optimal conditions for transmission.

Other concerns — Corrosive effects on rectal mucosa have also been demonstrated after application of hyperosmolar sexual lubricants [112]. Whether use of such lubricants leads to increased acquisition of HIV is unknown, although plausible.

Barrier methods — An open label, randomized controlled trial of a combined intervention with latex diaphragm, lubricant gel and condoms compared with condoms alone among women in South Africa and Zimbabwe found that diaphragm and lubricant provided no additive effect in preventing HIV infection [113]. In the same trial, reported condom use was statistically lower in the intervention arm compared with the condom only arm (54 versus 85 percent of visits, $p < 0.0001$). The intervention arm also did not have any significant effect on incident chlamydia or gonorrhea infections [114].

COUNSELING AND OTHER PREVENTION MODALITIES

Risk reduction counseling — Counseling on behavioral modification to reduce the risk of STIs has been a major element of the public health approach to STI control, but its efficacy may depend on how it is performed. Based on the available evidence, the United States Preventive Services Task Force (USPSTF) recommends high-intensity behavioral counseling, characterized by multiple sessions over several hours, often offered among groups, to prevent STIs for all sexually active adolescents and for adults at increased risk for STIs [115]. If high-intensity behavioral counseling interventions are not available in the surrounding health sector or community, longitudinal one-on-one education may be beneficial, but the additive benefit of single session individual counselling efforts during STI screening is uncertain.

In a systematic review of trials evaluating the efficacy of a variety of behavioral interventions in mainly high-risk adults, most trials suggested a modest reduction in bacterial STIs among high-risk adults receiving high-intensity counseling programs [116]. Similar findings were observed for sexually-active adolescents. Of note, there were limited data among pregnant women and non-sexually active individuals.

One large trial included in this review demonstrated a 30 percent reduction in STI incidence (HIV, gonorrhoea, chlamydia, and syphilis) at six months with direct counseling compared with non-interactive didactic messaging [117]. Direct counseling included four sessions of 200 minutes cumulative duration (high-intensity) or two 20-minute sessions (moderate-intensity); both strategies included the following components:

- Assessment of actual and self-perceived HIV or STI risks
- Assistance with recognizing barriers to risk reduction
- Negotiation of an acceptable and achievable risk-reduction plan (both short and long term)
- Support of patient-initiated behavior change

Specific high-risk sexual practices that are important to highlight include anal intercourse, multiple sex partners, and concomitant use of alcohol or illicit drugs, which can lead to disinhibition and risky behaviors [118]. Counseling should also encourage abstinence from sexual intercourse until the course of antibiotics for a specific STI has been completed [9].

However, high-intensity counseling is time-consuming and may not be widely available. Although the large trial above suggested that a more moderate-intensity counseling strategy of two 20-minute sessions is still effective, this has not been supported in other studies. In a trial of 5012 individuals presenting to several STI clinics across the United States, there was no difference in cumulative STI incidence (HIV, HSV-2, chlamydia, gonorrhea, trichomoniasis, and syphilis) at six months between those randomly assigned to receive one-time counseling on STI risk reduction (median of 35 minutes total) in addition to rapid HIV testing and those who received only basic information (median of six minutes total) with the rapid HIV test [119]. Among the subset of 1074 men who have sex with men (MSM) included in the study, counseling was actually associated with a higher incidence of STIs. This trial differed from the earlier one mainly in its inclusion of MSM, a higher retention rate at six months, and a single versus two-time counseling session.

Although we continue to believe in the value of risk-reduction counseling in general, these data suggest that efforts to expand screening for STIs, particularly HIV, should not be hampered by a presumed need to offer counseling sessions prior to test administration [120].

Outreach — Outreach approaches to provide testing or preventive services to at-risk individuals are frequently employed to engage populations who may not seek traditional facility-based health services [121,122]. With widespread use of the internet and mobile technology, these have emerged as avenues to reach individuals with preventive services [123]. As an example, increases in syphilis in the United States and Europe have been associated with meeting new and anonymous sex partners on the internet [124-126]. In response to this trend, some public health initiatives have created website-based prevention interventions and online syphilis testing recruitment programs [127,128]. (See "Epidemiology, clinical presentation, and diagnosis of syphilis in the HIV-infected patient".)

Strategies to improve sexual health — Some experts have argued that sexual health interventions in the United States are currently fragmented, leading to poor health outcomes (eg, STIs, teen pregnancy), decreased productivity among young adults, and overall higher health care costs. Some experts have suggested that a unified sexual health strategy should be developed to help decrease stigma, improve the delivery of care, enhance sex education, and ensure access to contraceptives [129].

Anti-poverty measures — Poverty has been shown to contribute to a woman's risk of HIV infection and other STIs [130]. A cluster-randomized trial in young women in Malawi suggests that anti-poverty measures and economic development can be important tools in STI prevention [131,132].

PARTNER NOTIFICATION — Through partner notification, the provider or public health officials learn from the patient about their sex partner or partners and help to arrange for evaluation and treatment [9]. The intensity of this effort varies among agencies and geographic areas. From a public health standpoint, partner notification can potentially decrease the spread of STIs and lower the risk of reinfection of the index patient.

Chlamydia and gonorrhoeae — When medical evaluation cannot be arranged for particular circumstances, another option is patient-delivered partner therapy (PDPT), in which partners of the patient are treated without medical evaluation or prevention counseling. Two randomized controlled trials of PDPT reported a 25 to 62 percent reduction in gonorrhea and/or chlamydia reinfection of the index patient [133,134]; however, other studies have produced variable results [58]. (See "Treatment of uncomplicated gonococcal infections" and "Treatment of Chlamydia trachomatis infection", section on 'Management of sex partners'.)

Syphilis — Sexual transmission of syphilis only occurs when mucocutaneous syphilitic lesions are present. However, persons exposed sexually to a patient who has syphilis in any stage should be evaluated clinically and serologically. (See "Pathogenesis, clinical manifestations, and treatment of early syphilis".)

HIV infection — The Centers for Disease Control and Prevention recommends that public health surveillance programs be actively linked to partner services for all persons who test positive for HIV and early syphilis [6].

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient information: Chlamydia and gonorrhea (The Basics)" and "Patient information: Genital herpes (The Basics)")
- Beyond the Basics topics (see "Patient information: Chlamydia (Beyond the Basics)" and "Patient information: Genital herpes (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS — We agree with the following recommendations of the United States Centers for Disease Control and Prevention as proposed in the 2010 sexually transmitted infection (STI) treatment guidelines [9]:

- Clinicians need to assess sexual risk for all patients during routine clinical visits, particularly in adolescents and men who have sex with men (MSM). (See 'Risk groups' above.)
- All patients being evaluated for STIs should be offered counseling and testing for HIV. (See 'Epidemiology' above.)
- We recommend hepatitis B immunization in susceptible MSM, persons with a history of multiple sex partners, HIV-infected patients, and persons with risk factors for an STI (**Grade 1A**). (See 'Vaccines' above.)
- We recommend hepatitis A immunization in seronegative MSM and in HIV-infected patients with chronic liver disease or risk factors for hepatitis A, including injection drug use (**Grade 1A**). (See 'Vaccines' above.)
- We recommend human papillomavirus (HPV) immunization to decrease the risk of cervical infection and cytologic abnormalities (**Grade 1A**). Immunization should be offered to girls, women, boys, and men 9 to 26 years of age, as recommended by the Advisory Committee on Immunization Practices (see 'Vaccines' above). The use of the vaccine is discussed in detail elsewhere. (See "Recommendations for the use of human papillomavirus vaccines".)
- STI prevention efforts should include the use of barrier methods, including male and female condoms. Use of male condoms has been associated with a decreased risk of transmission of HIV, chlamydia, gonorrhoea, herpes simplex virus, and HPV. (See 'Condom use' above.)
- Male circumcision can reduce HIV transmission, as illustrated by several trials from Africa. It has also been associated with a decreased risk of infection with herpes simplex virus and HPV. (See 'Male circumcision' above.)
- Post-exposure prophylaxis and pre-exposure prophylaxis with antiretroviral agents are possible options for the prevention of HIV infection in high-risk individuals. These are discussed in detail elsewhere. (See "Nonoccupational exposure to HIV in adults" and "Pre-exposure prophylaxis against HIV infection".)
- We recommend suppressive therapy with valacyclovir (500 mg daily) in patients with genital HSV who are

in a monogamous discordant relationship (**Grade 2A**). (See 'Suppressive therapy for HSV' above.)

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