Slowing resurgent syphilis and chlamydia in people with HIV

by Mark Mascolini

Tighter screening and follow-up: keys to better syphilis care with HIV

INTERVIEW WITH:
Khalil G. Ghanem, MD, PhD
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RITA! reports on issues in HIV/AIDS research and policy, and is intended for the HIV research, medical, and professional communities. The statements and opinions expressed herein do not imply recommendations or endorsement. Always consult your doctor before taking any drug or altering a prescribed drug regimen.

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Dear reader,

We were so close.

In 1945, the last year of World War II, syphilis prevalence in the United States topped out at 600,000 cases. By 2000, the number of cases had dropped more than 99%, to fewer than 6,000. The reduction in syphilis was so dramatic that the Centers for Disease Control (CDC) had actually launched a national plan to eliminate it. A disease that could trace its modern history to the French occupation of Italy in 1495 might finally be knocked out.

But just as the CDC was announcing its plan, syphilis began surging among men who have sex with men (MSM). In San Francisco, for example, the number of cases jumped from a barely detectable 44 in 1999 to 522 by 2002. By 2005, syphilis prevalence in the United States had jumped to 8,724 cases, more than 80% of which were in gay and bisexual men.

Today, the spread of syphilis among MSM, including those with HIV infection, is a topic of a conversation – and concern – among primary care providers and infectious disease specialists throughout the country. As Khalil Ghanem, MD, PhD, of Johns Hopkins University School of Medicine puts it, “... syphilis is a huge problem, particularly among MSM with or without HIV” (p. 29).

In this issue of RITA!, editor Mark Mascolini gives particular attention to slowing the resurgence of syphilis among people with HIV, including women and heterosexual males. He also looks at ways to prevent and control chlamydia, an often “silent” infection that significantly increases the risk of acquiring, or transmitting, HIV.

This RITA! also marks the first issue since The Center for AIDS (The CFA), RITA!’s publisher, merged with Legacy Community Health Services. The merger allows The CFA to expand its programs, reach a larger number of clients, and reduce costs, while adding value to Legacy’s services. Both organizations have a long history of serving people with HIV. The merger of the two helps to keep the treatment and research needs of people living with the virus in focus as the healthcare system undergoes substantial changes.

Until there’s a cure,

Katy Caldwell
Executive Director
Legacy Community Health Services

Paul Simmons
Former Executive Director
The Center for AIDS
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Abstract: After reaching historically low levels in the 1990s, syphilis prevalence began to climb in the United States, Western Europe and elsewhere, largely because of a surge in new infections among men who have sex with men (MSM). In the United States, a large proportion of people with newly diagnosed syphilis also have HIV infection. Like other sexually transmitted infections, syphilis can heighten the risk of HIV transmission. Because signs and symptoms of primary and secondary syphilis may be innocuous or hidden, experts advise routine syphilis screening in sexually active HIV-positive people. HIV infection complicates the course of syphilis and can lower rates of serologic response to syphilis therapy. Some evidence indicates that antiretroviral therapy lowers the risk of neurosyphilis and is associated with a better response to syphilis therapy. CDC treatment advice for syphilis does not differ for HIV-positive people and the general population, although some authorities believe people with HIV may need more intense therapy. Notifying sex partners of people with recently diagnosed syphilis—and perhaps presumptive treatment of sex partners—may slow the spread of syphilis.

They had syphilis, or the Neapolitan disease, or—from the Neapolitan point of view—the French disease. And while the French occupation of Naples in 1495 barely earns a footnote in geopolitical history, it marks day 1 of the European syphilis epidemic that claimed Schubert, Napoleon, Nietzsche, and countless less celebrated victims before penicillin offered a cure.

Thanks to Charles's transalpine excursions, syphilis ranks as one of the oldest recognized sexually transmitted infections (STIs). Whether Columbus brought it back from San Salvador, as some speculate, or whether it reached Naples by land, remains unknown. But epidemics of the Great Pox (so called to distinguish it from smallpox) soon flared in China, Japan, and India.

Within 50 years of the Neapolitan outbreak, Verona's Girolamo Fracastoro, a physician, geographer, and mathematician, published the epic poem “Syphilis sive morbus gallicus” (“Syphilis or the French disease,” a title suggesting where Fracastoro’s epidemiologic sympathies lay). The poem featured a hapless shepherd named Syphilus who ran afoul of Haiti’s sun god and got cursed with “disfiguring sores.” Sixteen years after penning this edifying epic, Fracastoro advanced the spore theory of epidemic disease, arguing that these vaguely defined entities can transmit infection through direct or indirect contact.

France’s Charles VIII, called “the Affable,” didn’t win many Italian friends when he invaded the peninsula with 25,000 men, eyeing Naples as his prize and subduing Florence along the way. And his troops probably found Charles less than likable when they left Naples with genital or oral sores and, soon enough, rash on the hands and feet.
Because no one knew what caused syphilis—much less how to treat it—this three-stage pox spread unabated for centuries. And it spread with great efficiency. Fracastoro’s 20th century scions figure that half of sex partners whose bedmate has primary or secondary syphilis get the disease. You don’t have to pull down your partner’s pants, either: *Treponema pallidum* jumps from oral chancres to oral abrasions with acrobatic ease. Among men who have sex with men (MSM), who spearhead today’s syphilis resurgence, researchers estimate that 20% in Chicago, 25% in Sydney, 37% in Brighton, and 46% in Northern Ireland owe their infection to oral sex.

The 21st century syphilis epidemic has its center among gay and bisexual men with and without HIV, though heterosexual men and women play their part. In the United States, for example, 36% of reported primary and secondary syphilis cases in 2006 involved women or heterosexual men, and new cases of congenital syphilis—a legacy of *T. pallidum*-positive mothers—inched up from 339 in 2005 to 349 in 2006. But syphilis incidence has climbed most steeply among MSM in North America and Europe, surely in part because of relaxed sexual prudence following the success of combination antiretroviral therapy in the mid-1990s. And the easy oral transmissibility of *T. pallidum* means even men who practice “safer sex” (from an HIV perspective) are not so safe (from a syphilis perspective). Because primary and secondary syphilis can run their course unnoticed, the risk of latent and deadly tertiary syphilis cannot be ignored.

This article analyzes recrudescent syphilis prevalence and incidence in the late 20th and early 21st century, the impact of syphilis on HIV and vice versa, and HIV-specific testing, diagnosis, treatment, and prevention. A companion article in this issue of RITA! takes the same approach with an even more prevalent bacterial pathogen in people with HIV, *Chlamydia trachomatis*.

### An epidemic ends—then resumes

Syphilis prevalence in the United States peaked at around 600,000 cases in the last year of World War II, 40 years after German scientists discovered that the spirochete now called *T. pallidum* causes syphilis and 2 years after research showed that penicillin cures it. By 1953 Eisenhower administration seers proposed mothballing the Public Health Service venereal disease program because its work was done. Primary and secondary syphilis cases in the United States hit a low of 5976 at the turn of the millennium, the nadir since reporting began in 1941.

Then everything changed.

From 1999 through 2005, California endured over a 700% jump in primary and secondary syphilis cases, 80% of them in MSM. Across the country, prevalence climbed from the 5976 low in 2000 to 8724 in 2005, with more than 80% in gay and bisexual men. Over the past decade syphilis prevalence rose among MSM in Chicago, Seattle, San Francisco, Southern California, Miami, and New York City, and 20% to 70% of men with syphilis had HIV. By 2006 the South accounted for 47.1% of primary and secondary syphilis cases. From 2005 to 2006, rates of primary and secondary syphilis rose 15.2% in the West, 13.2% in the South, and 13.0% in the Northeast, while staying flat in the Midwest.

In 1995 all European Union countries except Germany reported fewer than 300 syphilis cases; after 1996 Austria, Belgium, Denmark, France, Germany, Ireland, the Netherlands, the UK, Can-
ada, Australia, and New Zealand all reported big jumps—and most new cases involved MSM.¹ Across the world, researchers estimate that 50% to 60% of MSM with early syphilis have HIV.¹⁵

What accounts for the resurgent syphilis epidemic among gay and bisexual men? Research summarized below (see “Syphilis risk factors in gay and bisexual men,”) identifies specific risk factors for syphilis in MSM, which researchers group into a few broad categories (Table 1).¹¹²

Besides prompting gay men and others to abandon safer sex, the advent of potent antiretroviral medleys may have helped spark today’s syphilis epidemic by damping the AIDS death rate, the Centers for Disease Control and Prevention (CDC) suggests.¹⁶ Before the era of combination antiretroviral therapy, syphilis rates were probably lower in HIV-positive people because they died of other causes before syphilis could be diagnosed—or before they could get syphilis. So prolonged survival thanks to triple therapy could contribute to the surge in syphilis diagnoses over the past 15 years.

Modeling studies suggest that an interaction between T pallidum and natural immunity may cause cycles in epidemic syphilis, but some analysts are skeptical.¹¹⁷ In fact, analyzing longitudinal CDC data in 2008, some experts proposed “it is quite possible that the CDC could be successful in eliminating syphilis within the next few decades.”¹¹⁷ But research reviewed in this article suggests eliminating syphilis will require—for starters—a tectonic shift in sexual behavior among MSM.

Syphilis prevalence and incidence climbing

CDC officials chose 1999 to launch their National Plan to Eliminate Syphilis. The timing could not have been better—or worse. The timing looked good, the CDC explained, because efforts could “capitalize on a decade of declining rates of syphilis” with a strategy focused on groups that seemed most affected at that point—“heterosexual minority populations, particularly African Americans.”¹⁸ And between the 1999 launch date and 2004, progress looked promising: primary and secondary syphilis rates among blacks plunged 37%, from 14.3 to 9.0 cases per 100,000 people, and the black-to-white syphilis rate ratio shrunk from 28.6-to-1 to 5.6-to-1.

But the time could not have been worse for a reason few, if any, divined in 1999—the surge in syphilis incidence among gay and bisexual men. In the summer of 1999—just as the CDC rolled out its elimina-

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**Table 1. Factors that may contribute to resurgent syphilis among MSM¹¹²**

- Sexual disinhibition following success of combination antiretroviral therapy
- Perception that oral sex is safe
- Use of illicit drugs (such as crystal meth) and prescribed drugs (such as sildenafil)
- Increased serosorting (limiting sex to partners with the same HIV status, but disregarding other STIs)
- Growing use of Internet to meet partners
- Increased global travel and migration
- Underinvestment in public health

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tion plan—San Francisco saw a spike in early syphilis among MSM who corralled sex mates on the Internet (Figure 1). Over the next 4 years, syphilis incidence in San Francisco ballooned from 44 to 522 cases a year. The CDC revised its National Plan to Eliminate Syphilis in 2006.

![Spiking early syphilis* in San Francisco](image)

**Figure 1.** Just as the CDC launched a 1999 campaign to eradicate syphilis in the United States by focusing on heterosexual African Americans, incidence of this easily transmitted STI surged among San Francisco MSM prowling the Internet to meet sex partners. (Graph from *MMWR.*

By 2002 San Francisco earned the kind of first-place accolade cities hope to avoid—most cases of primary and secondary syphilis in any US metropolis. MSM accounted for 22% of early syphilis cases in 1998 and 88% in 2002. Among 151 MSM with early syphilis, 67 (44%) said they met sex partners online. Analysis of early-syphilis risk factors in this outbreak determined that having recent Internet partners independently doubled the odds of syphilis (odds ratio [OR] 2.1, 95% confidence interval [CI] 1.0 to 4.3). Having HIV infection quadrupled the odds of syphilis (OR 3.9, 95% CI 2.0 to 7.7). The CDC cautioned that Internet access makes it much easier to meet sex partners when traveling, a development that could contribute to the US and pan-European spread of syphilis. But San Francisco public health authorities turned this new partnering tool to their advantage, using e-mail addresses collected by men with early syphilis to alert recent sex mates.

A 27-state CDC analysis of primary and secondary syphilis reported from 2005 through 2008 figured that absolute increases in syphilis prevalence were 8 times higher in black MSM and 2.4 times higher in Hispanic MSM than in white MSM. The biggest prevalence jumps in this survey involved MSM from 20 to 29 years old, whereas US studies in the early 2000s found most syphilis cases in men in their 30s.

A CDC study of 73 US metropolitan areas with a population over 500,000 and at least 500 black men between the ages of 13 to 24 cataloged big jumps in new HIV and syphilis diagnoses over the 2004-2008 study period. Compared with 2004-2005, HIV diagnoses among young black MSM rose in 62 areas (85%) and new primary or secondary syphilis diagnoses in these men jumped in 51 areas (70%). Average HIV inci-
dence among young black MSM rose 68.7% over the study period, while syphilis incidence vaulted 203.5%.

A 2011 systematic review of STI coinfections in people already positive for HIV focused on 37 studies reported since 2000 from Africa, Asia, Europe, and North and South America. Trichomoniasis proved the most prevalent STI at 18.5%, with syphilis and gonorrhea tied for second at 9.5%. Coinfection occurred most often in people with newly diagnosed HIV.

A German study of 1052 MSM newly infected with HIV from 1996 through 2007 logged an overall syphilis prevalence of 26%. Syphilis prevalence in these members of the German HIV-1 Seroconverter Cohort surged from 10% in 1996-1999 to 35% in 2005. Syphilis prevalence at HIV diagnosis rose from 2.3% in 2000 to 16.9% in 2003 (P < 0.001), then fell back to 4.3% in 2007.

Although MSM account for most newly recorded syphilis cases in developed countries, syphilis remains a palpable threat to women, especially those with HIV. A 1999-2005 European Collaborative Study of HIV-positive pregnant women showed that syphilis prevalence was lower in European women than in MSM, but syphilis was the most common bacterial STI among women, affecting 2% of these 530 Western European women and 520 Ukrainian women.

In California, the epicenter of the US syphilis epidemic, researchers at Kaiser Permanente Northern California counted 622 new diagnoses of syphilis in 9989 HIV-positive people (6.6%) from 1995 through 2005, compared with 3584 new syphilis cases in 4,442,780 HIV-negative people (0.08%). Syphilis incidence stood at 62.3 per 1000 person-years in the HIV group versus 0.8 per 1000 person-years in the non-HIV group. Statistical analysis adjusted for age, gender, and HIV status determined that HIV-positive people had an 86 times higher syphilis risk (P < 0.01). In the same analysis, women had a 10% lower syphilis risk than men. In both HIV-positive and HIV-negative people, syphilis incidence waned from 1995 through 2000 but then rose sharply in the HIV group (from 3.1 per 1000 in 2000 to 17.4 per 1000 in 2005). Syphilis incidence did not rise in the HIV-negative group after 2000.

In the United States syphilis incidence dwindled consistently among US women after 1990, but a rebound began in 2004 as syphilis incidence rose from 0.8 per 100,000 women that year to 1.0 per 100,000 in 2006. Among US women the rate of primary and secondary syphilis climbed 11.1% from 2005 to 2006, nearly matching the 11.8% jump among US men in that period.

A 2002 CDC study matching reported cases of syphilis and HIV found that 1718 of 6862 cases of primary or secondary syphilis (25%) affected HIV-positive people. Syphilis incidence—the new diagnosis rate—was 77 times higher in HIV-positive people than in the general population. In 2002 new cases of primary or secondary syphilis occurred in 25 of 100,000 HIV-positive women, 60 of 100,000 HIV-positive men who had sex only with women, and 336 of 100,000 HIV-positive MSM.

In an Amsterdam Cohort Study of 863 gay men averaging 25 years in age, HIV and STI incidence paralleled each other through 1995. At that point—the threshold of the combination antiretroviral era—syphilis incidence rose significantly (from 0 to 1.4 cases per 100 person-years), while HIV incidence stayed flat (1.1 to 1.3 cases per 100 person-years).

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Syphilis risk factors in gay and bisexual men

Studies of MSM in New York City\textsuperscript{30} and San Francisco\textsuperscript{31} found that HIV infection independently raised the risk of syphilis—more than 7 times in New York and almost 4 times in San Francisco (Table 2). All five recent studies on syphilis risk factors in MSM identified some type of risky sex as an independent predictor of syphilis. In New York,\textsuperscript{30} Brighton,\textsuperscript{31} and Sydney,\textsuperscript{32} unprotected anal intercourse made syphilis

<table>
<thead>
<tr>
<th>Author, study year(s)</th>
<th>Site</th>
<th>Number of participants</th>
<th>Type of study</th>
<th>Syphilis risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paz-Bailey,\textsuperscript{30} 2001</td>
<td>New York City</td>
<td>88 cases, 176 controls</td>
<td>Case-control; cases diagnosed with primary or secondary syphilis and had sex with men in previous year; controls matched by age and type of health provider</td>
<td>HIV infection: OR 7.3 \n Income above $30,000/y: OR 2.7 \n Unprotected anal intercourse: OR 2.6 \n On cART: 69% with syphilis vs 44% without \n Undetectable viral load: 58% with syphilis vs 24% without</td>
</tr>
<tr>
<td>Wong,\textsuperscript{21} 2002-2003</td>
<td>San Francisco</td>
<td>1318 MSM</td>
<td>Survey of MSM attending city STD clinic</td>
<td>HIV infection: OR 3.9 \n Nonwhite race: OR 2.1 \n Using meth with Viagra: OR 6.2 \n Using meth without Viagra: OR 3.2 \n Strong gay community tie: OR 2.3 \n Recent Internet sex partners: OR 2.1</td>
</tr>
<tr>
<td>Imrie,\textsuperscript{31} 2002-2004</td>
<td>Brighton, UK</td>
<td>50 cases, 108 controls</td>
<td>Case-control study of MSM; cases with early syphilis, controls without syphilis</td>
<td>10 or more casual and/or anonymous sex partners: OR 2.09 \n 2 to 4 oral sex partners: OR 2.12* \n Any receptive anal intercourse: OR 2.93 \n Any unprotected receptive anal intercourse: OR 2.23</td>
</tr>
<tr>
<td>Jin,\textsuperscript{32} 1998-2007</td>
<td>Sydney</td>
<td>308 MSM with HIV, 1427 MSM without HIV in two community cohorts</td>
<td>Syphilis screening and survey of HIV+ and HIV- MSM</td>
<td>HIV+ MSM: \n Unprotected anal intercourse with HIV+ partner: HR 8.67 \n Unprotected anal intercourse with regular and casual partners: HR 3.71</td>
</tr>
<tr>
<td>Heiligenberg,\textsuperscript{23} 2007-2008</td>
<td>Amsterdam</td>
<td>659 MSM</td>
<td>STI testing and survey of MSM visiting HIV clinic</td>
<td>HIV- MSM: \n Multiple HIV+ partners: HR 9.60 \n Unprotected anal intercourse with HIV+ partner: HR 4.45</td>
</tr>
</tbody>
</table>

\textsuperscript{cART, combination antiretroviral therapy; fisting, anal penetration with hand; meth, methamphetamine; HR, hazard ratio; methamphetamine; OR, odds ratio; Viagra, sildenafil} \n* But having 5 to 9 oral sex partners or 10 or more oral sex partners did not raise the risk of early syphilis compared with controls.
more likely—and in Sydney that finding held true in HIV-positive and negative men.

The Brighton study found that having 2 to 4 oral sex partners doubled the syphilis risk compared with control MSM who did not have syphilis, and the Amsterdam survey determined that oral-anal sex—rimming—hiked the syphilis risk 5 times. A 2000-2002 CDC study in Chicago found that 20% of MSM with primary or secondary syphilis reported oral sex as the only kind of sex they had during the study period.

Having 10 or more casual sex partners doubled the risk of syphilis in Brighton. Finding partners on the Internet made syphilis twice as likely in San Francisco, as did reporting a strong gay community affiliation. Using methamphetamine with or without sildenafil upped the syphilis odds in San Francisco.

The New York City researchers tied antiretroviral therapy to syphilis risk, perhaps because good responses to combination therapy led New York MSM to take more risks during sex. Among HIV-positive men in that study, 69% with syphilis versus 44% without syphilis reported taking antiretrovirals (P = 0.05), and 58% with syphilis versus 24% without syphilis said they had an undetectable viral load (P = 0.02).

All these studies involve men in big cities with lengthy HIV epidemics, so syphilis risk factors may differ in other MSM populations. And none of these studies identified an intuitive risk factor for syphilis: people who get syphilis once run a high risk of getting it again. Christina Marra, who studies syphilis and HIV at the University of Washington, Seattle, told RITA that 123 of 901 people in her syphilis cohort (14%) have come back with recurrent infection from 1 to 5 times. Besides persistence of the same risk behaviors, she believes that evolution of the spirochete puts people at risk of reinfection.

The syphilis reinfection rate is even higher in a Baltimore cohort at Johns Hopkins University. In an interview in this issue of RITA, Khalil Ghanem estimates the overall reinfection rate at 30% in the 3 years of initial syphilis therapy.

### HIV incidence in people with syphilis

Intuition—if not hard numbers—suggests that HIV incidence should jump in tandem with syphilis incidence: Syphilitic chancres offer wide portals for HIV to enter the circulation; CD4-cell homing to inflamed lesions provides a brimming population of HIV-susceptible cells; and syphilis-induced immune activation would ratchet up HIV replication. Also, syphilis boosts HIV load in already infected people, and people with higher viral loads transmit HIV more readily than those with lower loads.

The CDC figures that people with syphilis run a 2 to 5 times greater risk of HIV infection if exposed to HIV when they have syphilis sores. But the CDC stresses that—at least through 2005—data collected in the United States make it impossible to say whether HIV incidence climbs among MSM during syphilis outbreaks in this country. Findings from San Francisco, Los Angeles, and Seattle-Kings County, Washington, uncovered no hint that HIV incidence jumped among MSM getting tested for HIV during syphilis outbreaks. And because most US data on HIV and syphilis incidence come from big cities with large gay populations and established HIV epidemics, those findings cannot explain what’s happening across the country.

Data from other countries are mixed. As already noted, syphilis incidence rose significantly after 1995 among MSM in the Amsterdam Cohort, while HIV incidence stalled. Germany, on the other hand, saw...
a surge in coincident HIV and syphilis from 2000 (2.3% of new HIV diagnoses) to 2003 (16.9%), then a decline (to 4.3%) in 2007.25

CDC researchers tried to pin down HIV incidence in men with primary or secondary syphilis in a 2004-2005 study of 357 men in Atlanta, San Francisco, and Los Angeles.35 Most of these men, 85%, were MSM, and 160 (45%) tested positive for HIV. Of those 160, 8 had recent infection, and 7 of those 8 were MSM. The CDC reckoned that HIV incidence among men with primary or secondary syphilis in these three cities stood at 9.5% per year—and at 10.5% per year in MSM.

Two other US studies suggest frequent HIV transmission just before, just after, or during a period of syphilis acquisition.36,37 Those findings, the CDC says, “are consistent with other studies indicating that a substantial proportion of recently and acutely HIV-infected persons have genital ulcer disease or other STDs and can be identified at the STD clinics.”15

But these findings35-37 do not mean HIV incidence billows whenever syphilis incidence climbs. The CDC concluded its 2005 review of HIV incidence in the midst of a syphilis epidemic by cautioning that, “with the limited existing data, we cannot say whether HIV incidence has been increasing among MSM during syphilis outbreaks in the United States.”15 But, the CDC analysts add, “we do know that, to date, syphilis outbreaks have been concentrated among urban MSM, the majority of whom are HIV infected.”15

What happened after 2005? As already noted,22 a 27-state CDC study confirmed an unabated surge in primary and secondary syphilis among MSM through 2008. Compared with white MSM, black MSM had an 8 times higher absolute increase in the rate of primary or secondary syphilis, and Hispanic MSM had a 2.4 times higher rate increase. Men from 20 to 29 years old endured the biggest syphilis hikes in this analysis. The CDC investigators believe their findings “suggest a marked shift in the epidemiology of primary and secondary syphilis in the United States in recent years, specifically with regard to MSM.”22 In the first years of this century, studies disclosed outbreaks of primary and secondary syphilis among MSM in their 30s, but the 2005-to-2008 CDC study found that men under 30—and black and Hispanic men—bore the brunt of new syphilis infections.

These syphilis findings track with the CDC’s most recent HIV incidence report, covering the years 2006 through 2009.58 In the United States overall HIV incidence stayed flat in those years, but incidence soared 34% among young MSM and 48% among young black MSM. Among all 13- to 29-year-olds, only MSM had a significant jump in HIV incidence, and among 13- to 29-year-old MSM, HIV incidence rose most among blacks. Together, these studies22,58 suggest that syphilis and HIV incidence are climbing in tandem—and climbing fastest in young, black MSM.

How syphilis starts, and how to spot it

Treponema pallidum is a spirochete—a spiral-shaped bacterium that corkscrews its ways through pinpoint spaces between endothelial cells to flood the bloodstream and invade the body.39 (Figure 2). (Borrelia burgdorferi, the Lyme disease provocateur, is the other famous spirochete.) Although an alerted immune system kills billions of treponemes after syphilis infection, enough can survive to kick off primary syphilis (Figure 3).1 T pallidum leaps with dreadful efficiency from someone with primary or secondary syphilis to a sex partner, infecting as many as half of
Figure 2. *Treponema pallidum*, the bacterium that causes syphilis, has a corkscrew shape that it exploits to prize its way between endothelial cells of a newly exposed person. This photomicrograph shows two bacteria magnified 36,000 times. (From the Centers for Disease Control and Prevention Public Health Image Library [PHIL].)

Figure 3. Syphilis proceeds from symptomatic primary and secondary syphilis to the asymptomatic early latent stage and—if left untreated—to the late latent stage and ultimately to potentially debilitating and deadly tertiary syphilis. (Adapted from Ho and Lukehart.39)
partners whose skin abrades an open sore. Transmission risk may be magnified when the infecting partner harbors both *T. pallidum* and HIV, because HIV-positive people tend to have larger, deeper lesions—and more of them.

*T. pallidum* starts replicating right at the infection site, dividing once every 30 to 33 hours and inciting an inflammatory response that yields the painless lesion of primary syphilis 10 to 90 days after exposure. This chancre heals without treatment after another 3 to 6 weeks. But if syphilis is left untreated, secondary syphilis develops, marked by a nonitchy rash on the palms, the soles of the feet, or other areas. Sometimes this rash appears as rough, red, or reddish-brown spots, but it may also mimic rashes seen with other diseases. Fever, swollen lymph glands, sore throat, patchy hair loss, headaches, weight loss, muscle aches, and fatigue all may—or may not—mark secondary syphilis.

If secondary-stage syphilis remains untreated, it proceeds to early and late latent stages with no signs or symptoms and ultimately to the complicated, life-threatening tertiary stage 10 to 20 years after primary and secondary syphilis in 15% of people. Tertiary syphilis may ravage the brain, nerves, eyes, heart, blood vessels, liver, bones, or joints. People with late-stage syphilis may have difficulty coordinating movement, they may become numb or even paralyzed, and they may go blind or endure dementia. They may die.

No one becomes immune to syphilis. Infected people who get cured can get syphilis all over again.

A century ago William Osler called syphilis “the Great Imitator,” and clinical diagnosis has not got much easier in the interim. Many people with syphilis—and their physicians—may miss primary and secondary infection entirely because the lesions are innocuous or hidden (in the anus, rectum, or vagina) and because the rash is faint or looks like any other rash. As a result, authorities recommend regular syphilis screening for people with HIV.

CDC opportunistic infection guidelines call for universal syphilis screening “conducted on the basis of the local area and institutional prevalence of early (primary, secondary, and early latent) infectious syphilis.” But those guidelines give little direction to localities and institutions without reliable syphilis numbers, and they offer no specific advice on people with HIV.

For HIV-positive people, the HIV Medicine Association (HIVMA) calls for routine serologic syphilis screening at the first visit then at least annually in sexually active people and every 3 to 6 months in people with (1) multiple partners, (2) a history of unprotected intercourse, (3) a history of sex while using illicit drug use, (4) a methamphetamine habit, or (5) sex partners who participate in such activities. In a 2007 review article on syphilis and HIV, Nicola Zetola (University of California, San Francisco) and Jeffrey Klausner (San Francisco Department of Public Health) also recommend at least yearly syphilis screening for people with HIV and screening 2 to 4 times yearly for high-risk groups “such as MSM.” They call HIV testing “critical for all patients with a new diagnosis of syphilis.”

In an interview in this issue of *RITA!*, Khalil Ghanem (Johns Hopkins University) says he tries to screen high-risk patients—such as those who meet anonymous partners on the Internet—every 3, 2, or even 1 month.

Are most sexually active MSM in the United States getting tested for syphilis every year? No. A CDC study of 10,030 sexually active, HIV-negative MSM
from 2003 through 2005 found that only 39% got an annual syphilis screen.42 Men 18 to 24 years old were twice as likely to get tested annually as men over 44 (OR 2.2, 95% CI 1.8 to 2.5), and men who told their clinician they had sex with men were twice as likely to get tested as men who did not (OR 2.2, 95% CI 2.0 to 2.5). Blacks were 30% more likely to get tested annually than whites (OR 1.3, 95% CI 1.1 to 1.4), as were men with private insurance versus no insurance (OR 1.3 95% CI 1.1 to 1.4).

Can men with HIV be taught to examine themselves for syphilis sores more often? Yes. A study of 689 HIV-positive men attending two big Phoenix-area HIV clinics found that provider counseling consisting of chancre photos, sexual risk assessment, and counseling on the impact of syphilis encouraged men to look for sores more often in oral and rectal areas.43 Self-exam rates rose from 60% to 80% among men with two visits during the study period ($P < 0.01$) and from 58% to 83% among men with three visits ($P < 0.001$).

Can MSM be screened for syphilis outside the clinic? Yes. In Brighton, a British seaside resort with a big gay population, researchers offered syphilis testing to MSM at popular gay hangouts, including bars, clubs, cruising haunts, and a sauna.44 Health workers tested 1090 men in 7 weeks, 64% of whom had 2 or more sex partners in the past 90 days. Syphilis diagnosis rates were similar with a blood test (1.4%) and a saliva test validated by the Health Protection Agency (1.8%). Notably, 62% of these men had not attended an STI clinic in the past year.

HIVMA experts say the standard approach to diagnosing syphilis starts with a nontreponemal test such as rapid plasma reagin (RPR) or the Venereal Disease Research Laboratory (VDRL) test.41 If this initial test proves reactive, it should be followed by a treponemal test such as FTA-ABS, MHA-TP, or TPPA. Zetola and Klausner agree these serologic tests can diagnose syphilis in most people with HIV.12 When this standard approach cannot confirm the diagnosis, they advise clinicians to consider direct testing methods such as dark-field microscopy, direct fluorescent antibody-treponema pallidum (DFA-TP), and PCR. They note that a multiplex PCR has sensitivities of 100% for herpes simplex, 98% for Haemophilus ducreyi, and 91% Treponema pallidum.

The CDC’s Kevin Fenton and colleagues suggest another approach, noting that the treponemal enzyme immunoassay is “increasingly used as the initial screening test” because of its high specificity, sensitivity, and suitability for automation.1 If the enzyme immunoassay is positive, these experts suggest confirmation with another treponemal test, usually TPPA or TPHA. Then a nontreponemal test can be used to stage the infection.

University of Washington syphilis expert Christina Marra warns clinicians to watch out for false-negative RPR results caused by the prozone phenomenon—antibody titers so high that they hinder formation of the antigen/antibody complexes that labs read to diagnose syphilis with nontreponemal tests. Marra noted that labs can check for the prozone phenomenon if technicians are the least bit suspicious about results, but sometimes the lab may miss these hints. So when providers have a high index of suspicion that a person has syphilis and the RPR results come back negative, she advises them to ask if the lab checked for the prozone phenomenon.

Syphilis breaches the central nervous system in about one of three people with primary syphilis, regardless of HIV status.12 But unlike HIV-negative people, HIV-positives usually get diagnosed with neurosyphilis when syphilis itself is first detected, a finding suggesting that HIV heightens the risk of neurologic complications.1 CDC guidelines say syphilis should be
part of the differential diagnosis of neurologic disease in people with HIV and advise that all HIV-positive people with syphilis and neurologic symptoms should have an immediate spinal tap.40

HIVMA guidelines call for a cerebrospinal fluid (CSF) exam in several circumstances for HIV-positive people:41

- Neurologic or ocular signs or symptoms
- Late latent syphilis (including syphilis of unknown duration)
- Active tertiary syphilis
- Syphilis treatment failure

Health Resources and Services Administration (HRSA) guidelines for HIV care list the same indications for spinal tap, adding that “routine CSF evaluation is not indicated for HIV-infected patients who have early syphilis without neurologic or ophthalmic signs or symptoms.”45 Zetola and Klausner do not recommend spinal tap for HIV-positive people with primary, secondary, or early latent syphilis “and a lack of neurologic, visual, or auditory signs or symptoms, regardless of the RPR titer or CD4 cell count.”12

Work by Christina Marra and University of Washington colleagues indicates that spinal fluid abnormalities can be predicted by serum RPR titers and a sub-350 CD4 count.46 “If you can predict who is going to have abnormal CSF, then you can target those people for lumbar puncture,” Marra suggested in an interview with RITA! “If they have abnormal spinal fluid, treat them for it and prevent them from developing neurologic complications.” She also observed that CDC guidelines take a conservative approach on lumbar puncture, recommending it only in people with neurologic symptoms. But Marra worries that HIV clinicians “may not screen for neurologic syphilis symptoms as carefully as might be needed.”

**Syphilis in the brain, syphilis in the eye**

Early neurosyphilis affects one third or more people with primary syphilis.12,39 Symptomatic neurosyphilis during primary or secondary syphilis may be more common in people with HIV than in the general population,47 and HIV-positive people with symptomatic neurosyphilis may have more striking symptoms18 and more severe CSF abnormalities49,50 (Figure 4).

But the University of Washington’s Christina Marra told RITA! it’s hard to say whether neurosyphilis is more common with than without HIV since a good population-based comparison may be impossible because of referral bias. The problem is that clinicians may worry about neurosyphilis more in HIV-positive people and so refer them for lumbar puncture more readily, regardless of symptoms. In contrast, HIV-negative people may be more likely to get referred for lumbar puncture because they have symptoms.

Neurosyphilis symptoms may include meningitis (marked by headache, fever, stiff neck), visual changes (blurred or lost vision, photophobia, other signs of ocular inflammation), hearing changes or loss, or facial weakness.39 The CDC also lists cranial nerve dysfunction, stroke, acute or chronic altered mental status, and loss of vibration sense as neurosyphilis signals.40 A reactive CSF VDRL indicates neurosyphilis, according to the CDC, if CSF is not substantially contaminated with blood.40

HIV load in CSF is higher in people with neurosyphilis than in those without neurosyphilis,51 a finding suggesting an interaction between syphilis and HIV in the central nervous system.39 Several studies yielded evidence that clinical and CSF abnormalities suggesting neurosyphilis are more common at CD4 counts under 350 cells/mm³ in people with HIV.48,46,52,53
One of these studies, a 1990-2006 prospective cohort study at Johns Hopkins University in Baltimore, found that 41 of 231 HIV-positive people (18%) with newly diagnosed syphilis had neurosyphilis. A CD4 count below 350 cells/mm³ at syphilis diagnosis almost tripled the odds of neurosyphilis (OR 2.87, 95% CI 1.18 to 7.02), whereas any combination antiretroviral therapy before a syphilis diagnosis lowered neurosyphilis odds 65% (OR 0.35, 95% CI 0.14 to 0.91). Those findings led other researchers to suggest that treatment-induced immune reconstitution improves the local immune response against *T. pallidum* and so controls syphilis infection better.

The Hopkins study identified two other factors that more than doubled the odds of neurosyphilis in this HIV cohort—an RPR titer above 1:128 (OR 2.82, 95% CI 1.11 to 7.26) and male gender (OR 2.46, 95% CI 1.06 to 5.70). Two thirds of the people with neurosyphilis had early neurosyphilis. Only 38% had

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**Figure 4.** Neurosyphilis and ocular syphilis are not rare in people with HIV and *T. pallidum* coinfection. These manifestations of syphilis often present special challenges in HIV populations. (Illustrations from Servier Medical Art, [http://www.servier.com/servier-medical-art](http://www.servier.com/servier-medical-art).)
resolution of all CSF abnormalities 1 year after lumbar puncture, and 38% had persistent neurosyphilis symptoms despite what appeared to be adequate treatment of neurosyphilis.

Hopkins researcher Khalil Ghanem stresses in an interview following this article that HIV clinicians should not overlook the possibility of early neurosyphilis and of neurosyphilis after appropriate syphilis therapy.

Ocular syphilis affects a disturbing proportion of HIV-positive syphilis patients, may be the first signal of HIV infection, may not result in abnormal CSF findings, and may not respond to treatment. Those findings emerge from a handful of case series and two systematic reviews of ocular syphilis in people with HIV.

A 5-year study of 509 HIV-positive people in Dijon, France found that 20 (3.9%) had syphilis, and 4 of them (20%) had ocular syphilis. In a Berlin series of 24 consecutive patients with ocular syphilis seen between 1998 and 2006, 11 (46%) had HIV infection. HIV infection had gone undetected in 7 of these 11 before diagnosis of ocular syphilis, and 6 of those 7 had early (CDC category A) HIV infection. A systematic review of 101 HIV-positive people with ocular syphilis found that ocular syphilis led to the HIV diagnosis in 28 of 54 people (52%) with available data, including some with a CD4 count above 200 cells/mm³.

Among 12 people with HIV-associated ocular syphilis at a Boston hospital, 6 people had normal CSF results. A systematic review of 93 HIV-positive people and 50 HIV-negative people with syphilitic uveitis found that 13 of those with HIV (14%) had normal lumbar puncture results. Three of 101 people in the other systematic review had a negative nontreponemal test for syphilis.

In the 101-person review, 97% of those with impaired vision improved with intravenous penicillin or ceftriaxone. Three of 12 people in the Boston case series required retreatment within 1.5 years. The 143-person review recorded 13 ocular syphilis treatment failures (9%), 11 of them in people with HIV. Among 110 people who had intravenous therapy in this series, some did not recover full vision.

The authors of the 143-person analysis list 4 hours of intravenous penicillin for 10 to 21 days as optimal therapy for ocular syphilis. They note, though, that some experts consider 10 days of intramuscular penicillin equivalent to intravenous therapy and that the CDC sanctions daily intramuscular penicillin if given with oral probenecid. (See “Syphilis treatment response in people with HIV” below.)

### How syphilis affects HIV and vice versa

Syphilis infection boosts HIV load and cuts CD4 counts, although those reversals tend to resolve when syphilis is treated. These trends lack complete consistency from study to study. For example, in a study of 52 US men with HIV, viral load did not flare during primary or secondary syphilis among men with antiretroviral-induced virologic suppression. That finding reflects a correlation discovered in a 118-person Spanish study, which associated not taking combination antiretrovirals with a viral load gain during syphilis. In an Italian series of 38 HIV-positive patients with syphilis, the group’s CD4 count barely changed from before syphilis to syphilis onset to after treatment for syphilis (573 to 589 to 573 cells/mm³),
and the same was true for viral load (3.3 to 3.2 to 3.5 log10 copies/mL). Considering all these studies, Ze-tola and Klausner warn that “syphilis may account for otherwise unexplained decreases in CD4 cell counts or increases in the plasma viral load in HIV-infected patients” and suggest that syphilis testing may be prudent when that happens.12

Analysis of data prospectively collected from 2239 people with estimated dates of HIV seroconversion uncovered no hint that syphilis coinfection hastens progression to AIDS or death.64 This study of US military personnel included 205 people with confirmed syphilis (9%) and 66 with probable syphilis (3%). The researchers devised a multivariate model that considered outcomes through the start of combination antiretroviral therapy or the last visit and adjusted for CD4 count, age, race, gender, hepatitis B and C status, and confirmed plus probable syphilis. In this analysis syphilis had no impact on risk of AIDS or death (hazard ratio [HR] 0.99, 95% CI 0.73 to 1.33).

In 2008 French experts offered a concise review of how HIV infection can affect the course and treatment of syphilis.65 Although their list of “atypical features” of syphilis in HIV-positive people rests on only a handful of studies, it is nonetheless daunting (Table 3).66-70 These authors65 observe, however, that “few of these features have been confirmed in large observational studies.”12,71

Table 3. How HIV may affect the course and treatment of syphilis

- Higher RPR or T pallidum hemagglutination assay titer
- False-negative syphilis serology
- More frequent prozone phenomenon*66
- Higher rate of asymptomatic primary syphilis66-68
- Multiple or deeper chancres during primary syphilis66
- Overlap of primary- and secondary-stage features of syphilis66,68
- Shorter latency period before meningovascular syphilis
- Increased rate of early neurologic and ophthalmic involvement66,68
- More rapid progression to tertiary manifestations66
- Reduced efficacy of standard therapy for early syphilis†66
- More frequent relapse†68,70
- Delayed normalization of CSF values after treatment69

Adapted from Pialoux et al.65
* The prozone phenomenon is a false-negative response resulting from antibody titers so high that they hinder formation of the antigen/antibody complexes read to diagnose syphilis with nontreponemal tests.
† Antiretroviral therapy improves chances of serologic response to standard syphilis therapy.
See section on “Syphilis treatment response in people with HIV.”

continued...
Syphilis treatment response in people with HIV

It took medical science 450 years to figure out how to treat syphilis. But once it got an answer, that remedy stuck. Compared with treating HIV infection, or even gonorrhea, treating syphilis remains blessedly simple—and cheap: Two shots of benzathine penicillin G and you’re good to go, even if you have HIV infection (usually).

“Syphilis sive morbus gallicus,” the 1530 admonitory epic that gave syphilis its name, also prescribed a treatment regimen: mercury plus guaiac oil from the palo santo tree.3 Neither did much to relieve syphilis, but mercury probably killed many who took it to treat their pox, possibly including Franz Schubert. “The best method of prescribing mercury is in the form of inunctions [rubbings],” one authority advised, “but these are useless, except in congenital syphilis, unless carried out by a trained rubber.”72

Paul Erhlich, the Nobel laureate famed for groundbreaking work in hematology and immunology, coined the term chemotherapy and discovered arsphenamine (Salvarsan), a form of arsenic and the first chemotherapeutic agent for systemic treatment of a microorganism.73 Salvarsan had to be injected weekly for up to a year10 and had “serious adverse consequences (including death).”78 The unhappy history of syphilis therapy reached its nadir with the notorious US Public Health Service “Tuskegee Study of Untreated Syphilis in the Negro Male.”74,75 The longest nontherapeutic human trial in medical history, the Tuskegee study ran for 40 years until exposed by the Associated Press.75

The story of effective syphilis therapy began in 1905 with Fritz Schaudinn and Erich Hoffmann, the scientists who described the bacterium now called Treponema pallidum.76 Working at the Public Health Service’s eponymous Venereal Disease Research Laboratory (VDRL) on Staten Island, John Mahoney discovered the antitreponemal properties of penicillin in 1943.10 Before World War II ended, trials established that penicillin cures syphilis—as it does today in most people with T. pallidum infection.

Parenteral penicillin G remains the preferred drug to treat syphilis, according to CDC guidelines.40 The preparation (benzathine, aqueous procaine, or aqueous crystalline), dose, and duration of treatment depend on the stage and clinical manifestations of the infection. Typically two 1.2 million-U shots of benzathine penicillin G get the job done in people with primary, secondary, or early latent syphilis40 (though some European countries opt for 600,000 IU of procaine penicillin for 10 to 14 days1).

This two-shot advice holds for people with or without HIV. Although some espouse a longer course of penicillin G—or doxycycline, tetracycline, or ceftriaxone instead of penicillin—for HIV-positive people, reviews by HIV/syphilis experts (including the CDC) see no merit in these alternatives.1,12,40 For late latent syphilis or syphilis of unknown duration, the CDC calls for 2.4 million units of benzathine penicillin G weekly for 3 weeks.40

The CDC recommends the same regimen for HIV-positive and negative people with neurosyphilis: 18 to 24 million U of aqueous crystalline penicillin G daily given intravenously as 3 to 4 million U every 4 hours or continuously for 10 to 14 days.40 An alternative regimen is 2.4 million U of intramuscular procaine penicillin once daily plus 500 mg of oral probenecid four times daily for 10 to 14 days. All these CDC recommendations also apply to pregnant women. But research summarized below leads some HIV/syphilis experts to question the CDC’s advice.
No matter which drug or course one prescribes for syphilis, the same benchmark indicates an appropriate response: a 4-fold drop in nontreponemal titers, for example, from 1:64 to 1:16, after 6 to 12 months. Authorities recommend follow-up 1, 3, 6, 12, and sometimes 24 months after treatment, though research suggests only 20% to 40% of syphilis patients get seen that regularly.

For HIV-positive people treated for syphilis, Zetola and Klausner recommend serologic response monitoring for up to 1 year for early syphilis and up to 2 years for late syphilis, before deciding whether treatment worked. But if nontreponemal titers climb during treatment or if symptoms emerge, they advise clinicians to suspect treatment failure or reinfection. Khalil Ghanem, who studies syphilis and HIV at Baltimore’s Johns Hopkins University, believes follow-up serology should be done every 3 months for at least 2 years in HIV-positive people with syphilis. “This recommendation is critical,” Ghanem stresses, “because this population has a higher probability of experiencing treatment failure and enhanced therapy has not been shown to decrease this risk.”

A systematic review of syphilis therapy in HIV-positive people suggested to the authors that “the optimal antimicrobial regimen to treat syphilis in HIV-infected subjects is unknown” and that “guideline recommendations in this population are based on little objective data.” This analysis involved 23 studies with at least 6 months of follow-up. Probability ranges for serologic failure were 6.9% to 22.4% with 2.4 million U of intramuscular benzathine penicillin G, 19.4% to 31.1% with 7.2 million U of benzathine penicillin G for late latent syphilis, and 27.3% to 27.8% with 18 to 24 million units of aqueous penicillin for neurosyphilis. A case-control study of 129 HIV-positive people with syphilis and 168 HIV-negative people with syphilis at Johns Hopkins University determined that HIV inflated the serologic failure risk 6 times (HR 6.0, 95% CI 1.5 to 23.9, P = 0.01).

This study also found that 64% of 450 HIV-positive people treated for syphilis did not have documented serologic follow-up within 1 year of treatment (see the interview with Khalil Ghanem in this issue).

In their review of syphilis and HIV, Emily Ho and Sheila Lukehart (University of Washington, Seattle) underline the shortcomings of syphilis treatment in people with HIV: (1) higher rates of serologic failure, (2) viable T. pallidum in CSF after standard treatment, and (3) longer time to resolve CSF abnormalities after treatment. Pondering these deficits, they note that the CDC still recommends the same syphilis therapy for HIV-positive and negative people and sees no need for lumbar puncture in people without neurologic signs or symptoms regardless of HIV status. “The long-term repercussions of these recommendations for CSF examination,” Ho and Lukehart remark, “are unclear at this time.”

But after reviewing many of these same studies, French investigators conclude that “if HIV has an effect on the course of syphilis, it is small and clinically manageable in most cases.” However, they stress that studies of syphilis treatment in people with HIV are limited by several shortcomings: (1) high rates of loss to follow-up, (2) lack of long-term follow-up, (3) lack of gold-standard criteria for treatment response, (4) small sample size, (5) lack of stratification by syphilis stage, ongoing antiretroviral treatment, CD4 count, or HIV load, and (6) possible publication bias. In their own retrospective study of consecutive syphilis cases from 2000 through 2007 at an academic STI center, the serologic response rate to syphilis therapy in 114 cases was marginally lower in people with HIV (91.8% versus 98.3%, P = 0.14), and median time to serologic response was similar with and without HIV (117 versus 123 days, P = 0.44).

continued...
Some research found that antiretroviral therapy improves chances of serologic response to syphilis or neurosyphilis therapy. A 1990–2006 study of 180 people with 231 cases of syphilis in the Johns Hopkins cohort determined, after a median 5.3 years of follow-up, that a CD4 count under 200 cells/mm³ at syphilis diagnosis more than doubled the risk of serologic failure (adjusted HR 2.48, 95% CI 1.26 to 4.88). Taking an antiretroviral combination lowered the serologic failure risk 60% (adjusted HR 0.40, 95% CI 0.21 to 0.75), regardless of CD4 response to therapy. Among 41 HIV-positive people with neurosyphilis studied by the same Johns Hopkins group, antiretroviral therapy after treatment for neurosyphilis marginally lowered the risk of serologic failure ($P = 0.2$). The same study, any combination antiretroviral therapy before a syphilis diagnosis cut the risk of neurosyphilis 65% (OR 0.35, 95% CI 0.14 to 0.91).

A study of 110 people with HIV and neurosyphilis in Seattle found that normalization of RPR titer predicted treatment success less accurately among those not on antiretroviral therapy. The same group studied 59 people treated for neurosyphilis who had repeated lumbar puncture. Among the 46 people with HIV, those with a CD4 count above 200 cells/mm³ were almost 4 times more likely to normalize CSF-VDRL reactivity than those with a lower count—a finding implying that antiretroviral therapy could improve response (HR 3.7, 95% CI 1.2 to 11.2, $P = 0.02$). Overall, though, people with HIV were 2.5 times less likely to attain normal CSF-VDRL reactivity than people without HIV, even after considering baseline CSF-VDRL titer and stage of syphilis at neurosyphilis diagnosis. Zetola and Klausner note that this study “raised concerns regarding the adequacy of the current recommended treatment for neurosyphilis” in people with HIV.

Single-dose benzathine penicillin G maintains treponemacidal levels of penicillin for at least 2 to 3 weeks—long enough to cure early syphilis. But benzathine penicillin G does not cross the blood-brain barrier, so it cannot control the $T$ pallidum that has been detected in CSF after single-dose therapy.

“Although serological and microbiological treatment failures have been reported following [benzathine penicillin G] treatment,” observe STI experts David Lewis (National Institute for Communicable Diseases, South Africa) and Sheila Lukehart (University of Washington, Seattle), “these may be due to sequestration of treponemes protected in the central nervous system or to re-infection.” They add that there have been no documented cases of $T$ pallidum resistance to penicillin or tetracycline, but resistance to macrolides has been verified.

Among people allergic to penicillin, alternatives include tetracycline and doxycycline, the macrolides erythromycin and azithromycin, and third-generation cephalosporins such as ceftriaxone. In their review of $T$ pallidum treatment and resistance, Lewis and Lukehart call penicillin desensitization “the preferred option to treating penicillin allergic patients who are pregnant or have neurosyphilis.” They believe doxycycline and tetracycline are options for nonpregnant patients with penicillin allergy, but because adherence to doxycycline and tetracycline may pose problems, “penicillin is preferred if possible.” Table 3 in this freely accessible article spells out current advice on antibiotic therapy for syphilis in light of penicillin allergy and resistance to macrolides (see references for link to article).
**Preventing syphilis: easy and hard**

Syphilis prevention campaigns have featured a giant, roving penis and a walking, raspberry-like syphilis sore. These eye-grabbing ploys may raise public awareness for a few minutes, but slowing the syphilis resurgence probably demands sterner tactics. Preventing syphilis remains frustrating because it is both simple and Sisyphean. It’s simple because everyone knows what’s required: better public understanding of how syphilis spreads, safer sexual gymnastics, more zealous syphilis and HIV screening, and earlier diagnosis and treatment of both STIs. It’s Sisyphean because progress on all these fronts comes slowly.

Even though *T. pallidum* can be transmitted orally, condoms do appear to mitigate transmission risk. Circumcision does not. A systematic review of studies addressing condom use and syphilis risk did more to highlight how poorly designed such studies have been than to suggest a conclusion. The two studies that examined both incident syphilis infection and consistent condom use both found that regular rubber wearing did lower syphilis risk, and in one study the association was statistically significant. None of the 12 studies evaluated assessed correct condom use or documented exposure to a sex partner with syphilis.

Researchers who prospectively study a cohort of HIV-positive and negative people in Rakai, Uganda famously demonstrated (with two other groups) that circumcision significantly lowers the risk of HIV acquisition by heterosexual men. Continuing research showed that circumcision also significantly cut HSV-2 infection incidence and HPV infection prevalence. But that analysis turned up no evidence that circumcision helps shield heterosexual men from syphilis.

A Cochrane Database review of 8 studies involving 34,999 MSM confirmed that circumcision does not stop syphilis in this population.

Scientists have sequenced the entire *T. pallidum* genome, a key step in identifying surface molecules and thus in designing a vaccine. Warning that development of a protective syphilis vaccine remains “formidable,” Ho and Lukehart note that studies are under way to test the ability of a “cocktail of conserved regions on *T. pallidum* antigens” that might confer immunity in a rabbit model.

In the meantime, notifying sex partners of people with recently diagnosed syphilis—and perhaps treating them presumptively—may slow the spread of this sinuous pathogen. HRSA HIV guidelines advise that sex partners of anyone diagnosed with primary, secondary, or early latent syphilis in the past 90 days “should be treated presumptively, as they may be infected with syphilis even if they are seronegative.” Sex partners exposed more than 90 days after such a diagnosis should be treated presumptively “if serologic test results are not available immediately and their follow-up is in doubt.” HRSA adds that some specialists recommend presumptive treatment for sex partners of people diagnosed with primary syphilis in the past 3 months, secondary syphilis in the past 6 months, or early latent syphilis in the past year.

From the first days of the US syphilis resurgence, Internet partnering has helped spread *T. pallidum*. Zeotola and Klausner believe public health officials and providers should not overlook the potential of this fluid medium to notify partners of syphilis patients, promote awareness of this tenacious STI, and offer testing to people who may need it.
References


Ten things people with HIV should know about syphilis

1. Syphilis is a growing threat to gay and bisexual men with and without HIV. Syphilis rates have also climbed recently in women with and without HIV.

2. Syphilis can spread through anal, vaginal, or oral sex. Oral sex is not “safe sex” when it comes to preventing syphilis.

3. Having HIV infection raises the risk of syphilis up to 7 times. Other syphilis risk factors include (1) anal sex without a condom, (2) oral-anal sex (“rimming”), (3) using drugs (including meth and Viagra) during sex, and (4) having many casual sex partners.

4. A person may not notice the first signs of syphilis because the sores it causes are not painful and look like sores caused by other diseases. These sores may appear on the penis (Figure 1), but they may be hidden from view inside the anus, rectum, or vagina.

5. The second stage of syphilis may be marked by rough, red, or reddish-brown spots that are not itchy (Figure 2 and 3). Other signals may include fever, swollen lymph glands, sore throat, patchy hair loss, headaches, weight loss, muscle aches, and fatigue—but these signals also occur with many other diseases.

6. The bacterium that causes syphilis can quickly get inside the brain and cause headache, fever, stiff neck, blurred or lost vision, sensitivity to light, hearing loss, or facial weakness.

7. Because syphilis can go unnoticed so easily, sexually active people with a high risk of syphilis (see 3 above) should get tested for syphilis regularly.

8. Detecting syphilis is important because it’s usually easy to cure with two shots of penicillin. But if syphilis is not treated, it can get much worse.

9. If you learn that you have syphilis, it is very important to tell your sex partners or let health authorities contact them so they can be tested and treated.

10. No one becomes immune to syphilis. Infected people who get cured can get syphilis all over again.

Figure 1. Syphilis sore on penis. (From the Centers for Disease Control and Prevention Public Health Image Library [PHIL], Susan Lindsley.)

Figure 2. Syphilis sores on soles of feet. (From the Centers for Disease Control and Prevention Public Health Image Library [PHIL], Robert Sumpter.)

Figure 3. Syphilis sores on chest. (From the Centers for Disease Control and Prevention Public Health Image Library [PHIL], Robert Sumpter.)
Tighter screening and follow-up: keys to better syphilis care with HIV

An interview with Khalil G. Ghanem, MD, PhD

Associate Professor of Medicine  
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Dr. Ghanem is Associate Professor of Medicine in the Division of Infectious Diseases at the Johns Hopkins University School of Medicine, Baltimore, Maryland, and Director of Sexually Transmitted Diseases/HIV/Tuberculosis Clinical Services for the Baltimore City Health Department. He earned his MD at Baylor College of Medicine and his PhD at the Johns Hopkins Bloomberg School of Public Health. Dr. Ghanem has authored reviews on syphilis and gonorrhea for leading journals and has contributed 11 book chapters on sexually transmitted infections.

Mascolini: Are syphilis rates changing in your patient population with HIV and at risk for HIV?

Ghanem: I’ll first give an overview of the US, then focus on Baltimore to give you a sense of how syphilis rates are changing. Within the US for the last 10 years we’ve seen increasing rates of syphilis in men. In 2010, which is the year with the latest nationwide data, overall syphilis rates went down for the first time in 10 years. But rates of syphilis in men and particularly among men who have sex with men (MSM) continued to go up.

The male-to-female ratio of syphilis was 1-to-1 or 1-to-2 back in 1996, and now it’s essentially 7-to-1 male to female, largely because syphilis rates in MSM have increased dramatically. If you look at early syphilis cases—the cases used to calculate syphilis incidence per year—almost 70% of new cases in 2010 are among MSM.

Of course, MSM are also at risk for HIV. We don’t have population-level data in the US on HIV and syphilis coinfection, but results of studies in different locales indicate that rates of HIV coinfection among people with early syphilis are anywhere between 20% and 70%. In other words about 20% to 70% of patients who have early syphilis are HIV infected.

So syphilis is a huge problem, particularly among MSM with or without HIV.
Mascolini: And what’s going on in your cohort?

Ghanem: Baltimore has had very high rates of HIV and syphilis for a long time. Heterosexual men and women had accounted for most syphilis cases in Baltimore until the last 5 to 7 years, when we saw a dramatic shift in the epidemiology of syphilis. Now the vast majority of our cases are occurring among men, particularly young men who have sex with men. And about 30% to 35% of our cases are occurring among HIV-infected men who have sex with men.

Thus Baltimore essentially mirrors the great shift that we’ve seen in syphilis epidemiology across the country over the last 10 years. For a while Baltimore lagged behind other major cities like New York and San Francisco in terms of this shift. It happened more recently in Baltimore, but the shift to MSM here has also been dramatic.

Mascolini: I know there’s a large HIV-positive injection drug-using population in Baltimore. Have you noticed anything about syphilis trends in injection drug users?

Ghanem: Gender is the most distinguishing feature of our syphilis cases—in other words young MSM and not so much underlying IV drug use. There is a strong association between meeting partners on the Internet and syphilis, and there is a strong association between syphilis and the use of drugs like crystal meth. But the typical IV drug population that we see has not been the main focus of these new syphilis infections.

Screening frequency really depends on patient risk factors and behaviors. Based on these factors you can make a decision on how frequently to screen for syphilis. Patients with new sex partners, patients who meet anonymous sex partners on the Internet—these types of patients need to be screened much more frequently for syphilis than once a year. I don’t think anybody would accuse you of screening too frequently. I think most clinicians don’t screen their patients nearly enough.

Mascolini: How do you get patients to come in for screening more often than they might for regular HIV checkups?
**Ghanem:** One thing we can do is remind our patients regularly about syphilis and about the risks associated with syphilis. And remember that patients don’t have to be seen by the physician to be screened for any STD. They can just stop by the clinic and get their blood drawn. I’ve done that with some patients who come for a regular checkup every 3 months but get screened for syphilis every month. They come by in the morning, get their blood drawn, and go to work.

The other option is to send them to the STD clinic for regular screening. I run the STD clinic here in Baltimore, and we see a lot of people who come in and request syphilis testing. We screen them without asking any questions or seeing how often they’ve been tested for syphilis. So I think the issue of inconvenience can be bypassed because the clinician doesn’t necessarily have to see the patient.

I think every 2 to 3 months is usually fairly adequate for someone who has very high risk. And I think yearly is pretty adequate for people who have a low to moderate risk.

**Mascolini:** Do you get good screening adherence from people you want to test every 2 or 3 months?

**Ghanem:** No. That’s the tough part. If you plan to test someone every 2 to 3 months, you’re lucky if you get them twice a year. When you try to test people yearly, you wind up actually testing them every other year. I feel by pushing it—by aiming for the ideal—you’re much more likely to get a reasonable screening frequency. I push to get very high-risk people tested every 2 to 3 months; I wind up getting them tested maybe once or twice a year. But I can live with that.

**Mascolini:** Do you have a handle on the syphilis reinfection rate in the people you see with syphilis?

**Ghanem:** In our population our reinfection rate in the 3 years after initial syphilis treatment is about 30%. It varies depending on the population and the locale, but reinfection rates between 10% and 40% have been documented. Of course someone who gets syphilis once is much more likely to get a new syphilis infection than a person who has never had syphilis. That’s why it’s really important to follow these patients up, not only to determine their response to therapy but also to make sure they didn’t get reinfected.

This is a common theme with almost all sexually transmitted diseases. That’s why the CDC recommends rescreening 3 months after treating for gonorrhea, chlamydia, or trichomoniasis. And it makes sense because someone who comes in with syphilis is telling you they have sex in a network that has a high rate of syphilis, and usually networks don’t change significantly after a person gets treated. As a result, they run a high risk of getting reinfected if they’ve already been infected once. It makes perfect sense on the network level, and it makes perfect sense on the biological level.

### When to do lumbar puncture

**Mascolini:** When should lumbar puncture be done for HIV-positive people with syphilis?

**Ghanem:** That remains an area of huge controversy for HIV-infected patients with syphilis. There are physicians who feel that all HIV-infected patients should undergo lumbar puncture. The CDC addressed this topic in its 2010 STD treatment guidelines.1

There are three categories of patients in whom lumbar puncture is clearly indicated (Figure 1). First, anyone who has syphilis and any neurologic sign or

*continued…*
symptom needs a lumbar puncture. The second and third categories involve patients who are neurologically asymptomatic. The first of these groups consists of patients with evidence of tertiary syphilis—such as cardiovascular syphilis or late skin manifestations of syphilis. These patients should have a lumbar puncture, but this category of patients is extremely rare in the antibiotic era.

The other category of patients without neurologic symptoms who should probably undergo a lumbar puncture consists of patients who get the appropriate treatment for syphilis and don't respond serologically to that treatment. If you rule out reinfection in these patients, they should probably undergo a lumbar puncture to make sure they don't have underlying asymptomatic neurosyphilis.

If you treated a patient for syphilis and their serological RPR titer has not declined, and if they say they had unprotected sex again and they noticed a lesion, you know they got reinfection and they don't need a lumbar puncture. But if a treated patient comes back with titers that didn't decline appropriately or even

**Figure 1.** A simple algorithm suggests when to do lumbar puncture in an HIV-positive patient with syphilis.
increased, and if that person says they’ve had no sex partner since starting syphilis therapy, they should undergo a lumbar puncture.

We know that patients with HIV and a CD4 count less than 350, or patients with HIV and syphilis and an RPR titer greater than or equal to 1:32, appear to be at increased risk of asymptomatic neurosyphilis. The problem is that in the antibiotic era we don’t have any data to show that doing a lumbar puncture on these individuals ultimately improves their outcomes. It doesn’t mean that lumbar puncture will not improve their outcome; it just means that we don’t have any data. Because of that, and because there are risks associated with a lumbar puncture, the CDC recommendations aim to highlight the issue and not to make any formal recommendations beyond explaining when lumbar puncture should be considered.1

I’ll tell you what I do: If I have an HIV-positive patient who is completely asymptomatic neurologically but has either a low CD4 count or a high RPR titer, I try to base my decision about lumbar puncture on how reliable that patient seems. If I think the patient is reliable and likely to come back for follow-up to make sure that they’re neurologically well, or if they’re likely to call me should any neurologic symptoms develop, I’m less inclined to do a lumbar puncture. But if I have a patient who’s shown clearly that they’re not reliable, they’re not going to call, I try to get a lumbar puncture just to make sure I rule out asymptomatic neurosyphilis. It’s not a perfect approach because sometimes it’s hard to tell who’s going to be reliable and who’s not. But at the same time it’s very difficult for us to schedule lumbar punctures on all our HIV patients. It’s just not feasible.

Watching for poor syphilis treatment response in people with HIV

Mascolini: Do syphilis treatment response rates in people with HIV differ from rates in the general population?

Ghanem: Several studies, including the only randomized trial addressing this issue,2 show that HIV-positive patients are slightly less likely to respond serologically to syphilis treatment than people without HIV. [See “Syphilis treatment response in people with HIV” in the review article, “Slowing resurgent syphilis in people with HIV.”] That’s why the CDC recommends close follow-up of HIV-positive patients treated for syphilis. To me, that is the single most important recommendation the CDC makes on syphilis because close follow-up lets you quickly identify individuals who don’t respond appropriately to therapy. When you identify a poor response, you can retreat those patients or work them up more fully. Closer follow-up of treated patients would prevent many of the complications that could occur in poor treatment responders.

The problem is that it’s hard to follow these patients up. For example, when we looked at rates of follow-up for HIV-positive patients in the Baltimore City Health Department, we found that about 65% of our patients treated for syphilis don’t have a follow-up RPR titer in the next year.3 And we’re confident in our results because we have access to RPR titers done throughout the state of Maryland. That’s a
huge number. I think close follow-up of treated patients is the most important thing we can do because it allows us to identify patients who are not responding adequately in a timely manner.

**Mascolini:** In your systematic review of syphilis treatment in people with HIV, you conclude that “guideline recommendations in this population are based on little objective data.” How do you advise HIV clinicians to treat patients diagnosed with syphilis?

**Ghanem:** We found that the published data are limited in terms of suggesting the best syphilis treatment approach for our HIV-infected patients. We didn’t intend to cause clinicians anxiety by stating this, because we have decades of experience in treating syphilis in people with HIV. What that experience tells us is that the vast majority of our patients coinfected with HIV and syphilis do very well on standard therapy.

Physicians can take heart in knowing that and in following the CDC recommendations, which state that the treatment of syphilis is virtually identical in HIV-infected and uninfected patients. The only difference is that HIV-infected patients should be followed up more aggressively after treatment. If we do that we could quickly identify the small subset of patients who don’t respond well to therapy and treat them more aggressively.

**Mascolini:** Can you summarize your research on how antiretroviral therapy affects syphilis treatment response?

**Ghanem:** We looked at our HIV cohort at Hopkins to see whether the immunologic status of our HIV-infected patients had an impact on the course of syphilis. We found that patients whose immunological status was impaired—in other words, those whose CD4 count was less than 350—had an increased risk of neurosyphilis if they had syphilis. We also found that they were less likely to respond as well serologically to syphilis therapy than patients whose CD4 count was above 350. And we found that use of highly active antiretroviral therapy tended to improve responses to syphilis therapy in these patients and to reduce the risk of neurological complications.

These finding were not really surprising because we already knew that successful treatment of syphilis depends on two things: You need a functioning immune system, and you need antibiotics. One without the other is not enough to control syphilis. In the preantibiotic era most syphilis patients had a good immune system, but we didn’t have any effective drugs, and it was hard to manage syphilis. In the pre-HIV antibiotic era, we had patients with a good immune system and we had good drugs; as a result, the number of syphilis cases dropped and people did very well with syphilis treatment. Then came the HIV era. We still had good drugs for syphilis, but in people with HIV we didn’t have an intact immune system. Clearly,

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### Four common clinical mistakes in managing syphilis in HIV-positive patients

- Not screening high-risk patients frequently enough for syphilis
- Failing to follow up patients aggressively after syphilis therapy to ensure adequate response and absence of reinfection
- Overlooking the possibility of neurosyphilis after appropriate syphilis therapy
- Overlooking the possibility of early neurosyphilis
what this tells us is that to manage syphilis we need good drugs and a good immune system.

**Clinicinist mistakes in managing syphilis**

**Mascolini:** What are the most common mistakes HIV clinicians make in managing HIV-positive people with syphilis?

**Ghanem:** There are several things I would focus on. The first, and I think the most important, is not screening for syphilis nearly enough. Clinicians need to screen high-risk patients more frequently.

The second problem is not being aggressive in following up HIV-infected patients after they get treated for syphilis. You really want to bring them back in after treatment to make sure they’re responding appropriately serologically.

Another thing clinicians tend to forget can be illustrated by this scenario: An HIV-infected patient comes in with early syphilis. They get the appropriate treatment. A week or 2 weeks later they call and say they’re having headaches. Some clinicians don’t think about the possibility of neurosyphilis because they think they’ve treated the syphilis and neurosyphilis can’t occur after treatment. Clinicians tend to forget that neurosyphilis can occur after appropriate syphilis therapy, particularly in HIV-infected patients.

That’s another reason why it’s important to follow up with patients and to explain to patients what to watch for after they get treated for early syphilis: “If you develop a headache, if you notice visual changes, if you develop any neurologic function abnormality, give me a call immediately.” Our study of HIV-positive people with syphilis showed that neurosyphilis can develop in those patients after they are appropriately treated for early syphilis.\(^6\)

A final mistake involves the issue of early neurosyphilis. Clinicians tend to forget that early neurosyphilis does occur. They assume that neurosyphilis develops many years after the initial infection. But particularly among patients who have an immune system defect, such as people with HIV, early neurosyphilis can occur literally within days of infection. In other words you can have neurosyphilis concomitantly with primary syphilis, secondary syphilis, or early latent syphilis. In fact in our study early neurosyphilis was far more common than late neurosyphilis.\(^6\)

Clinicians should remember that early neurosyphilis is something they have to look for. Whenever they’re evaluating an HIV-infected patient for early syphilis, clinicians have to ask about neurological symptoms including photophobia, headache, neck stiffness, visual changes, and cranial nerve abnormalities. Doing so will help ensure that they don’t miss a case of early neurosyphilis.

Someone who comes in with syphilis is telling you they have sex in a network that has a high rate of syphilis, and usually networks don’t change significantly after a person gets treated.
References

Preventing and controlling chlamydia—the silent STI—in people with HIV

By Mark Mascolini

Abstract: Every year nearly 3 million people in the United States get infected with *Chlamydia trachomatis*, the most frequently reported bacterial sexually transmitted infection (STI) in this country. An international review and a US study determined that about 5% of HIV-positive people have chlamydia infection. Because chlamydia—the silent STI—often causes no symptoms, regular screening of sexually active people is essential. Risk factors for chlamydia infection include prior chlamydia, multiple sex partners, unprotected sex, drug use during sex, younger age, and a CD4 count below 200 cells/mm². Rectal chlamydia infection can boost the risk of HIV infection in MSM nearly 9 times, and chlamydia doubles the risk of HIV shedding in the genital tract. Treating chlamydia significantly lowers cervical HIV shedding. Various strategies for getting antibiotics to sex partners of people diagnosed with chlamydia—without requiring partners to visit a clinic for an exam—have proved effective in treating more partners and preventing reinfection in index cases. But such strategies have some drawbacks. Chlamydia treatment guidelines are the same for people with and without HIV. Some research suggests that the simplest regimen—single-dose azithromycin—may be less than optimal for people with asymptomatic rectal chlamydia.

Chlamydia poses an insidious and ongoing threat to HIV-positive people—insidious because it usually causes no symptoms and so can easily go undetected, ongoing because people with HIV often remain sexually active and so risk picking up or passing along another STI.

*Chlamydia trachomatis* accounts for the highest proportion of reported bacterial STIs in the United States, about 3 million new infections yearly, representing about 2.7% of adults between 18 and 44 years old. And people with HIV do their share in sustaining that high rate. A systematic review of HIV-positive people across the world (but mostly in North America and Europe) figured that 5% have chlamydia. Chlamydia proved the fourth most prevalent STI in this review, following *Trichomoniasis* (at 18.8%) and syphilis and gonorrhea (tied for second at 9.5%).

Chlamydial urethritis usually does provoke symptoms in men, but most women with chlamydia-induced pelvic inflammatory disease have symptoms so mild or nonspecific that they never seek medical care. (A handout for patients at the end of this article lists chlamydia symptoms and other chlamydia prevention and care pointers.) Yet 20% of women with pelvic inflammatory disease become infertile, 18% succumb to “debilitating, chronic pelvic pain,” and 9% face life-threatening tubal pregnancy. *C trachomatis* infection during pregnancy can lead to postpartum endometritis in mothers and to conjunctivitis or pneumonia in infants.

Gay and bisexual men with and without HIV run a risk of asymptomatic rectal chlamydia if they practice receptive anal intercourse. A 3076-man study in...
Britain charted a 38% prevalence of HIV and rectal chlamydia coinfection, and two thirds of rectal infections caused no symptoms. Those findings prompted the investigators to call rectal chlamydia “a reservoir of undiagnosed infection” in men who have sex with men (MSM).

Besides causing pelvic inflammatory disease in women and epididymitis in men, chlamydia can trigger conjunctivitis or sexually acquired reactive arthritis in adults. And as with most STIs, chlamydia heightens the risk of acquisition or transmission of HIV and other sexually transmitted pathogens.

Although the CDC and other agencies and professional groups offer lengthy and detailed advice on chlamydia screening, diagnosis, and treatment in people with and without HIV, chlamydia experts acknowledge big holes in understanding the natural history of this pervasive infection. In 2008 the CDC gathered an advisory group to sort out what’s known—and not known—about the course of chlamydia in infected people. They homed in on four “key questions” whose answers bear heavily on chlamydia prevention and care guidelines. After parsing available data, the panel agreed that no one knows the answers (Table 1).
With those limits in mind, this review analyzes chlamydia risk factors, prevalence, and incidence in people with HIV; the impact of chlamydia on HIV risk and progression; screening for and diagnosing chlamydia in people with HIV; preventing chlamydia; and treating chlamydia in people with HIV. The article is limited to *C. trachomatis* serovars that cause urethritis, pelvic inflammatory disease, and the other conditions mentioned above. Three *C. trachomatis* serovars can cause lymphogranuloma venereum, a lymphatic system infection that spawned a concerning spate of outbreaks among MSM over the past decade,

<table>
<thead>
<tr>
<th>Key question</th>
<th>What data say so far</th>
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<tbody>
<tr>
<td>What is the duration of untreated, uncomplicated genital chlamydial infection in humans?</td>
<td>“Ethical considerations are a major challenge in studying the natural history of untreated chlamydia. . . . Taking these ethical challenges into consideration, designing longitudinal studies on the natural history of chlamydia will be difficult.”</td>
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<tr>
<td>Which clinical factors influence resolution of untreated, uncomplicated genital chlamydial infection in humans?</td>
<td>“. . . we have limited knowledge about the clinical factors that influence the duration of untreated, uncomplicated genital chlamydial infections in humans.”</td>
</tr>
<tr>
<td>Which host immune responses occur in uncomplicated genital chlamydial infections in humans, and which genetic determinants of the host modulate these immune responses?</td>
<td>“. . . there are few studies of host immune responses in humans with uncomplicated genital chlamydial infections.”</td>
</tr>
<tr>
<td>Which biological properties of <em>C. trachomatis</em> influence resolution of uncomplicated genital chlamydial infections in humans?</td>
<td>“. . . we have very limited knowledge of the impact of biological characteristics of <em>C. trachomatis</em> on outcomes of uncomplicated genital chlamydial infection in humans, including most importantly, the duration of infection.”</td>
</tr>
</tbody>
</table>

Source: Geisler et al. 

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Table 1. Key questions about the course of chlamydia remain unanswered.
Almost 3 million in US (many with HIV) have chlamydia

CDC case counters tallied 1,307,389 chlamydia infections in 2010. They note that this number underestimates the actual total because most people with chlamydia don’t know they’re infected, so their case doesn’t get reported. The CDC estimates the actual number of new chlamydia infections yearly (chlamydia incidence) at 2.8 million. Among women and girls, chlamydia rates are highest among teens (2536 per 100,000) and 20- to 24-year-olds (2447 per 100,000), while among men and boys prevalence peaks in the 20-to-24 age group (605 per 100,000). Because the cervix of teenage girls and young women is not fully matured and is probably more susceptible to chlamydia, the CDC notes, this age group runs a higher risk of infection than older sexually active women.

In 2011 a 37-study systematic review of STIs acquired after people became infected with HIV figured chlamydia prevalence at 5%. The analysis embraced 708,296 HIV-positive people, and 27 of the studies were from North America, Europe, or Australia. The highest STI co-infection prevalence came among people with newly diagnosed HIV, a result possibly reflecting a heightened HIV acquisition risk in people with an STI. Overall STI prevalence did not differ between men and women or between people taking or not taking combination antiretrovirals. The latter finding, these researchers cautioned, “suggests that STI co-infections could undermine efforts to use HIV treatments for prevention by increasing genital secretion infectiousness.”

A study of 235 HIV-positive gay men seen in Sydney in 2004 and 2005 found that 2% had urethral chlamydia and 6% had anal chlamydia, and these rates did not differ from prevalence in an HIV-negative cohort of gay men. At four HIV/STI clinics in London, a study of 3076 MSM seen in 2005 and 2006 recorded rectal and urethral chlamydia rates of 8% and 5%. Rectal rates reflected chlamydia variants causing lymphogranuloma venereum (LGV) as well as non-LGV variants. Of the 247 rectal infections, 171 (69%) evoked no symptoms and so would have been missed without screening.

Although chlamydia and most other STIs reach their highest prevalence in teens and young adults, an eye-opening 1996-2003 study of people attending genitourinary medicine clinics in the British Midlands shows that people over 44 years old contribute their share to STI prevalence. These investigators counted 4445 STI episodes in people 45 and older during the study period, including 801 chlamydia diagnoses (18%). Compared with 1996, the chlamydia rate was 3.6 times higher in 2003 (95% confidence interval [CI] 2.55 to 5.06, \( P < 0.0001 \)). That jump was bigger than the overall 2.27 times rise in STI prevalence. Over the study period, the overall STI rate rose more in men (rate ratio [RR] 2.51, 95% CI 2.14 to 2.94, \( P < 0.0001 \)) than in women (RR 1.85, 95% CI 1.50 to 2.28, \( P < 0.0001 \)). The researchers did not report HIV rates.

Chlamydia incidence remains poorly studied in HIV populations. The largest recent study involved 4461 HIV-positive people in the US Military Natural History cohort monitored 6 months or later after their positive HIV test. Through an average follow-up of 7.08 years, 278 people (6%) picked up chlamydia, a rate similar to the 5% chlamydia prevalence recorded in the 37-study systematic review of 708,296 people with HIV. In the military study, chlamydia or gonorrhea rates were significantly higher in younger, male African Americans with a history of either STI.
A 2004-2006 study of 557 HIV-positive people in four US cities detected new chlamydia infections only in 365 MSM, not in 73 men who have sex with women or 119 women. In MSM, incidence 6 months after they entered the cohort stood at 5% for anorectal chlamydia and at 2% for oropharyngeal chlamydia (Table 2).

A single-center nurse-led self-screening program for chlamydia and gonorrhea in Brighton, UK, involved 976 screens done over 8 months in HIV-positive people with no STI symptom. Screening detected 143 infections that would have been missed without this program. In MSM incidence measured 9.8% for rectal chlamydia, 2.6% for urethral chlamydia, and 1.7% for pharyngeal chlamydia. Chlamydia incidence in heterosexual men and women was 2.1%.

In the general US population, yearly chlamydia case rates among women vaulted 54% from 2000 to 2010 (Figure 1). The CDC cautions that this inexorable case-rate inflation could reflect more intense screening, more sensitive diagnostic tests, or improved surveillance and reporting systems, but “persistently high infection rates” probably figure heavily in the equation.

Table 2. Chlamydia prevalence and incidence in 527 HIV-positive US adults

<table>
<thead>
<tr>
<th></th>
<th>Baseline prevalence</th>
<th>Incidence at 6-month visit</th>
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<tbody>
<tr>
<td></td>
<td>MSM (n = 365)</td>
<td>MSW (n = 73)</td>
</tr>
<tr>
<td></td>
<td>Women (n = 119)</td>
<td>MSM (n = 365)</td>
</tr>
<tr>
<td></td>
<td>MSW (n = 73)</td>
<td>Women (n = 119)</td>
</tr>
<tr>
<td>Anorectal</td>
<td>7%</td>
<td>0%</td>
</tr>
<tr>
<td>Oropharyngeal</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>2%</td>
<td>0%</td>
</tr>
</tbody>
</table>

MSM, men who have sex with men; MSW, men who have sex with women.
Source: Mayer et al.12

Figure 1. Chlamydia case rates in US women rose every year from 2000 through 2010, the last year for which the CDC has data.14
A prospective study of 1427 HIV-negative MSM recruited from 2001 through 2004 in Sydney recorded urethral and anal chlamydia incidence rates of 7.43 and 4.98 per 100 person-years, higher than the 3.49 and 2.96 rates for urethral and anal gonorrhea.\textsuperscript{15} Chlamydia incidence in these HIV-negative MSM far outstripped incidence in the general population of US women in 2010—610.6 per 100,000 in the US women\textsuperscript{14} and 7430 and 4980 per 100,000 for urethral and anal chlamydia in the Australian MSM. In these men unprotected anal intercourse with HIV-positive partners and frequent insertive oral sex raised the risk of urethral gonorrhea or chlamydia, and receptive unprotected anal intercourse made anal infections more likely.

Researchers have not directly tried to gauge the impact of active chlamydia infection on HIV incidence, though evidence from a systematic review described above supports that intuitive association.\textsuperscript{2} One should not assume, however, that wider chlamydia control measures will necessarily trim HIV incidence. A 2011 Cochrane Database review of four trials “failed to confirm the hypothesis that STI control [through biomedical intervention] is an effective HIV prevention strategy” in the general population.\textsuperscript{16} However, all these trials took place in rural Africa. The Cochrane team did find “other compelling reasons why STI treatment services should be strengthened.”

### Chlamydia risk factors in people with and without HIV

Several big studies identified independent predictors of chlamydia and other STIs in HIV-positive people and the general population (Tables 3 and 4).\textsuperscript{12,17-21} Being young raises the risk of chlamydia. Having lots of sex—and lots of risky sex—raises the risk. But these are obvious indicators; a few risk factors are less evident.

For starters, “young” doesn’t necessarily mean under 25, at least not among gay and bisexual men. A study of 659 HIV-positive MSM in the Netherlands found that being 40 to 44 rather than older more than doubled the odds of chlamydia, gonorrhea, or syphilis\textsuperscript{17} (Table 3). In Australia a study of 3805 MSM seeking care at STI clinics found that those 30 to 39 had a 42% higher risk of chlamydia than older men\textsuperscript{20} (Table 4). In this study the heightened risk was similar in MSM under 25 and MSM 25 to 29.

Analysis of HIV-positive US SUN Study participants found that MSM who had 4 or more sex partners in the 6 months before STI testing ran a higher risk of both prevalent and incident chlamydia, gonorrhea, or syphilis\textsuperscript{12} (Table 3). Multiple substance abuse inflated the odds of incident STIs 5 times in these MSM. Among HIV-positive MSM in the Netherlands, sharing sex toys or having an enema before sex (a signal of receptive anal intercourse) more than doubled the odds of chlamydia, gonorrhea, or syphilis\textsuperscript{17} (Table 3). In these MSM using drugs during sex also more than doubled the STI risk. Among Australian MSM seen in STI clinics, smoking cigarettes boosted the odds of chlamydia 19%\textsuperscript{20} (Table 4). In the same study inconsistent condom use in the past 3 months made chlamydia 50% more likely in both MSM and women.

A study of HIV-positive pregnant women in Western Europe and Ukraine (Table 3) determined that a CD4 count below 200 cells/mm$^3$, being single, and having an injection drug user (IDU) sex partner made chlamydia, syphilis, or Trichomonas vaginalis
Table 3. Risk factors for chlamydia and other STIs in people with HIV

<table>
<thead>
<tr>
<th>First author</th>
<th>Location(s)</th>
<th>Year(s)</th>
<th>No. of participants</th>
<th>Risk factors (95% CI)</th>
</tr>
</thead>
</table>
| Mayer12      | SUN Study participants in Denver, Minneapolis, St. Louis, Providence | 2004-2006 | 365 MSM, 73 MSW, 119 women | **For prevalent STIs** in MSM: > 4 partners: OR 4.81 (2.59-9.13)  
**For incident STIs** in MSM: > 4 partners: OR 3.44 (1.82-7.56)  
Polysubstance abuse (not marijuana): OR 5.0 (1.82-13.2)  
*STIs include syphilis and oropharyngeal, rectal, or genitourinary tract N. gonorrhoea and/or C. trachomatis.* |
| Heiligenberg17 | Netherlands, academic hospital outpatient clinics | 2007-2008 | 659 MSM | **For CT, NG, or SY:**  
Age < 40: OR 2.5 (1.3-5.0)  
Sex with > 2 sex partners: OR 2.1 (1.2-3.5)  
Sharing sex toys: OR 2.2 (1.0-4.9)  
**For CT or NG:**  
Age 40-44 vs older: OR 2.4 (1.1-5.3)  
Age < 40: OR 2.4 (1.1-5.4)  
Enema before sex: OR 2.4 (1.3-4.4)  
Drugs during sex: OR 2.4 (1.4-4.0) |
| Landes18 | Western Europe and Ukraine | 1999-2005 | 1050 pregnant women | **For CT, SY, or TV:**  
Being single: OR 3.9 (1.2-12.7)  
Sex partner of IDUs: OR 3.8 (1.4-10.4)  
CD4 count <200: OR 5.4 (1.0-28.1) |

CT, *Chlamydia trachomatis*; MSM, men who have sex with men; MSW, men who have sex with women; NG, *Neisseria gonorrhoea*; OR, odds ratio; SY, syphilis; TV, *Trichomonas vaginalis*.

*STIs include syphilis and oropharyngeal, rectal, or genitourinary tract N. gonorrhoea and/or C. trachomatis.*

more likely.18

A 48-state US study of the general population found significant links between poverty or income inequality and chlamydia (Table 4).19 These associations are reflected in two other general-population studies that traced ties between chlamydia risk and minority status in US MSM20 or Australian men and women20 (Table 4).

Sociodemographic variables must also figure in consistent correlations between childhood sexual abuse and risk of HIV and other STIs. A 2004-2005 analysis of the US National Epidemiologic Survey on Alcohol and Related Conditions found that women or men reporting abuse during childhood ran a higher risk continued...
Table 4. Risk factors for chlamydia and other STIs in the general population

<table>
<thead>
<tr>
<th>First author</th>
<th>Location(s)</th>
<th>Year(s)</th>
<th>No. of participants</th>
<th>Risk factors (95% CI)</th>
</tr>
</thead>
</table>
| Holgrave     | 48 contiguous United States | 1999 | Not stated | For CT:*  
Poverty: $r = 0.358, r^2 = 0.128, P < 0.01$  
Social capital:† $r = -0.532, r^2 = 0.283, P < 0.01$  
Income inequality: $r = 0.395, r^2 = 0.156, P < 0.01$  

| Wand         | Sydney, Australia, sexual health clinics | 1998-2009 | 3805 MSM, 5313 MSW, 7084 women | For CT in MSM:‡  
Age < 25 vs 40+: OR 1.47, $P = 0.005$  
Age 25-29 vs 40+: OR 1.58, $P < 0.001$  
Age 30-39 vs 40+: OR 1.42, $P = 0.006$  
Current vs never smoker: OR 1.19, $P = 0.05$  
Genital or anal vs no symptoms: OR 2.86, $P < 0.001$  
Inconsistent condom use: OR 1.51, $P < 0.001$  

| Peterman     | STI clinics in Denver, Long Beach, Newark | 1999-2000 | 1236 women, 1183 men attending STI clinic | For recurrent CT:  
15-25 vs older: OR 2.2 (1.7-2.9)  
Black vs white: OR 2.0 (1.3-3.1)  
Hispanic vs white: OR 1.9 (1.2-2.9)  
Infection at initial visit: OR 1.6 (1.2-2.2)  
2-4 partners vs 1: OR 1.7 (1.3-2.3)  

CT, Chlamydia trachomatis; MSM, men who have sex with men; MSW, men who have sex with women; NG, Neisseria gonorrhoea; OR, odds ratio; SY, syphilis; TV, Trichomonas vaginalis.

*Stated as Pearson product moment correlation coefficients.
† The central features of social capital are "trust, reciprocity, and cooperation among members of a social network that aims to achieve common goals."‡
‡ Other variables—including 1, 2, or 3 or more sex partners in the last months versus none, STI symptoms, and contact with an STI case—were also associated with higher odds for chlamydia in MSM and women. Risk factors for heterosexual men were being single, minority status, being unsure about HIV status, inconsistent condom use, increased number of female sex partners in the past 3 months, anal/genital symptoms, and presenting for STI screening or being a contact of an STI case.
of HIV or other STIs as adults. Compared with people not abused as children, the STI risk was higher in abused men or women who also reported same-sex partners or attractions than in those who did not.

A study of 485 girls and 51 boys who were 13 or younger and evaluated for sexual abuse at four US centers found that 3% of girls had chlamydia and 3% had gonorrhea. No children tested positive for HIV and no boys had any STI, but 40 of 485 girls (8%) had one or more STIs. Girls with vaginal discharge had higher STI rates than girls without discharge (24.5% versus 6%), but 10 girls with STIs had normal physical exams. And 27 of 40 girls with an STI (67.5%) had normal or nonspecific anogenital exams. One expert in this field counsels that “specific [sexually transmitted] infections in prepubertal children, such as Neisseria gonorrhoeae or Chlamydia trachomatis, are due to abusive contact and should be reported to Child Protective Services.” Recently abused children, she adds, should be considered for HIV postexposure prophylaxis.

Adults who have had one STI are prime candidates for a second STI within a year, according to results of a 2419-person analysis of RESPECT-2, a study of HIV prevention counseling in STI clinics in Denver, Long Beach, and Newark. Follow-up continued for a year after 1236 women and 1183 men visited the clinic. During 8129 3-month follow-up intervals, 25.8% of women had one or more new STIs, including 9.4% with chlamydia. Among the 1183 men, 14.7% had a new STI, including 9.4% with chlamydia. Two thirds of people with a new STI reported no symptoms. Table 4 summarizes risk factors for a new STI in this study.

In England an 18-month 2002-2003 study of 1971 young women recruited from general practice, family planning clinics, and genitourinary medicine (GUM) clinics found a high chlamydia reinfection rate in all three settings. Chlamydia incidence in these 16- to 24-year-old women was higher in GUM clinics than in family planning clinics or general practices (10.6 versus 6.4 versus 4.9 per 100 person-years). But reinfection rates were high in all three settings (21.1 versus 22.3 versus 29.9 per 100 person-years respectively). Finding a new sex partner and failure to treat all partners made reinfection more likely.

An Australian study supports the intuitive assumption that MSM seeking HIV postexposure prophylaxis will likely benefit from STI screening. This 2001-2004 study found that 253 of 298 MSM (85%) agreed to STI testing. While 4.5% had rectal chlamydia, 2.5% had rectal gonorrhea. Only 6 men with an STI (19%) had symptoms at screening.

How chlamydia sets up infection and spreads

C. trachomatis infects epithelial cells at mucosal surfaces (Figure 2), ignoring an inflammatory response that can lead to tissue damage and scarring upon reinfection. But little was known about how chlamydia sets off and sustains an inflammatory response until US researchers infected cervical and colonic epithelial cells with C. trachomatis and C. psittaci. Infection prompted secretion of the proinflammatory cytokines IL-6, IL-8, GRO alpha, and GM-CSF. While other invasive bacteria provoke rapid but transient cytokine responses, chlamydia induced a response that began 20 to 24 hours after infection and persisted throughout the chlamydia growth cycle, which lasts 2 to 4 days.

This work also showed that IL-1alpha, which is released during lysis of chlamydia-infected epithelial
cells, may amplify the inflammatory response by churning up additional cytokines in uninfected neighboring cells. These investigators believe their findings “suggest a novel concept for chlamydial pathogenesis wherein the acute host response to chlamydia in the genital tract, and at other mucosal surfaces, is primarily initiated and sustained by epithelial cells, the first and main targets of chlamydial infection.”

Like HIV, C. trachomatis can jump from one person to another during vaginal or rectal sex. But while oral transmission of HIV is inefficient, C. trachomatis can exploit the oral route with relative ease, a factor that contributes to high chlamydia rates in sexually active people. C. trachomatis may also pass from mother to infant during vaginal delivery.

**Figure 2.** This photomicrograph (magnified 200×) shows C. trachomatis inclusion bodies in McCoy cell monolayers. Using cell cultures from the McCoy cell line is one method of diagnosing chlamydia infection. (From the Centers for Disease Control and Prevention Public Health Image Library [PHIL], Dr. E. Arum and Dr. N. Jacobs.)

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**Chlamydia raises risk of HIV infection and progression**

Rectal chlamydia infection can boost the risk of HIV infection in MSM nearly 9 times, and chlamydia doubles the risk of HIV shedding in the genital tract, upping the odds of HIV transmission from people infected with C. trachomatis. Treating chlamydia significantly lowers cervical HIV shedding.

A retrospective cohort study reported in 2010 by the San Francisco Department of Public Health assessed how the number of rectal infections with C. trachomatis or N. gonorrhoeae in the past 2 years affects the risk of getting infected with HIV. Among 541 initially HIV-negative men studied, 27 (5%) got infected for an estimated annual HIV incidence of 2.25%. Two rectal chlamydia infections or two rectal gonorrhea infections in the past year inflated the risk of HIV seroconversion nearly 9 times (hazard ratio [HR] 8.85, 95% CI 2.57 to 30.4). An early syphilis diagnosis in the past 2 years quadrupled the risk (HR 4.04, 95% CI 1.19 to 13.79).

A history of any STI in an HIV-negative woman with an HIV-positive male partner more than doubled the odds that the woman would get infected with HIV. This 10-year northern California study involved 360 HIV-positive men and their negative female partners and 82 HIV-positive women and their negative male partners. More than 90% of couples were monogamous. Because this study was reported in mid-1997, follow-up largely occurred before the triple-therapy era. Sixty-eight of 360 initially negative women picked up HIV, compared with only 2 of 82 initially negative men (18.9% versus 2.4%). A history of any STI in a female partner more than doubled the odds of male-to-female HIV transmission (OR 2.6, 95% CI 1.4 to 5.1).
Meta-analysis of 39 studies that weighed the impact of genital tract infections on genital HIV shedding determined that chlamydia nearly doubled the odds, while urethritis or cervicitis from any cause tripled the odds (at the following odds ratios and 95% CIs).30

- Chlamydia infection: OR 1.8, 95% CI 1.1 to 3.1
- Gonorrhea: OR 1.8, 95% CI 1.2 to 2.7
- Vulvovaginal candidiasis: OR 1.8, 95% CI 1.3 to 2.4
- Urethritis: OR 3.1, 95% CI 1.1 to 8.6
- Cervicitis: OR 2.7, 95% CI 1.4 to 5.2

These researchers stressed that “these infections are likely to be particularly important in promoting sexual transmission and mother-to-child intrapartum transmission of HIV-1.”30 Another pooled analysis of three studies in women also found that chlamydia nearly doubled the odds of HIV shedding (OR 1.85, 95% CI 1.1 to 3.2, \(P = 0.02\)).33

Given findings like these, it is not surprising that treating cervicitis decreases HIV shedding.31 This study involved 36 HIV-positive women treated for cervicitis in Mombasa, Kenya; 16 had \textit{N} gonorrhoeae, 7 had \textit{C} trachomatis, and 13 had nonspecific cervicitis. After treatment of cervicitis, cell-free and cell-associated HIV-1 RNA fell from 4.05 to 3.24 \(\log_{10}\) copies/swab overall (\(P = 0.001\)) and from 4.21 to 3.19 \(\log_{10}\) copies/swab in women with chlamydia (\(P = 0.02\)). Prevalence of HIV-1 DNA in cells dropped from 67% before treatment to 42% after treatment (OR 2.8, 95% CI 1.3 to 6.0, \(P = 0.009\)).

A study of urine-based chlamydia and gonorrhea screening in a New Orleans HIV clinic used a mathematical model to estimate that treating 56 chlamydia infections and 46 gonorrhea infections may have averted 9 HIV infections in sex partners “and saved far more in future medical costs than the cost of the screening.”34

Despite results of these two studies, another 2011 Cochrane Database review of four trials could not confirm that treating STIs “is an effective HIV prevention strategy” in the general population.16

CDC chlamydia screening guidelines released in 2002 offer advice on when to screen women but not men in the general population.4 The CDC recommends screening all women up to age 25 and older women with a higher chlamydia risk indicated by multiple sex partners, a history of STIs, or not using condoms consistently or correctly.

Health Resources and Services Administration (HRSA) HIV guidelines from 2011 outline chlamydia and gonorrhea screening guidance for women and men (Table 5). For pharyngeal or rectal infection, HRSA recommends a nucleic acid amplification test (NAAT) or culture of an oral swab or a rectal swab. For urethral or cervical infections, HRSA recommends NAAT on a first-catch urine or urethral specimen (in men) or cervical specimen (in women). One STI expert notes that NAATs have a low positive predictive value in populations with low chlamydia prevalence, such as older adults, so “positive test results should be interpreted with caution, and consideration should be given to use of a second testing modality for confirmation of the results.”35
Despite guidelines recommending frequent gonorrhea and chlamydia screening in people with HIV, a study of HIV-positive men in the Johns Hopkins University HIV cohort found that fewer than half were getting tested for these STIs. Among 1110 men studied in this 1999-2008 analysis, chlamydia and gonorrhea testing rates upon clinic enrollment rose from 4% before 2003 to only 16.5% afterwards. The proportion of men ever tested for these STIs

### Table 5. HRSA guidelines for chlamydia and gonorrhea screening in people with HIV

<table>
<thead>
<tr>
<th>Women</th>
<th>If negative</th>
<th>If positive</th>
</tr>
</thead>
</table>
| ► Screen sexually active women at risk  
► Screen all at baseline  
► Frequency of subsequent testing depends on risk factors  
► Screen all sites of possible exposure: pharynx (for gonorrhea screening); cervix/vagina; urethra; rectum | ► Counsel about safer sex and avoiding STIs  
► Repeat every 6 to 12 months; more frequently if at higher risk | ► Treat patient  
► Refer partner(s) of previous 60 days for evaluation and treatment  
► Counsel about safer sex |

<table>
<thead>
<tr>
<th>Men</th>
<th>If negative</th>
<th>If positive</th>
</tr>
</thead>
</table>
| ► Screen sexually active men at risk, especially MSM  
► Screen all at baseline  
► Frequency of subsequent testing depends on risk factors  
► Screen sites of possible exposure: pharynx (for gonorrhea screening); rectum; urethra (consider for MSM with history of unprotected insertive intercourse in preceding year) | ► Retest every 3 to 6 months for patients with risk factors | ► Treat  
► Refer partner(s) of previous 60 days for evaluation and treatment  
► Counsel about safer sex |

climbed from 34.2% before 2003 to 49.1% afterwards. Yet among 342 men ever tested, 5.2% had a positive result on their first test. A 2004-2010 analysis of HIV-positive men and women in 7 US cities found that syphilis testing rates reached 70% in 2009-2010, while chlamydia and gonorrhea testing rates languished below 40% in those years.37

Almost three quarters of 808 adults visiting a Colorado HIV counseling and testing center (71%) agreed to urine screening for C trachomatis, though only 8 of 560 urine samples processed (1.4%) were positive.38 One third of those who declined urine screening did so because they had no STI symptoms, even though chlamydia infection is often asymptomatic.

Although urine screening is easy, it will probably miss a fair proportion of chlamydia infections, both in men and women. A San Francisco study of 5539 MSM seen at an STI clinic and 895 seen at a gay community health center found the highest chlamydia prevalence in rectal samples (7.9%), followed by urethral (5.2%) and pharyngeal (1.4%) sites.39 More than half of chlamydia infections (53%) were nonurethral, and 85% of rectal infections were asymptomatic.

A study of people attending an STI clinic or one of three HIV clinics focused on those who reported anal intercourse or women with a high risk of chlamydia or gonorrhea.40 More than 80% of chlamydia infections would have been missed if rectal samples had not been tested. Culture of rectal swabs had chlamydia sensitivities ranging from 36.1% to 45.7%, while sensitivities of two NAATs were 91.4% to 95.8% for PCR and 100% for transcription-mediated amplification (TMA). Specificities of the two NAATs were also high.

People reluctant to get tested for chlamydia at an STI clinic or their provider’s office may try an Internet site offering STI testing. But a 2010 survey of such sites found them highly unreliable.41 These researchers identified 27 US or international sites offering STI self-collection kits and services for chlamydia, gonorrhea, syphilis, and other STIs. Only two sites completed a mailed or e-mailed survey about these services. Six sites appeared to be invalid because mail or e-mail to them was returned undelivered. Only 5 of 7 sites that provided test kits returned results. Two sites that were sent urine samples never responded. Two kits yielded false-negative results, while two kits yielded correct positive results.

Chlamydia prevention that works: condoms and beyond

Behavioral interventions have proved successful in curbing the risk of chlamydia infection, as has a partner-delivered azithromycin program. But steady condom use is the surest way to prevent spreading or acquiring chlamydia. Both the CDC1 and the Health Resources and Services Administrations (HRSA)3 stress the reliability of condoms: “Male latex condoms, when used consistently and correctly,” HRSA HIV guidelines say, “are highly effective in preventing sexual transmission of HIV and many other STIs, including syphilis, chlamydia, gonorrhea, and Trichomoniasis.”3

Inconsistent condom use upped the odds of chlamydia infection by 50% in an Australian study of 3805 MSM (Table 4).20 In the same study, women whose partners did not wear condoms consistently also had 50% higher odds of picking up chlamydia. CDC investigators examined the impact of consistent condom use in people enrolling in a trial of sex-counseling interventions at five publicly funded US STI clinics from 1993 through 1997.42 Among 429 participants with known exposure to chlamydia or gonorrhea, consistent condom use sliced the odds of prevalent

continued...
infection with one of those STIs by almost 60% (adjusted OR 0.42, 95% CI 0.18 to 0.99). Among 4314 participants with unknown exposure to chlamydia or gonorrhea, consistent condom use trimmed those odds by almost 20% (adjusted OR 0.82, 95% CI 0.66 to 1.01).

Some of the same CDC investigators conducted a systematic review of chlamydia and gonorrhea risk in 45 studies of condom use. All studies assessed male condom use and were published from 1966 through 2004. Most studies had methodologic limitations, such as failing to distinguish between consistent and inconsistent condom use. Despite these limitations, which probably resulted in underestimates of condom effectiveness, in the overall analysis condoms did lower chlamydia and gonorrhea rates in both men and women.

Asking women with chlamydia to hand-deliver antibiotics to their sex partners may lower the reinfection risk in those women. A randomized trial conducted by the CDC involved 1787 women from 14 to 34 years old with uncomplicated genital Chlamydia infection diagnosed in 5 US cities. The investigators randomized women to deliver a dose of azithromycin (a “partner pack”) to each of their sex partners or to refer their sex partners for treatment. Four months later, urine ligase chain reaction or polymerase chain reaction indicated a lower risk of chlamydia reinfection in women who took azithromycin to their partners (87 of 728, 12%) than in women who referred partners for treatment (106 of 726, 15%). Although that difference fell short of statistical significance (OR 0.80, 95% CI 0.62 to 1.05, P = 0.102), the CDC team suggested that patient-delivered treatment “may be an appropriate option for some patients” with uncomplicated chlamydia.

A randomized trial of expedited partner notification and treatment versus standard notification, described in the next section, found lower rates of persistent or recurrent chlamydia or gonorrhea in index patients. Two accelerated partner notification and treatment models tested in the UK, also described in the next section, documented higher chlamydia and gonorrhea treatment rates among partners benefiting from these approaches than among partners who received standard notification.

Three behavioral intervention studies found that these strategies cut the risk of chlamydia infection in adults and adolescents. “Intervention” is a term laden with visions of multimonth counseling conducted by specially trained (and richly paid) staff, but the Safe in the City approach involves only a video with STI prevention messages seen in the waiting room before appointments. This study involved 38,635 people who came to publicly funded STI clinics in three US cities between December 2003 and August 2005. Participants were randomized to the usual waiting-room environment or to watch a 23-minute video showing couples overcoming barriers to safer-sex behaviors. After an average 14.8 months of follow-up, the risk of incident lab-confirmed chlamydia, gonorrhea, Trichomoniasis, syphilis, or HIV was about 10% lower in the intervention group, a significant difference (HR 0.91, 95% CI 0.84 to 0.99). To access and preview this video, go to http://www.safeinthecity.org.

The WiLLOW Program involves four 4-hour sessions for women delivered over 4 consecutive weeks and emphasizing gender pride, maintaining current and identifying new network members, enhancing HIV transmission knowledge, improving communication and condom use skills, and developing healthy relationships (for details go to http://www.cdc.gov/hiv/topics/research/prs/resources/factsheets/WILLOW.htm#ref1). A trial reported in 2004 randomized 366 HIV-positive women in Alabama and
Georgia to the WiLLow Program or to no intervention. Through 12 months of follow-up, incidence of chlamydia or gonorrhea was about 80% lower in the WiLLow group (OR 0.19, P = 0.006). Women who completed WiLLow also reported significantly fewer episodes of unprotected vaginal intercourse and were significantly less likely to report never using condoms. The CDC ranks WiLLow as one of its “best-evidence” interventions to prevent infection with HIV and other STIs.

A culturally tailored STI/HIV intervention for African-American girls and young women involves two 4-hour group sessions and 4 telephone contacts during a 1-year period. A trial randomized 715 youngsters seeking sexual health services to receive the intervention or standard care. Participants completed a computer-assisted self-interview and gave self-collected vaginal specimens for STI testing. Girls and women randomized to the interview had a 35% lower risk of a new chlamydia infection (risk ratio [RR] 0.65, 95% CI 0.42 to 0.98, P = 0.04) and a 75% lower risk of recurrent chlamydia (RR 0.25, 95% CI 0.08 to 0.83, P = 0.02). Participants in the intervention group also reported a higher proportion of condom-protected sex acts in the previous 60 days and a higher rate of condom use at last intercourse.

STI screening itself may temper risk-taking behavior, according to results of a study in 636 sexually active African-American teens in two US cities with high STI prevalence. Among adolescents screened for chlamydia, gonorrhea, and Trichomoniasis, the 6.6% with positive tests received treatment and counseling, while those with negative results received no further intervention. Among the 85% of study participants who completed 3- and 6-month follow-up visits, teens with a positive STI result lowered their number of vaginal and oral sex partners and the number of unprotected sex acts. STI testing at the 6-month point determined that 4.3% of initially STI-negative youngsters had a positive test.

Work is under way to develop a T-cell vaccine against chlamydia infection. Researchers at the British Columbia Centre for Disease Control and the University of British Columbia formulated a vaccine with three chlamydia T-cell antigens that generated protection against infection in mice. These investigators cautioned that “an ongoing challenge for chlamydia vaccine research remains the discovery of strategies that maximize the protective effects of immune T cells while simultaneously preventing such cells from causing immune-mediated tissue damage.”

### Benefits reaped with better partner notification

Recent research details the benefits of prompt notification and treatment of chlamydia patients’ partners, and the CDC provides extensive advice on partner notification for chlamydia, HIV, and other STIs. Yet chlamydia partner notification rates in the United States were abysmal when last evaluated. In 1998 researchers asked US health departments in areas with the highest reported rates of chlamydia, syphilis, gonorrhea, and HIV to indicate how many people with these infections were interviewed for partner notification. Only 26,487 of 228,210 chlamydia patients (12%) were asked to provide partner contact information, below the rates for gonorrhea (17%), HIV (52%), or syphilis (77%). Twenty-seven of 60 responding health departments (45%) provided no routine partner notification services to chlamydia patients.

Given this lackluster health-department performance, clinicians might be expected to take up the continued...
slack. But that wasn’t happening the last time the CDC checked. A random survey of 7300 providers reported in 2002 found that 80% of respondents told chlamydia patients to notify their partners rather than doing so themselves. And only 20% of providers followed up with patients to see if partners had been referred for treatment.

The CDC says all sex partners of people with chlamydia should be contacted and tested, and the Health Resources and Services Administration (HRSA) says partners should be treated empirically if they had sex with the index patient within 60 days since that person’s symptoms began. If a person diagnosed with chlamydia cannot remember sex partners within the past 60 days, the most recent sex partners before that should be contacted and treated. The CDC urges people diagnosed with chlamydia to avoid sex with partners who are not examined and treated.

HRSA underscores the potential value of antibiotic “partner packs” delivered by the index patient to partners who may be unlikely to come to the clinic for evaluation. This approach, described in the preceding section, may result in a lower reinfection rate among index patients. A British trial of a similar but more comprehensive partner-treatment approach is described below. HRSA notes that most recurrent chlamydia infections occur in people whose sex partners are not treated. Anyone treated for chlamydia should be retested about 3 months later, regardless of whether they believe their sex partners got treated.

In 2008 the CDC released comprehensive guidelines on partner notification and treatment for people diagnosed with HIV, chlamydia, and other STIs, including a flowchart detailing the steps in contacting, notifying, treating, and monitoring partners (Figure 3). Among other things, these guidelines cover (1) counseling index patients about reducing their risk for acquiring or transmitting infection to others and referring them for additional prevention services, if needed, (2) notifying partners of their exposure, (3) counseling partners about reducing their risk for acquiring HIV infection and other STIs and referring them for additional prevention services, if needed, (4) offering partners STI/HIV testing, and (5) treating partners or linking them to medical care and treatment. The CDC also suggests which patients diagnosed with chlamydia fall into a high-priority group for partner notification, and which partners should be considered high-priority.

High-priority index patients for partner services, regardless of the STI:
- Pregnant women and male index patients with pregnant partners
- Index patients suspected of or known to be engaging in behaviors that substantially increase risk of transmission to multiple partners (for example, those with multiple sex partners or drug-injection partners)
- Persons coinfected with HIV and one or more other STIs
- Persons with recurrent STIs

High-priority index patients for partner services for chlamydia, syphilis, and gonorrhea:
- Persons with clinical signs or symptoms suggesting infection
- Infected persons from high STI prevalence areas

Partners with the highest priority for notification, regardless of the STI:
- Female partners who are known or likely to be pregnant
- Partners suspected of or known to be engaging in behaviors that substantially increase the risk for transmission to multiple other persons
- Partners with whom the index patient reports having had unprotected anal or vaginal sex
To determine whether faster notification and treatment of chlamydia and gonorrhea patients’ partners would lower rates of persistent or recurrent infection in the index case, researchers planned a randomized trial of expedited treatment (patients offered medication to give to sex partners or offered contact of partners by staff who gave partners medication without a clinic exam) or standard referral (patients asked to refer partners for treatment and offered assistance in finding partners). Patients included women and heterosexual men, but not MSM.
Three to 9 weeks after index patients got treated for chlamydia or gonorrhea, persistent or recurrent infection could be detected in 92 of 929 people (10%) assigned to expedited partner treatment and in 121 of 931 (13%) assigned to standard partner referral. Relative risk of persistent or recurrent gonorrhea or chlamydia infection was about 25% lower in the expedited group (RR 0.76, 95% CI 0.59 to 0.98). When the researchers assessed the impact of expedited partner treatment on the two STIs separately, the persistent or recurrent infection rate was significantly lower for gonorrhea (3% versus 11%, \(P = 0.01\)), but that difference fell short of statistical significance for chlamydia (11% versus 13%, \(P = 0.17\)). These researchers noted three potential disadvantages to treating partners without evaluating them:

- "Some partners may have allergic reactions or other drug-related adverse effects.
- "Partners treated without a clinical evaluation may have concurrent STIs identifiable only if they seek medical care.
- "An opportunity may be lost to counsel sex partners to refer their other partners for evaluation and treatment."

On the basis of these findings, the investigators argued that "the inadequacies of current approaches to partner notification and the persistence of unacceptably high levels of morbidity from sexually transmitted infections in the United States should motivate both clinicians and public health authorities to incorporate patient-delivered partner therapy and other approaches to expedited care of partners into clinical and public health policies."

British researchers conducted a preliminary, non-randomized comparison of two accelerated partner therapy (APT) models and routine partner notification for partners of people with a lab diagnosis of \(C. trachomatis\) and/or \(N. gonorrhoeae\) or nongonococcal urethritis (men only). The study involved 226 adults enrolled in a sexual health clinic or a genitourinary medicine clinic. The researchers did not specify how many were women, heterosexual men, or MSM.

The two accelerated partner therapy models involved (1) a hotline that sex partners called for a phone consultation with a qualified provider or (2) a pharmacy that sex partners visited for consultation. In both models partners picked up or received from the index patient an “APT pack” including (1) 1 g of azithromycin or 400 mg of cefixime, (2) relevant drug information sheets, (3) a urine NAAT sample collection kit for \(C. trachomatis\) and \(N. gonorrhoeae\) and appropriate packaging for mailing samples back to the study lab, (4) condoms, and (5) full details of the study. Partners in the comparison group had to attend the clinic for evaluation and treatment. Both APT options also featured an “assertive invitation” to the partner to get fast-track HIV and syphilis tests at a local sexual health clinic.

While 42 of 117 of contactable partners (36%) reached by routine partner notification got treated, 80 of 135 partners (59%) reached by the hotline and 29 of 44 (66%) who visited a pharmacy were treated (\(P = 0.003\) and \(P = 0.001\) compared with routine partner notification). From 40% to 60% of partners in the accelerated partner therapy groups returned urine samples for STI testing, but almost none followed up for HIV or syphilis testing. The investigators hope to test these approaches in a cluster-randomized trial.

A stochastic simulation model estimated the impact of chlamydia screening coverage and partner notification on positivity in the United States. The model described pair formation and dissolution in an age-structured heterosexual population of highly sexually active people. These researchers figured the impact of a chlamydia screening program reaching 20%, 35%, 50%, and 65% of women 15 to 24 years old, male partner notification rates of 20%, 40%, and 55%, screening rates of 20% and 35% in 15- to 24-year-old men, and female partner notification rates of 25% and 40%. The model estimated a 23% reduction in...
chlamydia positivity by increasing screening 3-fold or partner notification 2-fold.

**Treating chlamydia in people with HIV**

Treatment of *C. trachomatis* infection is the same in people with HIV as in those without HIV. Two regimens top the recommendation list:

- A single 1-g oral dose of azithromycin
- A 100-mg oral dose of doxycycline twice daily for 7 days

One-time azithromycin is preferred because of its simplicity. The CDC and the Health Resources and Services Administration (HRSA) guidelines for people with HIV list four alternative regimens:

- Erythromycin base 500 mg orally four times a day for 7 days
- Erythromycin ethylsuccinate 800 mg by mouth four times a day for 7 days
- Ofloxacin 300 mg by mouth twice daily for 7 days
- Levofloxacin 500 mg by mouth once daily for 7 days

For pregnant women, the CDC and HRSA recommend a single 1-g oral dose of azithromycin or 500 mg of amoxicillin by mouth three times a day for 7 days. CDC guidelines also spell out advice on treating chlamydia in infants and children.

HRSA guidelines suggest providers advise patients to take medications with food if they feel nauseated and to call immediately if they experience vomiting or cannot take their medications. Treated individuals should abstain from sex for 7 days after single-dose azithromycin or until a 7-day course is completed.

Except for pregnant women, infants, and children, the CDC does not recommend repeat testing 3 to 4 weeks after therapy “unless therapeutic compliance is in question, symptoms persist, or reinfection is suspected.” (Results of work described below suggest a test for cure may be advisable in people with asymptomatic rectal chlamydia.) If chlamydia symptoms persist after treatment, HRSA recommends evaluating patients for possible reinfection, treatment failure, or a different cause of symptoms. If the provider suspects treatment failure, HRSA recommends culture and antimicrobial sensitivity testing.

The CDC recommends rescreening all men and women treated for *C. trachomatis* 3 months after they finish therapy, “regardless of whether they believe that their sex partners were treated.” If a person cannot be retested 3 months after treatment, the CDC advises retesting whenever that person has a follow-up visit in the 12 months after finishing therapy.

Does single-dose azithromycin work consistently for people with asymptomatic rectal gonorrhea, a common presentation in MSM? A case series at an Edinburgh genitourinary medicine clinic suggests no. Edinburgh investigators reviewed all 101 cases of rectal chlamydia diagnosed from June 2005 to June 2006. After excluding symptomatic cases, they counted 9 failures of single-dose azithromycin in 68 people for a failure rate of 13%. The researchers believe this result “suggests that single-dose azithromycin may be a less than effective treatment in asymptomatic rectal *C. trachomatis* infection” and that “the potential treatment failure rate with this regimen emphasizes the need for a test of cure at the appropriate interval following treatment to ensure clearance of infection.”

In a 37-study systematic review of STIs acquired by people already infected with HIV, taking combination antiretroviral therapy did not affect STI incidence. On the basis of this finding, the investigators cautioned that “STI co-infections could undermine efforts to use HIV treatments for prevention by increasing genital secretion infectiousness.”
References


continued...


Pointers on chlamydia prevention and care for people with HIV

1. Chlamydia infection often has no physical signs or symptoms, so you may not know you’re infected unless you get tested regularly.

2. Sexually active men with HIV should be tested for chlamydia every 3 to 6 months, and sexually active women should be tested every 6 to 12 months.

3. How often a person gets tested depends on their individual risk of chlamydia infection.

4. People with a high risk of chlamydia infection include (1) those who have already had chlamydia, (2) those with many sex partners, (3) those who use drugs or alcohol during sex, (4) those who have sex without a condom, (5) younger people, and (6) people with a CD4 count under 200.

5. Chlamydia can pass from one person to another during oral, vaginal, or rectal sex, and it can pass from a mother to an infant during vaginal delivery.

6. Using male latex condoms correctly is the surest way to protect yourself from chlamydia.

7. If you get chlamydia, letting your sex partners know is very important—both so they can be treated and so you can avoid getting infected by them again.

8. If you get treated for chlamydia, do not have sex for 7 days after you start treatment. After the treatment period, do not have sex with partners who have not been tested for chlamydia—and treated if necessary.

9. Taking chlamydia drugs with food can lower the risk of nausea. If chlamydia drugs make you throw up, contact your provider immediately.

Possible signals of chlamydia infection

Chlamydia infection may cause no pain, discomfort, or any other signals of infection. But sometimes people infected with chlamydia feel pain or see signs in sex organs, in the anus or rectum (in people who practice anal sex), or in the abdomen or pelvis. If you notice one or more of the following signs, stop having sex. If these problems persist, see your healthcare provider as soon as possible.

**MEN**

- **Urination, penis, testicles**
  - Increased urinary frequency or urgency
  - Fluid with odor leaking from urethra (urine canal)
  - Red or swollen urethra
  - Incontinence (inability to control urination)
  - Pain on urination
  - Tenderness, swelling, or pain in testicles

- **Anus, rectum**
  - Rectal pain or bleeding
  - Fluid leaking from the rectum
  - Anal discomfort

**WOMEN**

- **Urination**
  - Urinary hesitancy
  - Pain or burning on urination

- **Sex organs**
  - Fluid with odor leaking from the vagina
  - Pain during sexual intercourse
  - Bleeding between menstrual cycles
  - Genital sores

- **Abdomen, pelvis**
  - Abdominal or pelvic pain
  - Low back pain

- **Mouth, throat**
  - Sore throat
  - Mouth sores

- **Anus, rectum**
  - Rectal pain or bleeding
  - Fluid leaking from the rectum
  - Anal discomfort

- **General**
  - Fever
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