Perspective

Syphilis and Other Sexually Transmitted Diseases in HIV Infection

An ongoing resurgence of syphilis and continued transmission of other common sexually transmitted diseases (STDs) in HIV-infected patients is fueled by a number of factors, including "prevention burnout" resulting from fatigue with long-term, safer-sex behavior, use of recreational drugs (notably methamphetamine), and false sense of security associated with HIV serosorting and elevated CD4+ cell count. Annual screening for common STDs is recommended for HIV-infected patients. Issues in syphilis and herpes simplex virus-2 (HSV-2) diagnosis and treatment are discussed. New problems are briefly reviewed, which include the increased reporting of lymphogranuloma venereum and the increased frequency of fluoroquinolone-resistant gonorrhea. The recently revised Centers for Disease Control and Prevention guidelines for treatment of syphilis, HSV-2 infection, chlamydial infection, and gonorrhea are summarized. This article summarizes a presentation on syphilis and other STDs made by Jeanne Marrazzo, MD, MPH, at an International AIDS Society–USA Continuing Medical Education course in New York, in October 2006. The original presentation is available as a Webcast at www.iasusa.org.

Syphilis and other sexually transmitted diseases (STDs) are resurgent in HIV-infected patients. Factors involved in ongoing STD transmission include: improvements in HIV therapy leading to increased well-being and survival attended by resumption of risky sex behaviors; "prevention fatigue" (ie, burnout over safer-sex practices); increased use of recreational drugs (eg, methamphetamines, poppers, and erectile dysfunction drugs); use of the Internet as a venue to meet sex partners, especially anonymous partners; and what appears to be false assurance afforded by HIV serosorting or elevated CD4+ cell counts. With regard to the latter, for example, a study of 338 men who have sex with men (MSM) in primary HIV care found that those who reported participating in insertive anal sex were 5 times less likely to use condoms when their partners were HIV seropositive than when they were HIV seronegative.

Similarly, those with higher CD4+ cell counts were 20% more likely to have unprotected receptive anal sex than those with lower CD4+ cell counts (Bachmann et al, *Sex Transm Dis*, 2005). For these reasons, annual screening for common STDs is recommended in HIV-infected patients, with more frequent screening being warranted if risk behaviors are reported.

Syphilis

After a 2005 STD update presentation made by Dr Marrazzo in Washington state, a course attendee opined "She spent too much time on syphilis. I'll never see a case." Such a mind-set probably ensures that this will be the case, since the diagnosis can easily be missed if one is not looking to make it.

Reported syphilis cases have increased markedly in MSM in King County, Washington since 1997 (Figure 1; Public Health-Seattle and King County [PHSKC] data, 2004). A similar resurgence is being observed in many metropolitan locales and more rural settings throughout the country. If one is not finding cases of syphilis among HIV-infected patients in metropolitan centers, one may not be looking hard enough. In Dr Marrazzo's venue, more than half of syphilis cases in MSM are in HIV-infected men, with 4% of cases in heterosexual patients occurring in those with HIV infection. The median

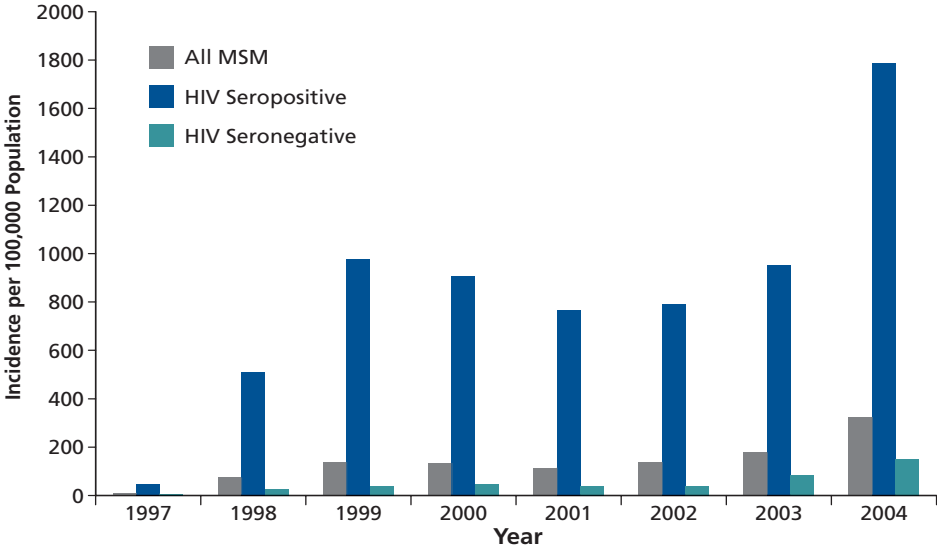

Figure **1**. Early syphilis incidence among men who have sex with men (MSM) by HIV serostatus in King County, Washington from 1997 to 2004. (Public Health-Seattle and King County data, 2004).

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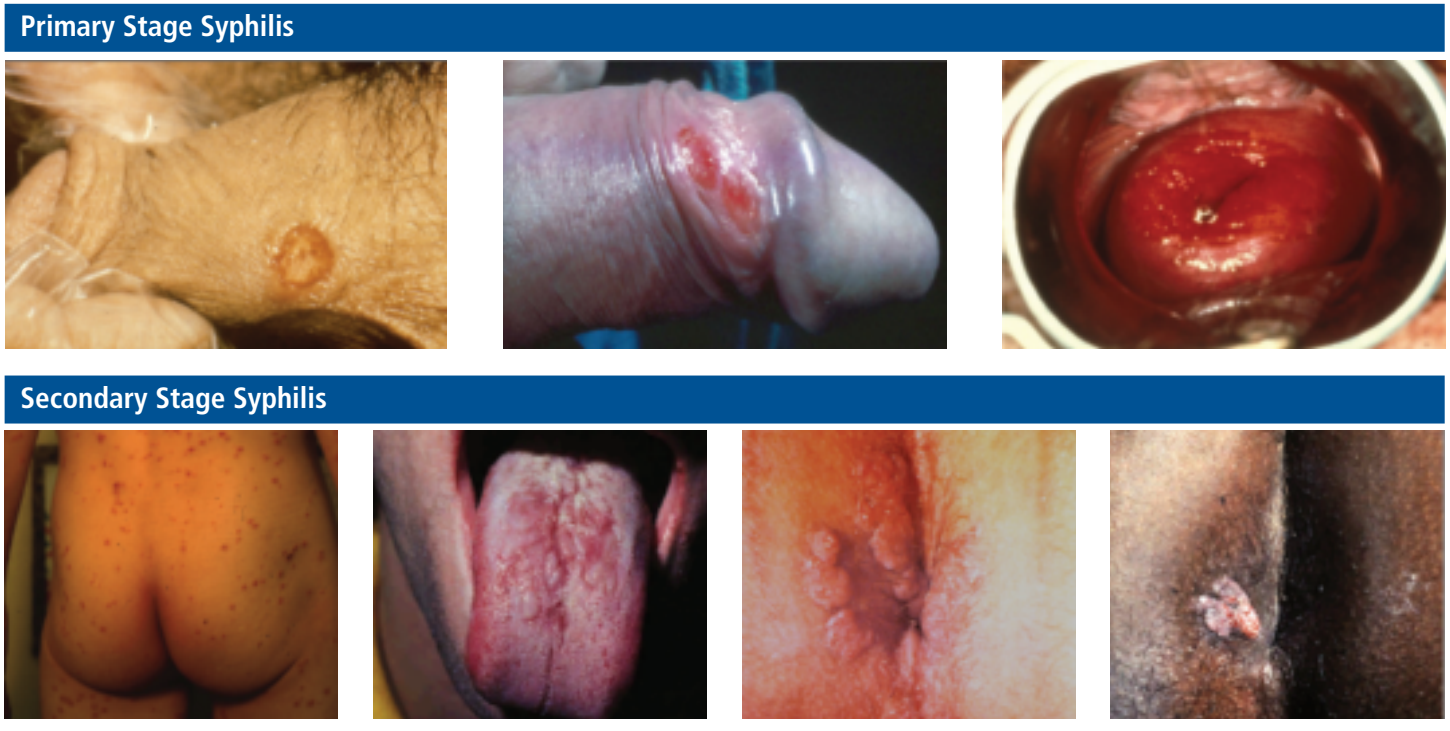

Figure **2**. Top: Typical features of primary stage syphilis include a painless, non-tender chancre that is indurated with a heaped-up border and clean (nonpurulent) base. Approximately 70% of primary stage chancres are positive in rapid plasma reagin or Venereal Disease Research Laboratory serology. Bottom: Typical features of secondary stage syphilis can include a maculopapular rash, classically involving the hands or soles of feet; a condyloma lata with fleshly, flat-topped appearance occurring at any moist body site; and oral mucous patches that are often misindentified as aphthous ulcers or other lesions. Reprinted with permission from Seattle STD/HIV Prevention Training Center at the University of Washington.

age of syphilis cases in MSM in Dr Marrazzo's venue is 34 years.

Methamphetamine deserves special mention as a risk factor for STD transmission. Its use is common on the West Coast and in rural areas and it is becoming more common on the East Coast. There are clear epidemiologic links between methamphetamine and the current syphilis outbreak in MSM. The drug, which is very easy to obtain or make (recipes can be found online), reduces social inhibitions, increases libido and prolongs sexual arousal, allows for sustained energy level and lack of sleep, and results in reduced use of barrier protection (Krawczyk et al, *MMWR Recomm Rep*, 2006). It may also exert an independent biologic effect in increasing HIV viral load and may directly suppress CD4+ cell function.

Syphilis is caused by *Treponema pallidum*. Primary syphilis often presents with a chancre, or ulcer, and is usually followed in 3 weeks to 3 months by secondary syphilis, evidenced by a "treponemic event" consisting of rash, fever, and neurologic symptoms. Nephrotic syndrome and even glomerulonephritis may occur in this stage. This is followed by a long latent period (eg, 5-50 years) before onset of tertiary syphilis consisting of neurologic disease, gummas (a necrotic lesion that can occur in bone or brain), and cardiac disease.

The identification and treatment of "early" syphilis (ie, primary, secondary, or latent syphilis) within 1 year of acquisition is crucial since there is low likelihood of transmission thereafter. The chancre of primary syphilis is typically (but not invariably) painless and has a heaped-up border and a nonpurulent base (Figure 2). In some cases, it can be mistaken for a herpes simplex virus (HSV) lesion. It can occur as a vaginal, vulvar, or cervical lesion in women; internal lesions (vaginal, vulvar) are nearly always asymptomatic. Chancres are associated with positive nontreponemal serology (ie, rapid plasma reagin [RPR] or Venereal Disease Research Laboratory [VDRL]) in only approximately 70% of cases. The rash in secondary syphilis (Figure 2) is typically maculopapular and classically involves the hands or soles of the feet. However, the rash can assume almost any form (eg, pustular, vesicular). Other characteristic findings include condyloma lata that may occur at any moist body site and are particularly common in the perianal area. Oral mucous patches are common and often are misidentified as aphthous ulcers or other types of lesions.

Standard serologic tests for syphilis are the RPR and VDRL, which provide quantitative measurement of antigen (cardiolipin–lecithin–cholesterol antigen) that is not specific to *T pallidum*. These tests are also used to assess treatment response, with a 4-fold decline in antigen titer over 6 months being considered evidence of adequate response. The test used in initial diagnosis should also be used for assessing response, since there can be a 2-fold difference in measured antigen titer between the different tests. The treponemal tests, *T pallidum* particle aggluti-

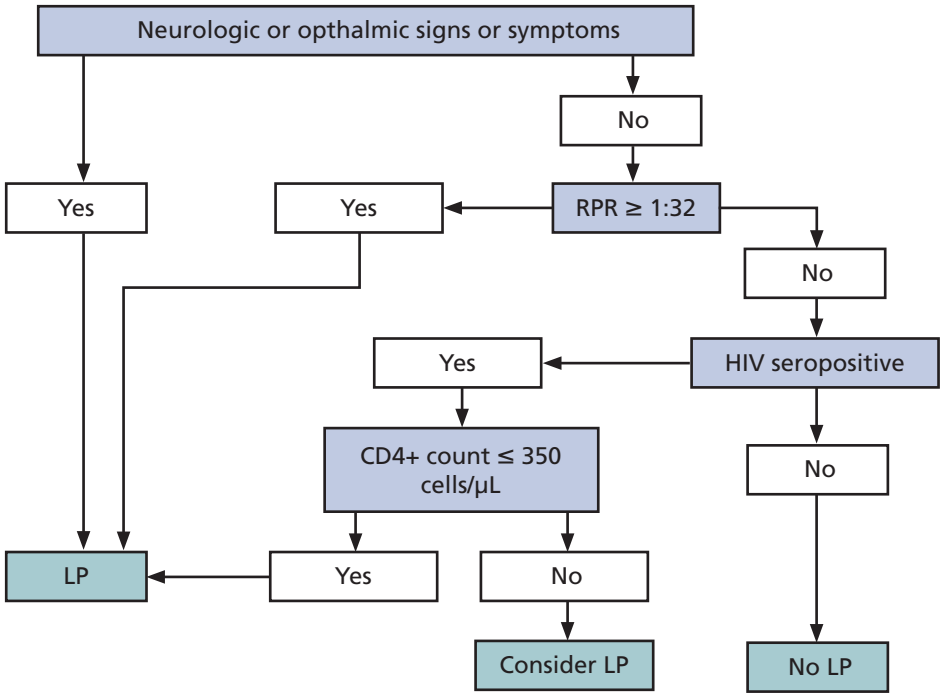

Figure **3**. One approach to decision whether to perform lumbar puncture in patients without neurologic or ophthalmic signs or symptoms of syphilis. Adapted from Marra et al, *J Infect Dis*, 2004.
LP indicates lumbar puncture; RPR, rapid plasma reagin.

nation (TP-PA) and fluorescent treponemal antibody absorption (FTA-ABS), are qualitative tests used to confirm initially positive VDRL or RPR results. A treponemal enzyme immunoassay is another test often used for screening. However, false-positive results can occur with this test, particularly in low-prevalence settings. Positive findings should be confirmed with a standard nontreponemal test titer to guide management. A different treponemal test should be performed if results of this confirmatory nontreponemal test are negative.

Treatment for syphilis in HIV-infected patients consists of standard stage-appropriate treatment (see below). Serologic follow up should be performed at more frequent intervals than in patients without HIV infection, with nontreponemal testing done at 3, 6, 9, 12, 18, and 24 months (compared with 6, 12, and 24 months in patients without HIV infection). Clearance of neurosyphilis is problematic in HIV-infected patients, with poorer response being observed in those with low CD4+ cell counts and those not on antiretroviral therapy.

Risk of neurosyphilis is increased 3- to 4-fold when the CD4+ cell count is below 350/μL and by 19-fold if there is also a finding of serum VDRL titer above 1:32. Currently, there is no consensus on the use of lumbar puncture (LP) to guide management. Some practitioners recommend LP for all HIV-infected patients with syphilis, regardless of disease stage. A more conservative approach is to perform LP in any patient with neurologic or ophthalmic signs or symptoms, and to base the decision in other patients on CD4+ cell count and syphilis titer (Figure 3; Marra et al, *J Infect Dis*, 2004).

Neurologic findings may include hearing loss or any other cranial neuropathy; ophthalmic findings can include uveitis or retinitis. Abnormality of any cerebrospinal fluid (CSF) parameter should be considered evidence of central nervous system (CNS) involvement in the setting of positive serology, consistent exam findings, or known exposure. Such abnormalities include elevated white blood cell (WBC) count (usually lymphocytes; a 5-fold or higher elevation is typical, although some authors have used an increase of 20-fold or higher to account for HIV-related pleiocytosis), elevated protein level, positive CSF VDRL (CSF VDRL has a false-negative rate of 30%-70%), and positive FTA-ABS or TP-PA (the latter 2 tests are very sensitive, but not specific when applied to CSF; this means they are helpful if they are negative).

All individuals who have had sexual exposure to a patient with syphilis within the past 90 days should have treatment. The Centers for Disease Control and Prevention (CDC) have recently issued revised recommendations for STD treatment. Those for syphilis are shown in Table 1. Benzathine penicillin (L-A, or long-acting) which contains 2.4 million units (MU) of benzathine penicillin G, is recommended for primary, secondary, or early latent syphilis. No other penicillin formulation should be used, including penicillin G benzathine, a mixture of 1.2 MU benzathine penicillin G and 1.2 million MU procaine penicillin G (which has been mistakenly used).

There has been some use of more than one injection of benzathine penicillin in HIV-infected patients in this setting, but there is no evidence to support any better outcomes using this approach. Further, benzathine penicillin is in short supply, and it is probably better to preserve additional doses for use in treating late latent infection. Use of azithromycin results in development of rapid resistance to the drug. For those who cannot tolerate penicillin or have a history of anaphylaxis, oral doxycycline can be used, although it is probably an inferior regimen.

A newer option for early syphilis is ceftriaxone 1g given intravenously or intramuscularly daily for 8 to 10 days. Parenteral penicillin G is used for neurosyphilis, with ceftriaxone 2g per day being an option in those who cannot tolerate penicillin. Desensitization can be considered in patients who are allergic to both penicillin and cephalosporins.

Herpes Simplex Virus-2

Genital infection with herpes simplex virus-2 (HSV-2) is a largely hidden epidemic. Approximately 20% of the adult US population is seropositive for

Table 1. Centers for Disease Control and Prevention Guidelines for Treatment of Syphilis

Primary, Secondary, and Early Latent

- Benzathine penicillin (L-A) single dose IM 2.4 MU
  - Do not use other penicillin formulations
  - Do not use azithromycin
- Doxycycline 100 mg po bid × 14 d (inferior)
- Ceftriaxone 1 g IV or IM daily × 8-10 d (alternative)

Late Latent

- Benzathine penicillin IM 2.4 MU weekly × 3 doses (7.2 MU total)
- Doxycycline 100 mg po bid × 28 d (inferior)

Neurosyphilis

- Aqueous penicillin G 18-24 MU/d × 10-14 d
- Procaine penicillin G 2.4 MU/d PLUS probenecid 500 mg po qid × 10-14 d
- Ceftriaxone 2 g IV daily × 10-14 d (alternative)

Adapted from Centers for Disease Control and Prevention, *MMWR Morb Mortal Wkly Rep*, 2006.
IM indicates intramuscularly; IV, intravenously.

HSV-2, but only 9.2% of seropositive individuals actually recognize a history of infection. Genital infection with herpes simplex virus-1 (HSV-1) also occurs, and appears to be increasing in prevalence in association with young people beginning to have oral sex at earlier ages. HSV-1 genital infection does not recur as frequently as HSV-2 and does not exhibit the persistent subclinical shedding virus over years that occurs with HSV-2.

The risk of HIV transmission to a vulnerable partner increases when the source (HIV-infected partner) is HSV-2 seropositive, even when analyses control for the source partner's plasma HIV RNA level. HSV-2 may increase susceptibility to HIV via disruption of normal barriers (eg, skin ulceration) and recruitment of target CD4+ cells to the site of viral activity, and directly promote replication of HIV. HSV-2 may increase infectiousness of HIV by increasing HIV shedding at the mucosal surface, irrespective of whether lesions are present, and via the increased recurrences and severity of recurrences of HSV-2 that occur with coinfection.

HSV-2 testing requires use of type-specific HSV-2 gG-based serology that accurately distinguishes HSV-2 from HSV-1 infection. Several type-specific kits are commercially available, with some variation in reported sensitivity, specificity, and cost. The Western blot assay is considered the gold standard but is not commercially available, is relatively expensive and is less specific and sensitive than some kit assays. Although the recently published CDC guidelines do not recommend universal screening for HSV-2, they recommend testing in all HIV-infected individuals, MSM, and individuals with multiple sex partners, as well as in individuals with recurrent symptoms and negative culture, those with clinical diagnosis without laboratory confirmation, those with sex partners who have genital herpes and who want to know their own infection status, and those who request testing.

Recommended treatment of first episodes and recurrences and recommended suppressive therapy in HIV-infected persons are shown in Table 2. One change in recommendations in the recent guidelines is the omission of the 5-times daily acyclovir regimen from the options for treating recurrence, simply because of its lack of convenience. The new guidelines add the possibility of using valacyclovir therapy (500 mg orally once daily) to prevent transmission of HSV-2 to uninfected partners. Indications may include serodiscordant couples (evidence of benefit is available only for serodiscordant heterosexual couples thus far), persons with numerous sex partners, MSM, and HIV-infected individuals. Annual assessment of the discordant partner for seroconversion is recommended if this strategy is used.

Proctocolitis: Lymphogranuloma Venereum

In a recent case, a 34-year-old man with HIV infection and CD4+ cell count of 200/μL presented with rectal discharge, bleeding, and pain that had begun 2 months before presentation. Colonoscopy showed rectal ulcers with inflammation, friable mucosa, and no abscess. He had been treated for chlamydial infection, gonorrhea, and syphilis. The symptoms had recurred recently, with severe pelvic pain radiating to his back. Diagnostic tests for *Chlamydia trachomatis* from the rectal mucosa were obtained and the patient was started on oral doxycycline. The patient was found to have lymphogranuloma venereum (LGV), which is caused by LGV strains of *C trachomatis*. LGV is endemic in Southeast Asia, South America, the Caribbean, and Africa.

The classic presentation involves inguinal lymphadenopathy and genital ulcers. Cases of LGV-related proctitis

Table 2. Centers for Disease Control and Prevention Guidelines for Treating Genital Herpes Simplex Virus-2 Infection in HIV-infected Patients

First Episode (Same as in HIV-seronegative Patients)

Acyclovir 400 mg tid × 7-10 d
Acyclovir 200 mg 5x/d × 7-10 d
Famciclovir 250 mg tid × 7-10 d
Valacyclovir 1 g bid × 7-10 d

Episodic Treatment of Recurrences

Acyclovir 400 mg tid × 5-10 d
Famciclovir 500 mg bid × 5-10 d
Valacyclovir 1 g bid × 5-10 d

Suppressive Treatment

Acyclovir 400-800 mg bid or tid
Famciclovir 500 mg bid
Valacyclovir 500 mg bid

Adapted from Centers for Disease Control and Prevention, *MMWR Morb Mortal Wkly Rep*, 2006.

Table **3**. Centers for Disease Control and Prevention Guidelines for Treatment of Chlamydial Infection

General

Recommended
- Azithromycin 1 g po, single dose, directly observed
- Doxycycline 100 mg po bid × 7 d

Alternative
- Ofloxacin 300 mg po bid or levofloxacin 500 mg qd × 7 d
- Erythromycin 500 mg po qid × 7 d

In Pregnancy

Recommended
- Azithromycin 1 g po × 1
- Amoxicillin 500 mg po tid × 7 d

Alternative
- Erythromycin base 500 mg po qid × 7 d
- Erythromycin base 250 mg po qid × 14 d
- Erythromycin ethylsuccinate 800 mg po qid × 7 d
- Erythromycin ethylsuccinate 400 mg po qid × 14 d

Adapted from Centers for Disease Control and Prevention, *MMWR Morb Mortal Wkly Rep*, 2006.

have been seen in the United States, usually involving HIV-infected individuals or MSM and usually involving the L2 LGV serovar. The cases typically have involved delayed diagnosis.

Proctocolitis can be caused by chlamydial infection, HSV infection (typically HSV-2), gonorrhea, syphilis, and occasionally enteric pathogens (more common when upper colon symptoms are present). Nucleic acid amplification tests have not been cleared by the US Food and Drug Administration (FDA) for use with rectal specimens, but they can be used in diagnosis if they are validated by a local laboratory. Cell culture also can be used if available.

Specific diagnosis of LGV is difficult. Identification of LGV serovars requires serotyping of isolates obtained by direct culture of the rectal mucosa, or nucleic acid amplification test genotyping, and neither is widely available. Serologic tests are recommended but can be done only by specialized reference laboratories (there are approximately 20 such laboratories in the United States). The tests are technically demanding and titers for LGV proctocolitis are not well defined. If LGV is suspected, presumptive treatment should be considered and the local health department contacted. Treatment consists of doxycycline 100 mg twice daily for 21 days, longer than the recommended treatment duration for other chlamydial infections (Table 3).

Gonorrhea

In another recent case, a 28-year-old HIV-infected man presented with purulent urethral discharge. Gram stain revealed Gram-negative intracellular diplococci. He had no known allergies to medications. He reported unprotected receptive oral sex with other men. Management of this case may include presumptive treatment with a single oral dose of cefixime, if available (see Table 4 for other options) and should include empiric treatment for all sex partners within the previous 60 days. Since the finding of chlamydial infection is common when gonorrhea is present (the converse is not true), the patient should also be given a regimen aimed at both gonorrhea and chlamydial infection (eg, addition of azithromycin or doxycycline).

Management in this case should not include presumptive treatment with a single dose of a recommended fluoroquinolone if oral cefixime is not available. Rates of fluoroquinolone resistance in *Neisseria gonorrhoeae* are increasing and are very high among MSM throughout the United States, in general in West Coast states, and in individuals who have acquired a resistant strain of the organism prevalent in Southeast Asia and Hawaii. In the United States, overall rates of resistance are approximately 8% in heterosexual persons and 23% in MSM. Current CDC guidelines thus recommend against using fluoroquinolones for gonorrhea in MSM. For these reasons, a sexual history and travel history should be taken before prescribing a fluoroquinolone for gonorrhea. Current general recommendations for gonorrhea treatment are shown in Table 4. It should be noted that a CDC recommendation against using quinolones for *any* gonorrhea is expected.

A Piercing Observation

A 20-year-old woman presented to the emergency department anxious because her partner's "Prince Albert" penile piercing was noted to be missing soon after vaginal intercourse (Das et al, *Obstet Gynecol*, 2005). Exams were

Table **4**. Centers for Disease Control and Prevention Guidelines for Treatment of Gonorrhea*

Recommended
- Cefixime 400 mg po x 1
  - Currently available only as a suspension formulation
- Ceftriaxone 125 mg IM x 1
- †Ciprofloxacin 500 mg po x 1
- †Ofloxacin 400 mg po x 1
- †Levofloxacin 250 mg po x 1

Alternative
- Cefpodoxime 400 mg po x 1
- Cefuroxime 1 g po x 1
- Spectinomycin 2 g IM x 1
- Single-dose injectable cephalosporin regimens
- †Single-dose oral quinolone regimens

*All patients with gonorrhea should also be treated for chlamydial infection, unless chlamydial infection is ruled out with highly sensitive testing (eg, nucleic acid amplification test).

†Fluoroquinolones should not be prescribed for men who have sex with men or patients with infection in or from California, Hawaii, or abroad. Adapted from Centers for Disease Control and Prevention, *MMWR Morb Mortal Wkly Rep*, 2006. IM indicates intramuscularly.

unremarkable. However, pelvic film revealed a small discoid shape, consistent with the metal bearing used to fasten the penile ring, in the lower abdomen-upper pelvic region, suggesting the object had migrated through the cervix and uterus into the fallopian tubes. The patient had been prepared for diagnostic laparoscopy when an astute physician obtained a complete sexual history, finding that the patient had performed oral sex on her partner prior to vaginal intercourse. Laparoscopy was postponed, and the follow-up pelvic film 1 week later was normal.

A thorough sexual history is invaluable to accurate diagnosis and management.

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Suggested Readings

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